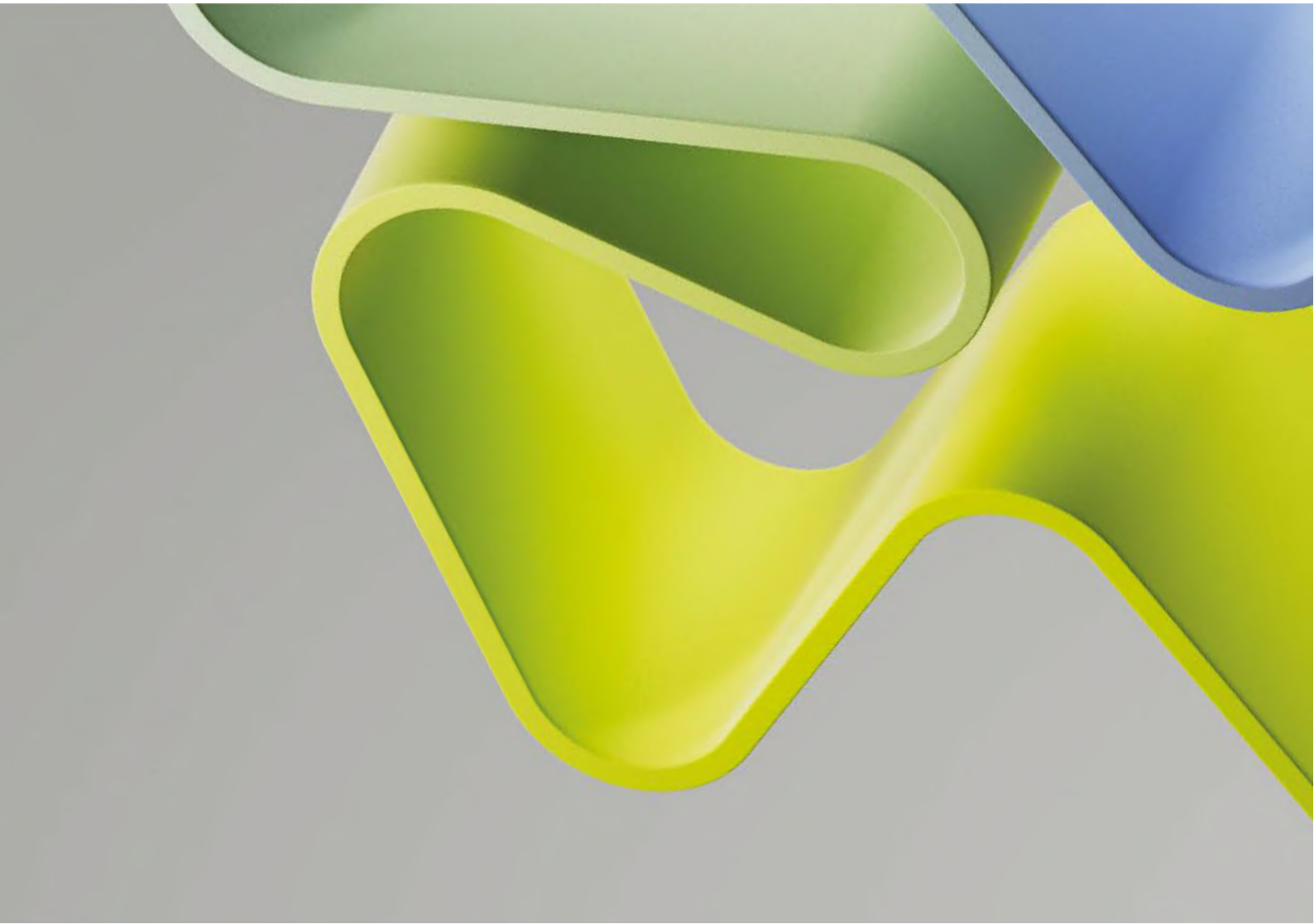
The Research Council of Norway

Evaluation of Medicine and Health (EVALMEDHELSE) 2023-2024

Impact cases



Introduction

Administrative units that participated in the Evaluation of Medicine and Health research in Norway 2023-2024 were invited to submit case studies documenting the societal impact of their research. In this report the impact cases will be presented in the way they were submitted by the institutions using the template for impact cases (see attachment) which were sent to the 68 enrolled administrative units 15. September 2023 with a deadline of 31. January 2024. Impact cases from 66 administrative units are presented here. Some of the cases are also presented in the National report for Medicine and Health research.

Definition

The definition of, and model for, societal impact was derived from the 2021 Research Excellence Framework (REF) in the United Kingdom:

> Definition of Societal impact: an effect on, change or benefit to the economy, society, culture, public policy or services, health, the environment or quality of life, beyond academia.
>
> Impact includes the reduction or prevention of harm, risk, cost or other negative effects.
>
> Academic impacts on research or the advancement of academic knowledge are excluded. Impacts on students, teaching or other activities both within and/or beyond the submitting institution are included.
>
> Impact includes, but is not limited to, an effect on, change or benefit to:
> - the activity, attitude, awareness, behaviour, capacity, opportunity, performance, policy, practice, process or understanding
> - of an audience, beneficiary, community, constituency, organisation or individuals
> - in any geographic location whether locally, regionally, nationally or internationally

Impact case guidelines

Each case study should include sufficiently clear and detailed information to enable the evaluation committee to make judgements based on the information it contains, without making inferences, gathering additional material, following up references or relying on members' prior knowledge.

Timeframes

- The impact must have occurred between 2012 and 2022
- Some of the underpinning research should have been published in 2011 or later
- The administrative units were encouraged to prioritise recent cases

Maximum number of cases permitted per administrative unit

For up to 10 researchers: one case; for 10 to 30 researchers: two cases; for 30-50 researchers: three cases; for 50-100 researchers: four cases, and up to five cases for units exceeding 100 researchers.

The impact cases are presented alphabetically by administrative unit.

Akershus University Hospital and Institute of Clinical Medicine, University of Oslo (Campus Ahus) – Impact case #1

Institution: **Name:** Akershus University Hospital and Institute of Clinical Medicine, University of Oslo **Short name:** Ahus and Campus Ahus
Administrative unit: **Name:** Akershus University Hospital and Institute of Clinical Medicine, University of Oslo **Short name:** Ahus_Campus Ahus
Title of case study: Cardiac biomarkers
Period when the underpinning research was undertaken:2012-present
Period when staff involved in the underpinning research were employed by the submitting institution: 2012-present
Period when the impact occurred: 2012-present

1. Summary of the impact (indicative maximum 100 words)

This section should briefly state what specific impact is being described in the case study.

The Cardiovascular Research Group at Akershus University Hospital (Ahus, hospital) and Campus Ahus (University of Oslo) is a leading international group in studies on cardiac biomarkers. The group received a prestigious grant as a K. G. Jebsen Center for Cardiac Biomarkers in 2022: K.G. Jebsen Centre for Cardiac Biomarkers - Stiftelsen Kristian Gerhard Jebsen (stiftkgj.no). The work from 2012-2022 includes clinical studies with established cardiac biomarkers, which have had direct relevance on patient care, and integrated, translational research on novel cardiac biomarkers. The work was performed in close collaboration with industry partners and has led to significant advancements for clinical care, intellectual property rights (IPR), and the establishment and development of two Norwegian biotechnology companies.

2. Underpinning research (indicative maximum 500 words)

The Cardiovascular Research Group, led by Professor Omland, aims to improve diagnostics and care for patients with cardiovascular disease through studies on novel and established cardiac biomarkers. We combine excellent large-scale clinical cohorts and state-of-the-art laboratory research. The group utilizes a bed-to-bench strategy to advance our understanding of the complex pathophysiology of cardiovascular disease- see **Fig.1** for research strategy:

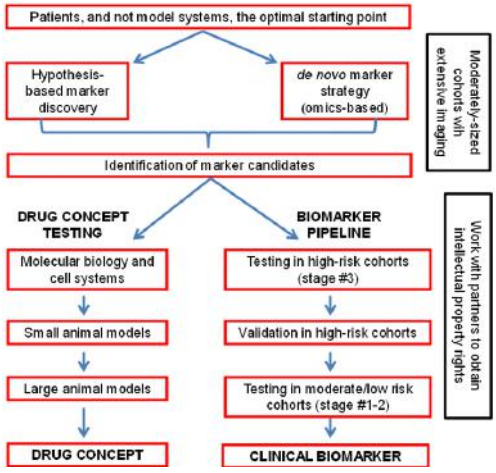


Fig.1. Bed-to-bench strategy to identify and test candidates as biomarkers and drug concepts

We will present two main research focuses of the period to exemplify the work: ***(1)*** use of high-sensitivity (hs) cardiac troponin I and T to identify subclinical and clinical myocardial injury, and ***(2)*** translational research to develop secretoneurin (SN) as a novel cardiac biomarker and potential therapeutic strategy. For hs-troponin work, we have collaborated closely with major international industrial partners such as Abbott Diagnostics and Roche Diagnostics, and with the local Norwegian partner SpinChip Diagnostics (https://spinchip.no).

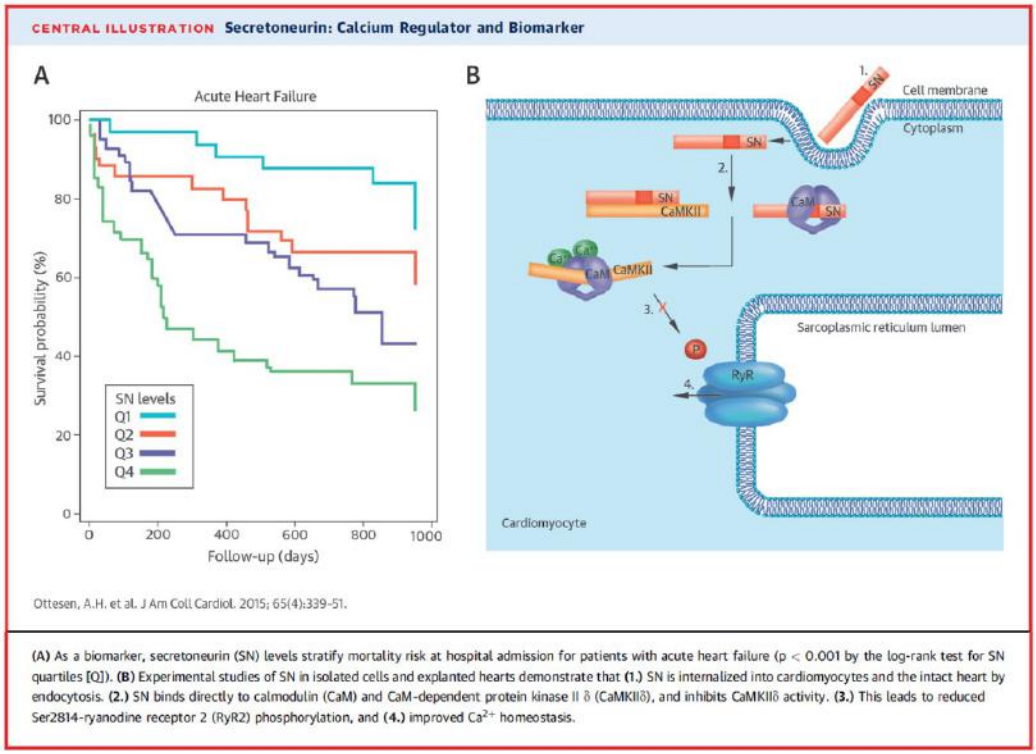
SN is currently being commercialized by the Norwegian company CardiNor AS (https://cardinor.com) and Professors Omland and Røsjø share IPR for SN as a cardiac biomarker.

In patients with chronic cardiovascular disease, we were among the first groups to demonstrate that hs-troponin concentrations represent early and accurate markers of pathological left ventricular

remodeling (*Ref. 1, Section 4*). We advanced this work by validating hs-troponin measurements as markers of heart failure risk in the general population, prior to the development of symptoms (i.e., subclinical disease) (*Ref. 6, Section 4*). For the work on subclinical disease, we designed and executed the Akershus Clinical Examination (ACE) 1950 Study between 2012-2015 with extensive clinical, biochemical, and imaging phenotyping of 3706 subjects from general population. Using data also from the large-scale Trøndelag Health (HUNT) Study, we found hs-troponin measurements to provide especially strong prognostic information in women (*Ref. 3, Section 4*). Contrary to the initial hypothesis, we also found lower hs-troponin concentrations in current smokers than in non-smokers (*Ref. 4, Section 4*). Our competence in clinical trials and established research infrastructure at Ahus enabled us to perform important studies on cardiac biomarkers during the covid-19 pandemic. In covid-19 patients from Akershus University Hospital, we identified growth-differentiation factor-15 as a strong marker for adverse outcome, while hs-troponin or natriuretic peptide concentrations did not significantly improve risk prediction (*Ref. 5, Section 4*).

We have since 2012 been the principal clinical partner for SpinChip Diagnostics, who develop a state-of-the-art hs-troponin point-of-care (POC) assay. We recently validated the SpinChip troponin I POC assay to have similar performance as the best laboratory-based hs-troponin assays (Abbott, Roche), and the SpinChip troponin I POC assay can be used for assessing chest pain patients according to the ESC 0/1 h triage pathway (*Ref. 4, Section 6*). Professor Røsjø is co-PI of a pan-European prospective multicentre study to validate the SpinChip troponin I POC assay in the ED setting.

During the period, we have performed studies of several biomarkers according to the strategy reported in **Fig.1**. The work on SN has been most advanced, and we have identified SN as a strong and independent prognostic cardiovascular biomarker, and as a direct inhibitor of Ca^{2+}/calmodulin (CaM)-dependent protein kinase II δ (CaMKIIδ) activity (**Fig.2**, from *Ref. 2, Section 4*):



(A) As a biomarker, secretoneurin (SN) levels stratify mortality risk at hospital admission for patients with acute heart failure ($p < 0.001$ by the log-rank test for SN quartiles [Q]). **(B)** Experimental studies of SN in isolated cells and explanted hearts demonstrate that **(1.)** SN is internalized into cardiomyocytes and the intact heart by endocytosis. **(2.)** SN binds directly to calmodulin (CaM) and CaM-dependent protein kinase II δ (CaMKIIδ), and inhibits CaMKIIδ activity. **(3.)** This leads to reduced Ser2814-ryanodine receptor 2 (RyR2) phosphorylation, and **(4.)** improved Ca^{2+} homeostasis.

Fig.2. SN is a strong and independent prognostic cardiovascular biomarker, and a direct inhibitor of CaMKIIδ activity

As the principal partner to CardiNor AS (Oslo, Norway), we have helped develop a CE-approved SN ELISA assay, which we currently are validating in clinical studies. In parallel molecular work, we are also pursuing SN as a drug concept for treatment of ventricular arrhythmias with on-going IPR work.

3. Names of the key researchers and what positions they held at the administrative unit at the time of the research

Professor Torbjørn Omland MD, PhD, MPH: Primary investigator, Head of research group and Head of the K. G. Jebsen Center for Cardiac Biomarkers. Responsible for work on hs-troponin and covid-19 studies, and Steering board member for the Norwegian biotech company CardiNor AS.
Torbjørn Omland - Institute of Clinical Medicine (uio.no)

Professor Helge Røsjø MD, PhD: Deputy Head of research group and Deputy Head of the K. G. Jebsen Center for Cardiac Biomarkers. Responsible for translational work and work on SN, and for the collaboration between Akershus University Hospital and SpinChip Diagnostics. Røsjø coordinates collaboration with Uppsala Clinical Research Center (UCR) and SWEDEHEART after his post-doctoral and clinical stay in Uppsala 2017-2019.
Helge Rørvik Røsjø - Institute of Clinical Medicine (uio.no)

Associate Professor Magnus N. Lyngbakken MD, PhD: Research fellow (2013-2016), post-doctoral fellow 50% (2017-2025), and Associate Professor from 2021. Local PI for the ACE 1950 Study and important for work on hs-troponin in the Trøndelag Health (HUNT) Study.
Magnus Nakrem Lyngbakken - Institute of Clinical Medicine (uio.no)

Associate Professor Peder L. Myhre MD, PhD: Research fellow (2013-2017), post-doctoral fellow 50% (2017-2022), and Associate Professor from 2022. Performed work on SN and has central role in the covid-19 projects. Leading important collaborative projects with researchers at Harvard Medical School, Brigham and Women's hospital (Boston, MA) after post-doctoral research visit (2017-2018).
Peder Langeland Myhre - Institute of Clinical Medicine (uio.no)

Senior researcher Anett H. Ottesen PhD: Research fellow (2012-2017), post-doctoral fellow (2017-2021), and special advisor for research from 2021. PI for basic science work on SN, circulating micro-RNAs, and for demonstrating the importance of glycosylation for NT-proBNP and chromogranin A measurements and processing.

4. References to the research (indicative maximum of six references)- *Ahus/ Campus Ahus-affiliated researchers are highlighted by blue color.*

1) Omland T, Pfeffer MA, Solomon SD, de Lemos JA, Røsjø H, Šaltytė Benth J, Maggioni A, Domanski MJ, Rouleau JL, Sabatine MS, Braunwald E. Prognostic Value of Cardiac Troponin I Measured With a Highly Sensitive Assay in Patients With Stable Coronary Artery Disease. *J Am Coll Cardiol* 2013;61:1240-9. **IF 27.21**, **Times cited: 345**
https://pubmed.ncbi.nlm.nih.gov/23414791/

2) Ottesen AH, Louch WE, Carlson CR, Landsverk OJB, Kurola J Johansen RF, Moe MK, Aronsen JM, Høiseth AD, Jarstadmarken H, Nygård S, Bjørås M, Sjaastad I, Pettilä V, Stridsberg M, Omland T, Christensen G, Røsjø H. Secretoneurin is a novel prognostic cardiovascular biomarker associated with cardiomyocyte calcium handling. *J Am Coll Cardiol* 2015;65:339-51. **IF 27.21**, **Times cited: 51**
https://pubmed.ncbi.nlm.nih.gov/25634832/

3) Omland T, de Lemos JA, Holmen OL, Dalen H, Šaltytė Benth J, Nygård S, Hveem K, Røsjø H. Impact of Sex on the Prognostic Value of High-Sensitivity Cardiac Troponin I in the General Population: The HUNT Study. *Clin Chem* 2015;61:646-56. **IF 12.11, Times cited: 116**
https://pubmed.ncbi.nlm.nih.gov/25695851/

4) Lyngbakken MN, Skranes JB, de Lemos JA, Nygård S, Dalen H, Hveem K, Røsjø H, Omland T. Impact of smoking on circulating cardiac troponin I concentrations and cardiovascular events in the general population: The HUNT Study. *Circulation* 2016;134:1962-72. **IF 39.92, Times cited: 45**
https://pubmed.ncbi.nlm.nih.gov/27815376/

5) Myhre PL, Prebensen C, Strand H, Røysland R, Jonassen CM, Rangberg A, Sørensen V, Søvik S, Røsjø H, Svensson M, Berdal JE, Omland T. Growth Differentiation Factor 15 Provides Prognostic Information Superior to Established Cardiovascular and Inflammatory Biomarkers in Unselected Patients Hospitalized With COVID-19. *Circulation* 2020; 142(22):2128-2137. **IF 39.92, Times cited: 83**

https://pubmed.ncbi.nlm.nih.gov/33058695/

6) Lyngbakken MN, Aagaard EN, Kvisvik B, Berge T, Pervez MO, Brynildsen J, Tveit A, Steine K, Røsjø H, Omland T. Cardiac Troponin I and T Are Associated with Left Ventricular Function and Structure: Data from the Akershus Cardiac Examination 1950 Study. *Clin Chem* 2020;66(4):567-578. **IF 12.11, Times cited: 23**
https://pubmed.ncbi.nlm.nih.gov/32227098/

5. Details of the impact (indicative maximum 750 words)

Cardiovascular disease and myocardial dysfunction are among the leading causes of death in the Western world. Accordingly, biomarkers that reflect disease progression and response to therapy will prove important information and improve treatment for large patient groups. Biomarkers may also reflect cardiovascular pathophysiology and thereby also help to identify new drug candidates.

Several conditions and exposures (triggers or risk factors) can result in myocardial injury, dysfunction, and cardiomyopathy (**Fig.3**). Regardless of the trigger, myocardial dysfunction normally develops through distinct disease stages and the common endpoint is end-stage heart disease (**Fig.3**). Sensitive molecular markers may identify patients at risk, prior to the development of symptoms (subclinical disease). Hence, we have focused on the identification of biomarkers that are associated with outcome in state-of-the-art clinical and population-based cohorts.

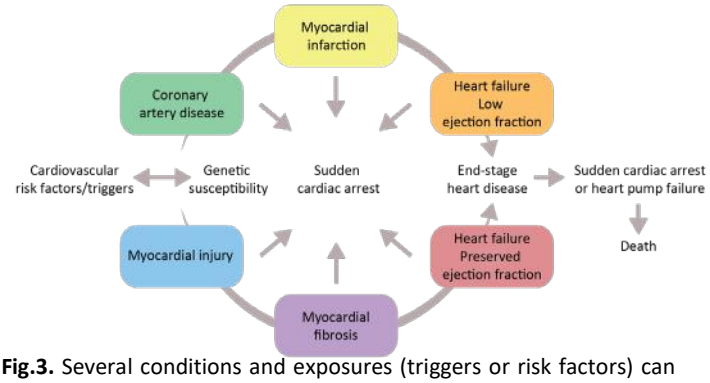


Fig.3. Several conditions and exposures (triggers or risk factors) can result in myocardial injury, dysfunction, and cardiomyopathy

Chronic, low-level elevations of hs-troponins reflect subclinical myocardial injury and cardiac remodeling and are strong predictors of heart failure, a paradigm first introduced by Prof Omland *et al.* in the *New England Journal of Medicine* in 2009. During the period from 2012-2022, our research group has validated this model and hs-troponins are currently considered the leading candidate biomarkers for early detection of cardiac remodeling and heart failure development. We are still leaders in this field internationally, and based on our work, hs-troponin I (Abbott Diagnostics, Abbott Park, IL) has received CE-approval in the EU as screening tools for cardiovascular disease in the general population. The use of hs-troponins as biomarkers of subclinical injury and myocardial dysfunction, and our contribution to this work, is recognized by international research colleagues (*Ref. 1, Section 6 as an example*). The innovative work related to cardiac biomarkers, and especially hs-troponins, was the basis for Professor Omland to be honored with the Prize for cardiac research from the Norwegian Health Organization in 2019, with the prize being presented to Professor Omland by His Majesty King Harald V of Norway (**Fig.4**, *Ref. 2*).

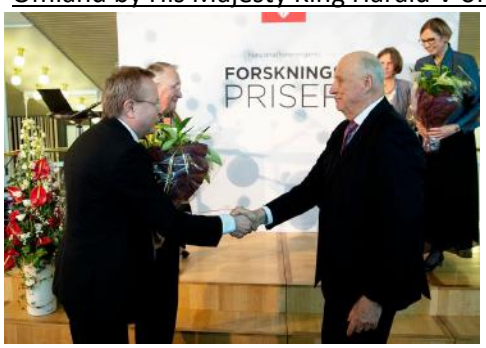


Fig.4. Professor Omland (front left) receiving the prestigious Prize for cardiac research from His Majesty King Harald V of Norway.

The Cardiovascular Research Group have been the principal clinical partner for the Norwegian biotechnology company SpinChip Diagnostics to develop hs-troponin I Point-of-Care (POC) assay since 2012 (*Ref. 3, Section 6*). We recently found the SPINCHIP hs-troponin I POC assay to fulfil requirements as a high-sensitivity cardiac troponin assay and to be useful for the ESC 0/1 h algorithm (*Ref. 4, Section 6*). By moving high-sensitivity assays out to pre-hospital services and health care facilities in primary care, the collaborative work

between our research group and SpinChip Diagnostics will provide a fundamental change in early triage of patients with suspected acute coronary syndrome. We are committed to continue our close collaboration with SpinChip to make a full cardiovascular panel on the SPINCHIP POC platform. The Cardiovascular Research Group has also performed extensive testing of biomarkers from established IVD companies like Roche Diagnostics and Abbott Diagnostics, and this work has also been highlighted in the press (*Ref. 5 and 6, Section 6*).

Professors Røsjø and Omland are also inventors of secretoneurin (SN) as a cardiac biomarker. As outlined in **Fig. 2**, we have performed extensive experimental and clinical studies on SN and we find that SN directly can influence cardiomyocyte function by inhibiting the key intracellular kinase CaMKIIδ, which we currently are pursuing as therapeutic strategy for ventricular arrhythmias. Moreover, SN is also recognized as a promising novel cardiovascular biomarker, which seems to provide additional prognostic information to established risk indices by integrating information on cardiac status, systemic stress, and renal dysfunction. Our work on SN has received substantial interest from leading scientists across the world (**Fig.2** and *Ref. 7, Section 6*) and from the press (*Ref. 8, Section 6)*. The work on SN has led to the establishment of a Norwegian biotechnology company (CardiNor AS, Oslo, Norway) and the development of a CE-marked SN ELISA assay.

During the covid-19 pandemic, we also performed important clinical studies, both relating to cardiac biomarkers and clinical interventional trials. By utilizing data warehouse Ahus for patient identification and inclusion, we could include 75% of all eligible covid-19 patients at Ahus during the first wave for epidemiological/ biomarker studies and 42% of all eligible patients for the pharmacological randomized-controlled trial of testing hydroxychloroquine for treating covid-19. These studies received significant academic interest and impact with publications in the leading cardiology journals for the biomarker work (*Ref 5, Section 4* as an example) and two high-impact publications in Nature Communication for the randomized-controlled trial (*Refs. 9 + 10, Section 6).* The work on covid-19 received significant interest from the press (*Refs. 6 + 11, Section 6).* In addition to the academic value of our covid-19 work, we collaborated with international colleagues and demonstrated a significantly increase in morality in covid-19 patients treated with hydroxychloroquine (*Ref. 10, Section 6*). Hence, in addition to advancing research, we informed the public that hydroxychloroquine should be avoided for treatment of covid-19, which had a direct and important contribution to patient safety across the world (*Ref. 11, Section 6*).

6. Sources to corroborate the impact (indicative maximum of ten references)

1) Cardiac Troponins and the Future of Precision Medicine | Circulation: Cardiovascular Interventions (ahajournals.org)
2) Viktig forskning hedret av Kongen | Nasjonalforeningen for folkehelsen (ntb.no)
3) Hjem - SpinChip
4) Koechlin L, [….], Omland T, Lyngbakken MN, Røsjø H, Mueller C. Clinical and Analytical Performance of a Novel Point-of-Care High-Sensitivity Cardiac Troponin I. *Submitted.*
5) https://www.forskning.no/royking-hjertet/vanskelig-a-forutsi-hjerteproblemer-hos-roykere/380654)
6) Norske forskere tror blodprøve kan avdekke koronarisiko (aftenposten.no)
7) Will Secretoneurin Be the Next Big Thing?∗ (sciencedirectassets.com)
8) Ny prognostisk biomarkør ved hjertesvikt | Tidsskrift for Den norske legeforening (tidsskriftet.no)
9) A pragmatic randomized controlled trial reports lack of efficacy of hydroxychloroquine on coronavirus disease 2019 viral kinetics - PMC (nih.gov)
10) Mortality outcomes with hydroxychloroquine and chloroquine in COVID-19 from an international collaborative meta-analysis of randomized trials - PubMed (nih.gov)
11) Studie: Lovprist covid-medisin øker risikoen for å dø (dagensmedisin.no)

Akershus University Hospital and Institute of Clinical Medicine, University of Oslo (Campus Ahus) – Impact case #2

Institution: **Name:** Akershus University Hospital and Institute of Clinical Medicine, University of Oslo **Short name:** Ahus and Campus Ahus
Administrative unit: **Name:** Akershus University Hospital and Institute of Clinical Medicine, University of Oslo **Short name:** Ahus_Campus Ahus
Title of case study: Cardio-oncology
Period when the underpinning research was undertaken:2012-present
Period when staff involved in the underpinning research were employed by the submitting institution: 2012-present
Period when the impact occurred:2015-present

1. Summary of the impact (indicative maximum 100 words)

This section should briefly state what specific impact is being described in the case study.

The cardio-oncology research at Akershus University Hospital has the been in the international research forefront in this developing field. The pioneering, randomized, placebo-controlled PRADA trial assessed the cardioprotective effect of beta adrenoceptor and angiotensin receptor blockade during adjuvant breast cancer therapy using state-of-the-art imaging and biomarker methods. The results have been published in leading academic journals and have been frequently cited. This work contributed significantly to enhanced co-operation between oncologists and cardiologists, benefitting this vulnerable patient group, and led to the establishment of Norway's first cardio-oncology outpatient clinic. Furthermore, external funding has been secured for two new cardio-protective interventional trials.

2. Underpinning research (indicative maximum 500 words)

During the past 15 years, professor Omland and collaborators have conducted high impact research on the prognostic value of asymptomatic, subclinical myocardial injury. Using a novel, prototype high sensitivity assay that for the first time permitted high precision measurement of cardiac troponin T, a biomarker of myocardial injury, these studies demonstrated a very strong and independent association between low level elevation of cardiac troponins and the risk of subsequent heart failure development and death in patients with chronic coronary syndrome and in the general population (Omland et al, N Engl J Med 2009;26:2538-47, de Lemos et al. JAMA 2010.

Advances in cancer therapy has improved cancer outcomes and contributes to an increasing number of long-term survivors, but also raised concern over potentially serious side effects. In adjuvant breast cancer therapy, potentially cardiotoxic agents like anthracyclines, monoclonal antibodies and radiotherapy have been associated with chronic myocardial injury with troponin elevation and cancer therapy–related cardiac dysfunction (CTRCD). Prior small-scale studies indicated promising effects of early or preventive neurohormonal blockade on the cardiotoxic effects of anthracyclines but were limited by methological weaknesses. The 2x2 factorial, placebo-controlled, double-blind "PRevention of cArdiac Dysfunction during Adjuvant breast cancer therapy" (PRADA) trial was conducted at Akershus University Hospital between 2011 and 2015. 130 patients with early breast cancer were randomized to the angiotensin receptor blocker candesartan vs placebo and the beta beta-blocker metoprolol vs placebo, and examined serially with state-of-the-art cardiovascular magnetic resonance (CMR), circulating biomarker measurements and echocardiography. In the primary results, preventive angiotensin blockade significantly attenuated a small reduction in left ventricular systolic function at the end of adjuvant

therapy, while no effect of beta blockade on ventricular function was observed. However, during anthracycline therapy concomitant beta-blockade was associated with attenuated myocardial injury, expressed as circulating cardiac troponin I and T concentrations. The PRADA trial was at the time the largest randomized, placebo-controlled preventive study in the field of cardio-oncology. The 2-year follow-up results were published in 2021 in the leading journal Circulation, (2022 IF 37.8). At follow-up there was a persistent small decline in systolic function, but significant myocardial dysfunction was uncommon and there was no persistent effect of either intervention. The study results demonstrated that adjuvant breast cancer therapy is safe in patients without pre-existing cardiovascular disease, and highlighted the need to identify patient groups at high risk who will benefit from cardioprotective therapy. The PRADA trial also provided unique longitudinal assessment of myocardial function and structure during cancer therapy using state of the art CMR and circulating biomarker analyses. By implementing novel CMR sequences, data from the trial demonstrated that higher anthracycline doses were associated with expansion of the myocardial extracellular space as an expression of myocardial edema or fibrosis. The study also confirmed that low-level myocardial injury assessed by cardiac troponins is very common at the end of anthracycline therapy, and troponin elevation has been implemented in the definition of CTRCD in the first European Guidelines of CardioOncology that were published in 2021.

Names of the key researchers and what positions they held at the administrative unit at the time of the research

Professor Torbjørn Omland Primary investigator and head of research group
Geeta Gulati (in charge of patient inclusion and echocardiography)
2010- 2018 PhD candidate In PRADA
2018-to date postdoctoral researcher (20%) in the PRADAII trial
Siri Lagethon Heck (in charge of CMR)
2011- 2018 PhD candidate In PRADA
2018-2023 postdoctoral researcher (50%) in the PRADAII trial
2023-to date Associate Professor II
Albulena Mecinaj PhD candidate 2020-to date in the PRADAII trial (patient inclusion and echocardiography)
Victoria Vinje PhD candidate 2022-to date in the PRADAII and NARNIA trials (patient inclusion and study coordinator)

3. References to the research (indicative maximum of six references)

Gulati G, Heck SL, Ree AH et al. Prevention of cardiac dysfunction during adjuvant breast cancer therapy (PRADA): a 2 x 2 factorial, randomized, placebo-controlled, double-blind clinical trial of candesartan and metoprolol. Eur Heart J 2016;37:1671-80. **Times cited: 388 (Web of science)**

1. Heck SL, Mecinaj A, Ree AH et al. Prevention of Cardiac Dysfunction During Adjuvant Breast Cancer Therapy (PRADA): Extended Follow-Up of a 2x2 Factorial, Randomized, Placebo-Controlled, Double-Blind Clinical Trial of Candesartan and Metoprolol. Circulation 2021;143:2431-2440. **Times cited: 51**
2. Omland T, Heck SL, Gulati G. The Role of Cardioprotection in Cancer Therapy Cardiotoxicity: JACC: CardioOncology State-of-the-Art Review. JACC CardioOncol 2022;4:19-37. **Times cited: 35. Most read/downloaded**
3. Gulati G, Heck SL, Rosjo H et al. Neurohormonal Blockade and Circulating Cardiovascular Biomarkers During Anthracycline Therapy in Breast Cancer Patients: Results From the PRADA (Prevention of Cardiac Dysfunction During Adjuvant Breast Cancer Therapy) Study. J Am Heart Assoc 2017;6. **Times cited: 25**

4. Heck SL, Gulati G, Hoffmann P et al. Effect of candesartan and metoprolol on myocardial tissue composition during anthracycline treatment: the PRADA trial. Eur Heart J Cardiovasc Imaging 2018;19:544-552. **Times cited: 17**
5. Heck SL, Gulati G, Ree AH et al. Rationale and design of the prevention of cardiac dysfunction during an Adjuvant Breast Cancer Therapy (PRADA) Trial. Cardiology 2012;123:240-7. **Times cited: 39**
6. Mecinaj A, Gulati G, Heck SL et al. Rationale and design of the PRevention of cArdiac Dysfunction during Adjuvant breast cancer therapy (PRADA II) trial: a randomized, placebo-controlled, multicenter trial. Cardiooncology 2021;7:33. **Times cited: 10**

4. Details of the impact (indicative maximum 750 words)

Although cardiovascular side effects of cancer therapy have been known since the late seventies, the medical field of cardio-oncology gained momentum around 2015 coinciding with the publication of the primary results of the PRADA trial. The publication in European Heart Journal gained both scientific acclaim and to date 388 citations including eight citations in central European and US cardiology guidelines and position statements. In addition, there was considerable media attention with several interviews and > 2 million unique hits on the internet of the initial presentation at the American Heart Association's 2015 Scientific Sessions. (Figure 1)

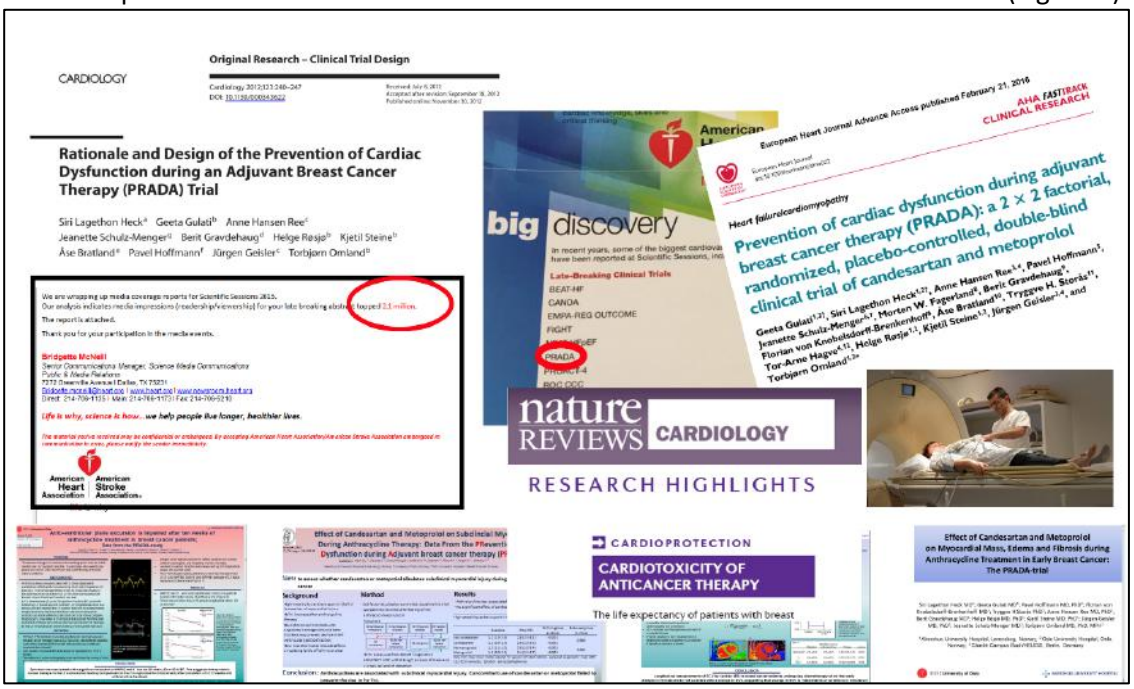


Figure 1 Examples of the impact of the cardio-oncology research at Akershus University Hospital

The experiences and collaborations established during the trial contributed to the establishment of Norway's first cardio-oncology outpatient clinic at Akershus University Hospital. In 2018 the PRADA trial was selected as the main study presented to the Minister of Health, Bent Høie at the annual research meeting of the Regional Health Authorities in Norway. Following the presentation, the Minister of Health was given a tour of the Cardio-Oncology outpatient clinic (Figure 2), praising this initiative in national media.

Kreftbehandling:

Ny studie: Slik kan hjertemedisin forebygge seinskader av brystkreft

- Viktig å behandle tidlig i forløpet.

GODE RESULTATER: Etter behandling her ved den nye Kardio-onkologiske poliklinikken på Ahus, er pumpekraft til Anne-Grethe Delets (53) hjerte nå oppe i 56 prosent - godt innenfor normalen. Helseminister Bent Høie blir vist rundt på poliklinikken, her sammen med Tone Nerdrum, overlege i kariologi.
Foto: Thomas Rasmus Skaug

Figure 2: Dagbladet, tirsdag 12. juni 2018 Health minister Bent Høie visits the Cardio-oncology outpatient clinic

Drs Geeta Gulati and Siri Lagethon Heck, research fellows in the project, obtained their PhDs from the PRADA trial, and both are pursuing a combined clinical and academic career. Dr Gulati, now a cardiologist, has founded and is chair of the Nordic Cardio-Oncology Society as well as a member of the Cardio-Oncology nucleus of the European Society of Cardiology. She is now in charge of the cardioloncology outpatient clinic at Oslo University Hospital Ullevål. The key researchers have been invited to write editorials and a state-of-the-art review on the role of cardioprotection in cancer therapy cardiotoxicity in leading journals like Circulation and JACC Cardio-Oncology and a chapter in a leading cardiology textbook (European Society of Cardiology Textbook of Cardiology), as well as to participate in international conference debates. The review paper was the most read article in the hjgh-ranking scientific journal JACC CardioOncology in 2022.

In the future, a main focus will be to identify patients at risk for CTRCD and those who will benefit from cardioprotective treatment. In 2017, professor Omland received two grants from the National Program for Clinical Treatment Research in the Specialist Health Service (KLINBEFORSK) and the Norwegian Cancer Society (Open Call) totaling 25 million NOK to conduct PRADA II, a Norwegian multicenter study of the cardioprotective effect of the Angiotensin Receptor-Neprilysin Inhibitor (ARNI) during adjuvant breast cancer therapy. By including more patients and patients with more risk factors, the study aims to identify subgroups who will benefit most from cardioprotective therapy. Recently, the team initiated another randomized, placebo-controlled interventional study in collaboration with the award-winning Akershus University Hospital researcher Evandro Fei Fang. The aim of the study is to assess whether prevention of CTRCD is achievable by Nicotinamide Riboside (NAD+) supplementation in patients with metastatic breast cancer. In 2022, the research group of professor Omland was awarded a grant of 55 million NOK from Kristian Gerhard Jebsen Foundation, the University of Oslo and Akershus University Hospital to establish the K.G. Jebsen Centre for Cardiac Biomarkers. One of the main focuses of the new center is cardiooncological research. In addition to the ongoing randomized controlled preventive

trials, the center will conduct studies on changes in plasma proteomics during cancer therapy and studies on the complex interaction between heart failure and cancer using data from large population based studies like the HUNT (Helse-undersøkelsen I Trøndelag) study.

5. Sources to corroborate the impact (indicative maximum of ten references)

1. McDonagh TA, Metra M, Adamo M et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2021;42:3599-3726.
2. Heidenreich PA, Bozkurt B, Aguilar D et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 2022;145:e895-e1032.
3. Visseren FLJ, Mach F, Smulders YM et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice: Developed by the Task Force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies With the special contribution of the European Association of Preventive Cardiology (EAPC). Eur Heart J 2021.
4. Lyon AR, Lopez-Fernandez T, Couch LS et al. 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). Eur Heart J 2022.
5. Omland T. Cardio-Protective Therapy in Cardio-Oncology: Quo Vadis? Circulation 2021;144:667-669.
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8. Omland T, Heck SL, Gulati G. The role of cardio-protectionin cancer therapy cardiotoxicity. JACC CardioOncol 2022; 4:19-37. doi: 10.1016/j.jaccao.2022.01.101.
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10. Ghosh A. PRADA–the dawn of high-end Cardio-Oncology research? British Cardiovascular Society 16/08/2016.
11. https://www.dagbladet.no/tema/ny-studie-slik-kan-hjertemedisin-forebygge-seinskader-av-brystkreft/69893830

Akershus University Hospital and Institute of Clinical Medicine, University of Oslo (Campus Ahus) – Impact case #3

Institution:
Name: Akershus University Hospital and Institute of Clinical Medicine, University of Oslo
Short name: Ahus and Campus Ahus

Administrative unit:
Name: Akershus University Hospital and Institute of Clinical Medicine, University of Oslo
Short name: Ahus_Campus Ahus

Title of case study: Investigator-initiated prospective randomized controlled trials in orthopedic trauma surgery

Period when the underpinning research was undertaken: 2012-2022

Period when staff involved in the underpinning research were employed by the submitting institution: 2012-2022

Period when the impact occurred: 2017-2022

1. Summary of the impact

During the last five years, the Orthopedic Research Group has conducted five RCTs on hip, wrist, clavicular fractures and the world´s largest RCT on Achilles tendon ruptures (ATRs) influencing treatment for common orthopedic injuries. Two RCTs defined indications for internal fixation, hemiarthroplasty and total hip replacement for femoral neck fractures. Two RCTs investigating surgical treatment for displaced wrist fractures have defined the optimal implant choice and post-operative rehabilitation demonstrating that volar plate fixation is safe, cost-effective and returns the patients' independence quicker than traditional cast treatment. The multicenter RCT on ATRs demonstrated no difference in result between operative and non-operative treatment.

2. Underpinning research

High-quality, well-powered, randomized controlled trials (RCT) with minimal loss-to-follow-up are rare in surgical fields. The present impact case describes a series of such RCTs, influencing the routine management of common injuries like hip fractures, distal radius fractures and Achilles tendon injuries.

Hip fractures cause significant morbidity and are associated with increased mortality. It has previously been shown that displaced hip fractures in the elderly are better treated with hemiarthroplasty than internal (screw) fixation. However, it was unclear if elderly patients with undisplaced fractures would benefit equally from arthroplasty. We therefore randomized 219 patients >70 years to either screw fixation or hemiarthroplasty in a multicenter trial. We found that hemiarthroplasty improved mobility and led to fewer major reoperations. Following this study, we sought to explore whether younger hip fracture patients would benefit from total hip arthroplasty (THA) compared to fixation of the fracture. Thus, 102 patients aged 55-70 with a low-energy

displaced hip fracture were randomized to screw fixation or THA. The patients receiving a THA experienced better outcomes and less pain.

Volar locking plates were introduced in the early 2000s to treat distal radius fractures (DRFs). At the time, surgical fixation with external fixation (EF) was common. Thus, we randomized 266 patients to EF or volar locking plate fixation (VLP). Although there were no statistically or clinically relevant differences between the groups at two years, patients receiving VLP recovered quicker, reported less pain in the first six months, and returned to work earlier. VLP was also cost-effective compared to EF, which led to more minor complications and longer work absenteeism. In another RCT, post-operative care after VLP was randomized to either immobilization in a cast for two weeks or early mobilization. Early mobilization lead to earlier return to activity with no risk of increased complications.

Whether surgical repair of an acute Achilles tendon rupture is associated with better outcomes than nonsurgical treatment is not clear. We initiated a multicenter RCT that compared non-operative treatment, open repair, and minimally invasive surgery in adults with acute Achilles tendon rupture who presented to four trial centers. A total of 554 patients underwent randomization, and 526 patients were included in the final analysis. Pairwise comparisons provided no evidence of differences in patient-reported outcomes between the groups. The changes from baseline in physical performance and patient-reported physical function were similar in the three groups. The number of tendon re-ruptures was higher in the non-operative group (6.2%) than in the open-repair or minimally invasive surgery group (0.6% in each). There were nine nerve injuries in the minimally invasive surgery group (in 5.2% of the patients) as compared with five in the open-repair group (in 2.8%) and one in the non-operative group (in 0.6%). We conclude that in patients with Achilles' tendon rupture, surgery (open repair or minimally invasive surgery) was not associated with better outcomes than non-operative treatment at 12 months.

3. References to the research

Dolatowski FC, Frihagen F, **Bartels S**, Opland V, Šaltytė Benth J, Talsnes O, Hoelsbrekken SE, **Utvåg SE**. Screw Fixation Versus Hemiarthroplasty for Nondisplaced Femoral Neck Fractures in Elderly Patients: A Multicenter Randomized Controlled Trial. J Bone Joint Surg Am. 2019. doi: 10.2106/JBJS.18.00316.

Bartels S, Kristensen TB, Gjertsen JE, Frihagen F, Rogmark C, Dolatowski FC, Figved W, Benth JŠ, **Utvåg SE**. Total Hip Arthroplasty Leads to Better Results After Low-Energy Displaced Femoral Neck Fracture in Patients Aged 55 to 70 Years: A Randomized Controlled Multicenter Trial Comparing Internal Fixation and Total Hip Arthroplasty. J Bone Joint Surg Am. 2022. doi: 10.2106/JBJS.21.01411.

Hammer OL, **Clementsen S**, Hast J, Šaltytė Benth J, Madsen JE, **Randsborg PH**. Volar Locking Plates Versus Augmented External Fixation of Intra-Articular Distal Radial Fractures: Functional Results from a Randomized Controlled Trial. J Bone Joint Surg Am. 2019. doi: 10.2106/JBJS.18.00014.

Clementsen SØ, **Hammer OL**, Šaltytė Benth J, **Jakobsen RB**, **Randsborg PH**. Early Mobilization and Physiotherapy Vs. Late Mobilization and Home Exercises After ORIF of Distal Radial Fractures: A Randomized Controlled Trial. JB JS Open Access. 2019. doi: 10.2106/JBJS.OA.19.00012.

Myhrvold SB, Brouwer EF, **Andresen TKM**, Rydevik K, Amundsen M, Grün W, Butt F, Valberg M, **Ulstein S**, Hoelsbrekken SE. Nonoperative or Surgical Treatment of Acute Achilles' Tendon Rupture. N Engl J Med. 2022. doi: 10.1056/NEJMoa2108447.

4. Details of the impact

Our research on hip fracture treatment has directly influenced treatment choice for this common and severe injury. The Norwegian Hip Fracture Register reports an increased use of arthroplasty (both hemi and total) and a decline in the use of screw fixation following the dissemination of our results on national scientific conferences and in publications. The paper by Dolatowski et al. on screw fixation vs. hemiarthroplasty in elderly patients (2019) has over 100 citations, including an updated Cochrane review [1] and several updated systematic reviews (some referenced below) [2-12]. The study was cited in the Evidence-Based Clinical Practice Guideline for the Management of Hip Fractures in Older Adults (2021) issued by the American Academy of Orthopedic Surgeons (AAOS): https://www.aaos.org/globalassets/quality-and-practice-resources/hip-fractures-in-the-elderly/hipfxcpg.pdf

The RCT by Hammer comparing plate fixation and external fixation of wrist fractures has directly changed the guidelines for distal radius fractures issued by the American Academy of Orthopedic Surgeons (AAOS) [13]. The Guidelines mention Hammer´s paper and only two other high-quality RCTs as the basis for the recommendation. In addition, the project has led to changes in postoperative rehabilitation and follow-up algorithm following surgically treated distal radius fractures in our institution, and nationally. The cost-effective analysis has had an impact on healthcare services internationally and is included in the Swedish national guidelines for the treatment of distal radius fractures:
https://figshare.com/articles/journal_contribution/Summary_of_the_Swedish_national_guidelines_/19155305

The study by Myhrvold et al. is the world's largest RCT comparing conservative treatment with surgery for Achilles tendon rupture. The results will change management and reduce Low-Value Care internationally, and its results have already had an impact on treatment algorithm for this common but potentially serious injury. The research provides high-level quality evidence to guide healthcare workers and patients in reaching a treatment strategy based on a shared decision-making progress, which ultimately reduces the number of unnecessary surgeries, benefiting the institutions, patients, and society as a whole. The study immediately attracted attention globally, with several media houses, news outlets, and academic journals publishing editorials, debate articles, and commentaries on the results and their consequences for treatment options. The study was highlighted by the Associated Press and picked up by newspapers such as the Chicago Sun-Times in the USA and the Independent in the UK. The New England Journal of Medicine published an editorial regarding the impact of the study (see links below). Within the first 18 months after publication in April 2022, the paper was cited 50 times. The paper has won several awards, including Best Paper for Akershus University Hospital 2022.

Newspapers, journals and media outlets discussing the Achilles tendon study:

Barfod KW, Hölmich P., Hölmich D. Acute Achilles' Tendon Rupture - Surgery or No Surgery. N Engl J Med. 2022. doi: 10.1056/NEJMe2202696

Maria C. For weekend warriors, most Achilles tendon ruptures heal as well without surgery, study finds. Chicago Sun Times. April 14. 2022.
https://chicago.suntimes.com/2022/4/14/23025012/achilles-tendon-rupture-surgery-options-new-england-journal-medicine-stale-myhrvold-medical-research

Associated Press Health. Heal Thyself: Most who tear Achilles tendon can skip surgery. The Seattle Times Apr 13, 2022. The Independent. April 13, 2022.
https://www.seattletimes.com/seattle-news/health/heal-thyself-most-who-tear-achilles-tendon-can-skip-surgery/
Heal Thyself: Most who tear Achilles tendon can skip surgery | The Independent

Tassone P, Morris L. Acute Achilles tendon rupture: Skip the surgery? J Fam Pract. 2023 June. doi: 10.12788/jfp.0604

Phend C. Achilles' Tendon Rupture Surgery Not So Necessary? — Randomized trial suggests one advantage despite similar outcomes to nonoperative treatment. MedPage Today April 13, 2022.
https://www.medpagetoday.com/surgery/orthopedics/98197

Norton A. What Works Best for Ruptured Achilles Tendons? Health Day, April 14, 2022.
https://www.healthday.com/health-news/general-health/4-14-what-works-best-for-ruptured-achille-s-tendons-2657123373.html

Medical Dialogues Editorial Team. Should surgery be opted for Achilles Tendon rupture? Study says no benefit. Medical Dialogues, May 18, 2022.
https://medicaldialogues.in/surgery/news/should-surgery-be-opted-for-achilles-tendon-rupture-study-says-no-benefit-92762

Ebell MH. Surgery Is No Better Than Nonoperative Treatment for Achilles Tendon Rupture in Adults Am Fam Physician. 2022. (editorial)
https://www.aafp.org/pubs/afp/issues/2022/0900/poems-achilles-tendon-rupture.html

5. Sources to corroborate the impact

1. Lewis SR, Macey R, Stokes J, Cook JA, Eardley WG, Griffin XL. Surgical interventions for treating intracapsular hip fractures in older adults: a network meta-analysis. Cochrane Database Syst Rev. 2022 Feb 14;2(2):CD013404.
2. Kumar J, Symonds T, Quinn J, Walsh T, Platt S. What is the best method of fixation for minimally displaced subcapital neck of femur fractures? A systematic review. J Orthop. 2023 Nov;45:54-60.
3. Ramadanov N, Jozwiak K, Hauptmann M, Lazaru P, Marinova-Kichikova P, Dimitrov D, et al. Cannulated screws versus dynamic hip screw versus hemiarthroplasty versus total hip arthroplasty in patients with displaced and non-displaced femoral neck fractures: a systematic review and frequentist network meta-analysis of 5703 patients. J Orthop Surg Res. 2023 Aug 26;18(1):625.
4. Jiang J, Chen J, Xing F, Liu H, Xiang Z. Comparison of femoral neck system versus cannulated screws for treatment of femoral neck fractures: a systematic review and meta-analysis. BMC Musculoskelet Disord. 2023 Apr 13;24(1):285.
5. Wang W, Huang Z, Peng J, Fan J, Long X. Preoperative posterior tilt can be a risk factor of fixation failure in nondisplaced femoral neck fracture: a systematic review and meta-analysis. Eur J Orthop Surg Traumatol. 2023 Oct;33(7):3197-205.
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7. Zelle BA, Salazar LM, Howard SL, Parikh K, Pape HC. Surgical treatment options for femoral neck fractures in the elderly. Int Orthop. 2022 May;46(5):1111-22.

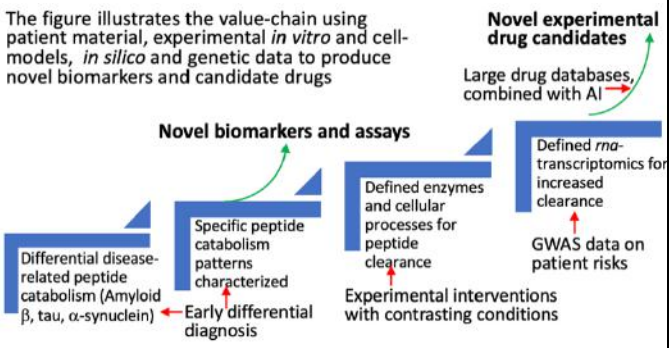
8. Xu WN, Xue QY. Long-Term Efficacy of Screw Fixation vs Hemiarthroplasty for Undisplaced Femoral Neck Fracture in Patients over 65 Years of Age: A Systematic Review and Meta-Analysis. Orthop Surg. 2021 Feb;13(1):3-13.
9. Cui S, Wang D, Wang X, Li Z, Guo W. The choice of screw internal fixation and hemiarthroplasty in the treatment of femoral neck fractures in the elderly: a meta-analysis. J Orthop Surg Res. 2020 Sep 21;15(1):433.
10. Kim SJ, Park HS, Lee DW. Complications after internal screw fixation of nondisplaced femoral neck fractures in elderly patients: A systematic review. Acta Orthop Traumatol Turc. 2020 May;54(3):337-43.
11. Lutnick E, Kang J, Freccero DM. Surgical Treatment of Femoral Neck Fractures: A Brief Review. Geriatrics (Basel). 2020 Apr 1;5(2).
12. Ma HH, Chou TA, Tsai SW, Chen CF, Wu PK, Chen WM. Outcomes of internal fixation versus hemiarthroplasty for elderly patients with an undisplaced femoral neck fracture: a systematic review and meta-analysis. J Orthop Surg Res. 2019 Oct 11;14(1):320.
13. AAOS. Management of Distal Radius Fractures Evidence-Based Clinical Practice Guideline. 2020 5.12.2020. Report No.: www.aaos.org/drfcpg.

Akershus University Hospital and Institute of Clinical Medicine, University of Oslo (Campus Ahus) – Impact case #4

Institution: **Name**: Akershus University Hospital and Institute of Clinical Medicine, University of Oslo **Short name:** Ahus and Campus Ahus
Administrative unit: **Name:** Akershus University Hospital and Institute of Clinical Medicine, University of Oslo **Short name:** Ahus_Campus Ahus
Title of case study: Dementia Disease Initiation: Predictors for dementia, biomarkers and novel drug candidates
Period when the underpinning research was undertaken: 2008-2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2008-2022
Period when the impact occurred: 2012-2022 (ongoing)

1. Summary of the impact

Our research on biomarkers with data and samples from longitudinal pre-dementia cohorts impacts early differential diagnosis of major dementia-giving diseases, gives improved prediction of prognosis and future precision interventions. Early Alzheimer's and Lewy Body diseases (AD, LBD), Late-Life Depression and small vessel disease develop insidiously with overlapping clinical presentations making diagnosis contingent on biomarkers (fluid/proteomic, imaging, genetic) and improved neuropsychological tests. Brain pathologies are currently irreversible, and early personalized intervention is needed. We introduced fluid biomarkers for neurodegenerative diseases in Norway, following this Ahus still is the center for this type of analyses. We have also developed and implemented advanced MRI imaging techniques tested and validated in large in-house cohorts staged with fluid biomarkers and neuropsychology. Multi-modal data reciprocally underpins results from applied technologies, with increasing impact from a planned value-chain (biomarkers -> early differential diagnosis -> novel treatment alternatives, see **figure**) leading to innovation and commercialization via licensing to biotech firms and foundations combined with R&D contracts (21.3 mill to CNG 2018-2022) and further new academic research contracts (e.g. JPND DEBBIE).



2. Underpinning research (indicative maximum 500 words)

Development of novel markers for preclinical or prodromal diseases leading to dementia is contingent on advances in proteomics, imaging, genetics and neuropsychology. To find biomarkers, evaluate performance and predictive power (i. e., prediction of clinical progression to dementia) we established a large national and European longitudinal cohort. Corresponding customized data- and biobanks serve to study and improve marker performance and develop and evaluate novel treatments.

Cohorts and biobanks. NFR NASATS ("Nasjonale Satsninger") for DDI (Dementia Disease Initiation) funding in 2012, and ensuing funding from EU/JPND (BIOMARKAPD, APGeM (Pre -clinical genotype -phenotype predictors of Alzheimer's disease and other dementias, PMI-AD (Precision Medicine in Alzheimer's Disease), DEBBIE (Developing BBB-ASL as a non-Invasive Early biomarker) has been used to establish a unique national and European longitudinal cohort with biennial follow-ups of control, at-risk, preclinical and prodromal (mild cognitive impairment) cases over up to 10 years (as of 2022) with dementia as the final outcome variable. Deep phenotyping (neuropsychology, imaging, blood, CSF at every visit) and GWAS at baseline of > 1000 included cases (2022) allow study of biomarkers, mechanisms for disease initiation and clinical progression through the pre-dementia disease processes.

Clinical trials. The cohorts are "*trial ready*", i. e. patients are investigated (every two years) to such an extent that we already know with a fairly high degree of certainty whether they confirm to or fall outside of inclusion/exclusion criteria for any given trial. This means that costly screening failures can be avoided, and recruiting and entering of patients in trials is effective. Thus, we have been running a continuous set of trials (phase I-III) on pre-dementia AD and Lewy-body patients during the period (2012-2022), see citation (Andreasen et al. section 3).

Fluid biomarkers and proteomics. Our early research (pre-2012) employed fairly simple neuropsychological testing, but more advanced MRI imaging and proteomics incl. mass spectrometry on in-house pre-dementia AD and LBD cohorts. This enabled us to introduce fluid biomarker testing as diagnostic tool for Alzheimer's Disease in Norway, as our practice was adopted at the Ahus' clinical chemistry lab (increasingly used, 2400 samples/patients tested in 2020), and it gave spin-offs also for Creutzfeld Jacob testing. Testing on cerebrospinal fluid (CSF) and plasma from smaller longitudinal cohorts allowed us to file early patents on blood and CSF biomarkers, finally granted in 2014-2017 [a,b section 3]. As of 2013 these and later patents are licensed by a biotech start-up, Pre Diagnostics. Lisbeth Johnsen, Hanne Mali Møllergård and Kaj Blennow (Gothenburg University)were main collaborators at the early stage.

Unique AD-related degradation patterns of Aβ, the main peptide forming brain amyloid plaques implied dysfunctional endolysomal enzymatic activity, in accordance with ultrastructural observations in AD brain with evidence for similar dysfunction in other neurodegenerative diseases with CNS peptide deposition (e. g. Lewy Body diseases) and tauopathies. For this, we employed Mass Spectrometry using biobanked patient material combined with *in vitro* experiments with endolysosomal enzymes and customised peptides. Marianne Wettergreen and Magnus Røgeberg (post doc) as well as Berglind Gisladottir were the main responsible on these series of experiments. Emerging evidence from our cooperation with large GWAS consortia pointed to a major involvement of myelogenic cells in AD pathogenesis, spurring use of a hybridoma monocyte cell model and patient-derived stem cells to further study peptide degradation patterns and how this could be modified leading to novel candidate therapeutic drug combinations[c, d, section 3]. Testing these drugs in combination with stressors, mechanistic analysis based on RNA*seq* on model cells combined with AI led to later DOFIs on novel drug targets and drugs (not yet patented 2022). Kulbushan Sharma (post doc at the lab, now head of the Ahus stem cell facility), Marianne Wettergreen, Berglind Gisladottir, Per Selnes (bioinformatics) and Bjørn-Eivind Kirsebom (statistics) were main responsible during this phase with Panpan You (molecular biology) and Peter Arnesen (bioinformatics, AI) joining in 2022.

Imaging MRI is essential in early diagnosis, non-invasive and relatively accessible. Increasingly advanced protocols and post-processing including AI-based techniques has made this a preferred tool for supporting studies for us, also thanks to a tight collaboration with CRAI at OUS/Rh (prof. Atle Bjørnerud, Per Selnes/CNG key collaborator). At an early stage we adopted morphometric and diffusion-weigthed techniques. Combined with our clinical cohort, molecular/pathological staging with CSF fluid biomarkers and PET imaging, this has given new insights into disease-specific mechanisms for neurodegeneration.

Neuropsychological testing is essential for the study of disease-initiation and progression as well as underpinning of fluid and imaging biomarkers, but inadequate norms have hampered early

detection of clinically relevant symptoms. To alleviate this problem, we have employed our large national database, combined with other Scandinavian databases and developed and published updated regression-based norms for cognitive tests. This is an ongoing project, but fairly well cited and uptake across Norway is good also outside of our group.

Collaboration with industry. The DDI cohort, and innovations described above (citations section 3) has also formed the basis for extensive collaborations with Pre Diagnostics (the licensing partner for our patents) in several projects, e. g. the EU Horizon 2020 project "Verdad" (https://pre-diagnostics.com/eu-horizon-2020/), with a EUR 3.36 mill. total cost.

3. References to the research

a) EP2245463/ US9625474: Diagnostic method. Granted EU 2014/US 2017.
Inventors: Tormod Fladby, Lisbeth Johnsen, Kaj Blennow.

b) EP2646462/13/989959: Methods and compositions for monitoring phagocytic activity. Granted EU 2017/Undergoing examination US. Inventors: Tormod Fladby. .

c) PCT/EP2020/061018: Combination therapy comprising an ffar4 agonist and an alpha-7 nAcChr agonist or positive modulator. EU, US, India, Mexico appl. ongoing. Inventors: Tormod Fladby. .

d) PCT/EP2022/055950: Clearance assay. EU, US, India, Mexico, China patent application ongoing. Inventors: Tormod Fladby, .

Academic reports on this research include:

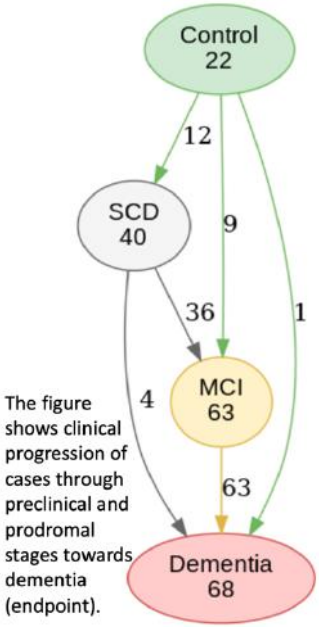
Andreasen N . . Fladby T . . First administration of the Fc-attenuated anti-β amyloid antibody GSK933776 to patients with mild Alzheimer's disease: a randomized, placebo-controlled study PLos One 2015 Mar 19;10(3) doi: 10.1371/PMID: 25789616

Rogeberg M . . Fladby T. **Isobaric Quantification of Cerebrospinal Fluid Amyloid-β Peptides in Alzheimer's Disease: C-Terminal Truncation Relates to Early Measures of Neurodegeneration.** J Proteome Res. 2015 Nov 6;14(11):4834-43. doi: 10.1021/PMID: 26452689.

Nordengen K,. . Fladby T. **Phenotype-informed polygenic risk scores are associated with worse outcome in individuals at risk of Alzheimer's disease**. Alzheimers Dement (Amst). 2022 Aug 15;14(1):e12350. doi: 10.1002/ PMID: 35991219

4. Details of the impact

With the DDI-NASATS project in 2012, we set up 4 linked goals: 1) To explore the underlying mechanisms involved in the initial development of the major neurodegenerative dementia diseases in the elderly: AD and PD / DLB at early stages of development that are accessible for preventive strategies; 2) To identify early diagnostic markers for AD and DLB at pre-dementia stages; 3) To identify prognostic markers towards dementia (AD, PD dementia, and DLB),in pre-clinical and pre-dementia cognitive impairment; 4) To improve and harmonize pre-dementia diagnostic procedures at the national level, including large clinical and control cohorts, standardizing assembly of clinical- and biomaterial in biobanks and imaging databanks, and making this available at the different research centers nationwide and internationally.

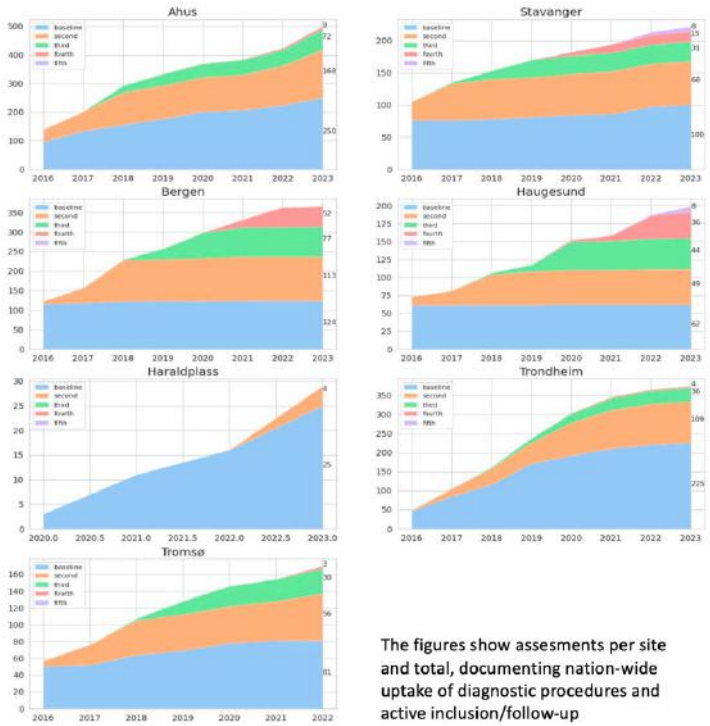


The figure shows clinical progression of cases through preclinical and prodromal stages towards dementia (endpoint).

Establishing a national network was crucial for all the goals. We invited leading colleagues within neurology, geriatrics, old-age psychiatry and neuropsychology from all university hospitals, and Helse Fonna (Haugesund) and established standardized protocols / CRFs for clinical examinations and testing, scanning, blood, CSF based on international standards as developed in our BIOMARKAPD/ JPND project. To explore risk factors for dementia, we focused on at-risk (i. e. first-degree relatives with dementia), preclinical and early stages (subjective cognitive decline (SCD) and mild cognitive impairment (MCI)) as well as age-matched controls (largely spouses and patients admitted for orthopedic surgery), with dementia as the endpoint (see figure). Sub-cohorts with Parkinson's disease and age-related neuropsychiatric disorders (including LLD) have also been included using

the same protocols. All examinations, including repeat CSF are performed at baseline and at 2-year intervals for all clinical subgroups and controls. Close to 1000 baseline cases were included as of 311223 (see figure). Centralized GWAS has been performed at inclusion, also contributing to the material of large international consortia with large impacts on the genetic understanding of AD. This has been provided and organized by prof. Ole Andreassen/Norment (a partner in JPND/APGeM).

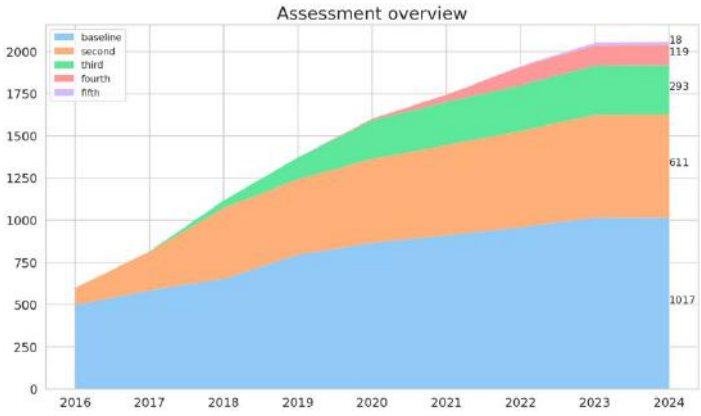
Inclusions and follow-ups have been diligent from all sites, ultimately depending on local resources but with biobank- and databank-service supplied from CNG/Ahus. In return, access to material from an increasingly valuable bio- and databank has been provided. We have also developed a customized searchable database containing all raw and derived measures including MRIs using the XNAT platform, contained on TSD/UiO (a secure server, accessible for co-workers). External data access is also provided upon request and approval form data protection officers etc.



The figures show assesments per site and total, documenting nation-wide uptake of diagnostic procedures and active inclusion/follow-up

The main collaborators at UiT/UNN (Tromsø) are prof. Knut Waterloo, Stein Harald Johnsen and Bjørn-Eivind Kirsebom, at NTNU/St. Olav (Trondheim), prof. Geir Braathen and Sigrid Sando , at Haraldsplass/Bergen Ragnhild Eide Skogseth, at SUS (Stavanger) prof, Dag Aarsland and at Haugesund Arvid Rongve. (Validation cohorts have been contributed by several European partners as parts of APGeM and PMI-AD, but are not described here.)

As the focus has been on early and incipient stages (Dementia Disease Initiation), fairly long follow-ups have been necessary but as the bio- and database is being completed with 8- and 10-year follow-ups the value increases rapidly. Development and validation of non-invasive and accessible biomarkers (MRI and plasma), including those based on in-house IP (see above) will be essential going forward. Applications using AI on MRI and multimodal data is being explored.



As for existing impacts, a large number of publications have been submitted, largely on baseline and cross-sectional data but lately also on longitudinal data outlining use of fluid, MRI, neuropsychology and genetic data in diagnosis and risk-factor assessments. We believe the data- and biobank is unique and surpasses e. g. the ADNI database (US) in breadth of phenotypes, early-stage cases and depth of phenotyping.

5. Sources to corroborate the impact

Description of cohort:

Fladby T, . . Aarsland D. **Detecting At-Risk Alzheimer's Disease Cases.** J Alzheimers Dis. 2017;60(1):97-105. doi: 10.3233/JAD-170231.PMID: 28826181.

Kirsebom BE, . . Blennow K, Fladby T. **Stable cerebrospinal fluid neurogranin and β-site amyloid precursor protein cleaving enzyme 1 levels differentiate predementia Alzheimer's disease patients.** Brain Commun. 2022 Sep 24;4(5):fcac244. doi: 10.1093/braincomms/fcac244. eCollection 2022. PMID: 36262371.

Identification of amyloid beta mid-domain fragments in human cerebrospinal fluid. Rogeberg M, Wettergreen M, Nilsson LN, Fladby T. Biochimie. 2015 Jun;113:86-92. doi: 10.1016/j.biochi.2015.03.022. Epub 2015 Apr 10.

Siafarikas N, . . . Fladby T. **Cerebrospinal fluid markers for synaptic function and Alzheimer type changes in late life depression**. Sci Rep. 2021 Oct 13;11(1):20375.

New insights into the genetic etiology of Alzheimer's disease and related dementias. Bellenguez C et al. Nat Genet. 2022 Apr;54(4):412-436. PMID: 35379992

Brain amyloid and vascular risk are related to distinct white matter hyperintensity patterns Lene Pålhaugen, . . , Tormod Fladby J Cereb Blood Flow Met 2021 May;41(5):1162-1174

Amyloid Plaques and Symptoms of Depression Links to Medical Help-Seeking due to Subjective Cognitive Decline. Espenes R, Kirsebom BE, Eriksson C, Waterloo K, Hessen E, Johnsen SH, Selnes P, **Fladby T.** J Alzheimers Dis. 2020;75(3):879-890. doi: 10.3233/JAD-190712.PMID: 32333584

Akershus University Hospital and Institute of Clinical Medicine, University of Oslo (Campus Ahus) – Impact case #5

Institution: **Name:** Akershus University Hospital and Institute of Clinical Medicine, University of Oslo **Short name:** Ahus and Campus Ahus
Administrative unit: **Name:** Akershus University Hospital and Institute of Clinical Medicine, University of Oslo **Short name:** Ahus_Campus Ahus
Title of case study: The NAD^+-mitophagy pathway in human ageing and its broad clinical applications
Period when the underpinning research was undertaken: Sep. 2017-present
Period when staff involved in the underpinning research were employed by the submitting institution: Sep. 2017
Period when the impact occurred: Jan. 2019 and onwards

1. Summary of the impact (indicative maximum 100 words)

This 6-year research (and also continuing) generates big impacts

- **Science:** Provides novel mechanisms of human ageing and the causes of dementia with tier-one level publications;
- **Education:** trained over 40 students from more than 10 countries; initiated the first-ever PhD course on ageing 'Biology of Ageing' (MF9246) open to all the EU countries;
- **Clinic:** propelled 5 clinical trials, with one finished with success;
- **Collaboration with Industry:** issued one 'discovery' to a company for business development and is involved in a big business company in making the research-evidenced Norwegian Krill oil as a diet supplement (one of the best sellers in the world);
- **Social impact:** improved general population's awareness of the risks and protective factors of ageing and dementia, enabling them to improve their quality of life through publicly easy accessible approaches; and
- **Diversity:** As a scholar from China with 3-year trainings in Hong Kong, 6-year in the USA, and 6-year in Norway, the PI Evandro Fang is now leading a big international team of around 15 students from around 10 countries. The Fang Lab is an LGBTQ-friendly society. The diversity of the Fang Lab also has a positive impact to Epi-Gen and Ahus, bringing more scientific and social exposures of Epi-Gen/Ahus to the world.

2. Underpinning research (indicative maximum 500 words)

2.1 Roles for DNA damage-induced NAD^+ depletion in accelerated ageing (period 2017-2019, led Fang)

Mitochondrial dysfunction is a hallmark of neurodegeneration and aging, but the underlying mechanisms are largely unclear. DNA damage accumulates during life and is thought to contribute to aging and genomic instability. Thus, defining those proteins and pathways that maintain genome stability and mitochondrial health may be critical in preventing aging and age-related degeneration. Following the discoveries of the NAD^+/SIRT1-PGC1α (NSP) signaling in healthy ageing **[1, 2]** during his postdoc period at NIA/NIH, USA, the Evandro Fang lab at Ahus/UiO continued further mechanist studies from Sep. 217. The novel discoveries show impaired mitophagy is an accelerator of ageing, providing scientific evidence of turning up mitophagy as a maneuverable target to improve healthspan **[3]**. This study was started between 2017-2019 with funding supports from HELSE SØR-ØST (#2017056) and the Research Council of Norway (RCN) Young Talent grant (#262175) to Fang.

2.2 Compromised NAD^+-mitophagy axis contributes to cognitive impairment in Alzheimer's disease (Period 2017-2022, onwards, led by Evandro Fang)

Alzheimer's disease (AD) constitutes 70% of dementia cases and affects over 50 million individuals worldwide. Continued failure in drug development for AD suggests the importance in exploring alternative molecular mechanisms and drug targets for AD. Neurons affected in AD experience mitochondrial dysfunction and a bioenergetic deficit that occurs early and promotes the disease-defining amyloid beta peptide (Aβ) and Tau pathologies. We have proposed that defective mitophagy contributes to AD **[4]**. We have demonstrated that mitophagy is impaired in postmortem human brain tissue and iPSC-derived neurons from AD as well as in Aβ, Tau, and ApoE4 animal models of AD **[5]**; genetic and pharmacological upregulation of mitophagy inhibit AD pathologies and retain memory in AD animal models. Based on the studies from us and others, we propose that age-dependent reduction of mitophagy is a shared contributor to common neurodegenerative diseases **[6] (Fig. 1)**.

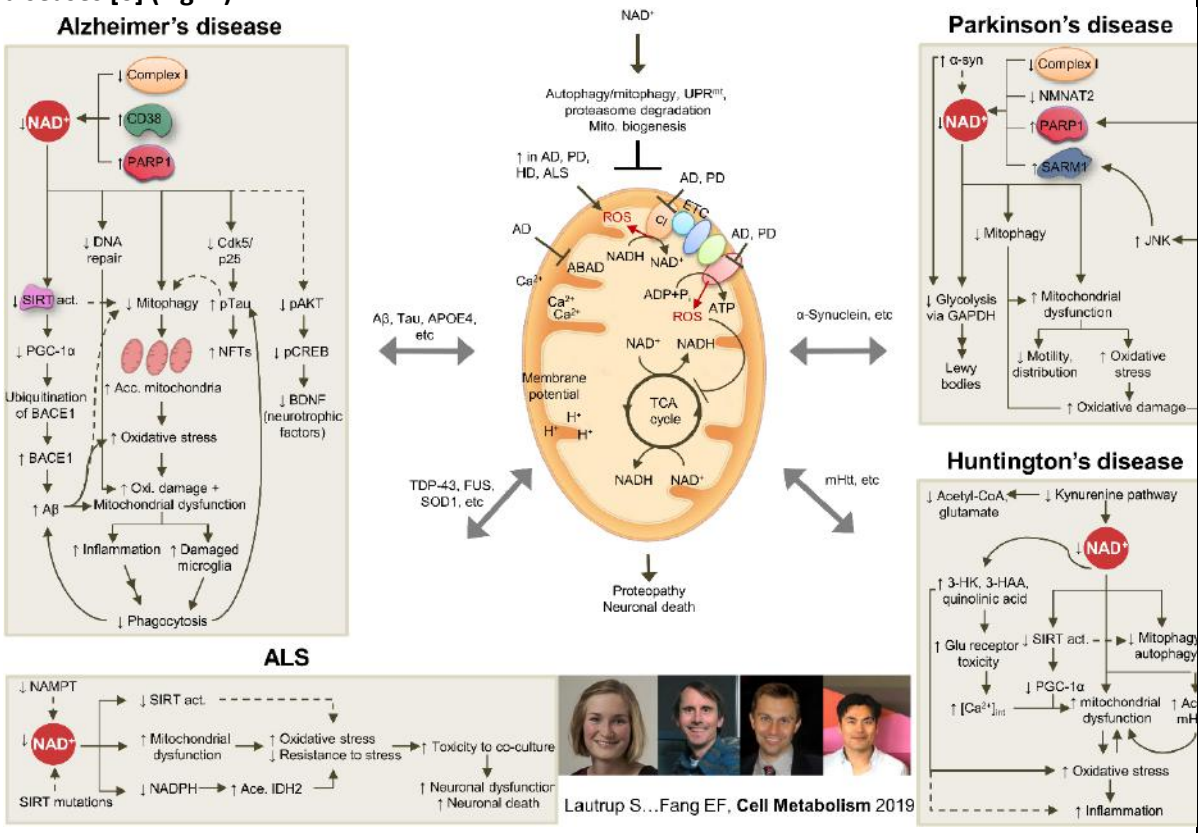


Fig. 1. A summary on the importance of the NAD⁺-mitophagy axis in inhibiting common neurodegenerative diseases.

3. References to the research (six maximum; #First author, *corresponding author)

1. **Fang EF#,** Scheibye-Knudsen M#, Brace L, Kassahun H, et al., Croteau DL, Bohr VA*. Defective Mitophagy in XPA via PARP1 hyperactivation and NAD⁺/SIRT1 reduction, ***Cell***, 2014, 157(4): 882-896. https://pubmed.ncbi.nlm.nih.gov/24813611/ (citations: 625 by 12 Jan. 2014, source Google Scholar, same below; the landmark paper linking reduced NAD+-mitophagy way as a common cause of many premature ageing diseases; with Prof. Hilde Nilsen/Ahus as coauthor).

2. **Fang EF#**, Kassahun H, Croteau DL, Scheibye-Knudsen M, Marosi K, Lu H, Shamanna RA, Kalyanasundaram S… Wollman BN, Morevati M, Li J, Kerr JS, Lu Q, Waltz TB, Tian J, Sinclair DA, Mattson MP, Nilsen H, Bohr VA*. NAD⁺ replenishment improves lifespan and healthspan in Ataxia telangiectasia models via mitophagy and DNA repair, ***Cell Metab***, 2016, 24(4):566-581. https://pubmed.ncbi.nlm.nih.gov/27732836/ (citations: 467; a landmark paper showing NAD+ supplementation improved lifespan and healthspan in a premature ageing Ataxia telangiectasia, the base of the 2-year clinical trial Nilsen/Fang just finished; with Prof. Hilde Nilsen/Ahus as coauthor).

3.**Fang EF#,*,** Hou Y#, Lautrup S#, Jensen MB, Yang B, SenGupta T, Caponio D, Khezri R, Demarest TG, Aman Y, Figueroa D, …, Jasper H, Nilsen H, Bohr VA*. NAD + augmentation restores mitophagy and limits accelerated aging in Werner syndrome. ***Nat Commun***, 2019. https://pubmed.ncbi.nlm.nih.gov/31754102/ (citations: 175; a landmark paper showing NAD+ supplementation improved lifespan and healthspan in a premature ageing Werner syndrome, base of the following clinical trial in Chiba Japan).

4. Kerr JS[#], Adriaanse BA, Greig NH, Mattson MP, Cader MZ, Bohr VA*****, **Fang EF***. Mitophagy and Alzheimer's disease: Cellular and molecular mechanisms, ***Trends Neurosci***. 2017, 40(3):151-166. https://pubmed.ncbi.nlm.nih.gov/28190529/ (Citations: 607; my hypothesis of compromised mitophagy as a driver of Alzheimer).

5. **Fang EF[#,]***, Hou Y[#], Palikaras K[#], Adriaanse BA, Kerr JS, Yang B, Lautrup S, Hasan-Olive M, Caponio D, Dan X, Croteau DL, …, Cader MZ, Mattson MP, Tavernarakis N, Bohr VA*. Mitophagy inhibits Aβ and p-Tau pathologies and cognitive deficits in experimental models of Alzheimer's disease. ***Nature Neurosci***, 2019. https://pubmed.ncbi.nlm.nih.gov/30742114/ (**Citations: 1051**; the landmark paper evidenced compromised mitophagy contributes to AD and is a druggable target; one of the high cited papers in the field).

6. Lautrup S, Sinclair DA, Mattson MP, **Fang EF***. *NAD^+ in brain ageing and neurodegenerative disorders. **Cell Metab**, 2019, 30 (4): 630-655.* https://pubmed.ncbi.nlm.nih.gov/31577933/ (Citations: 434; proposed a hypothesis on why ageing is the primary driver of common neurodegenerative diseases).

4. Details of the impact (indicative maximum 750 words)

4.1. **Science: Provides novel mechanisms of human ageing and the causes of dementia**

As detailed in sections 2 and 3, these studies in-depth our understandings of the molecular mechanisms of human ageing and the age-predisposed Alzheimer's disease. These discoveries have fostered intensive scientific studies in this field (as evidenced by over 15000 citations and so on) and provided evidence for clinical trials (detailed in 4.3.).

4.2. **Education: opened a new course and trained many students**

Within the past 5 years, the Fang Lab has mentored (and is mentoring) more than 40 young scientists who are interested in ageing research. Among them, 32 students have graduated/worked in the Fang lab. All the 4 former postdocs have secured good positions: Dr. Domenica Caponio (postdoc 2019-2022), a teacher; Dr. Yahyah Aman (postdoc 2018.02-2021.01), an editor in Nature Ageing (London Office); Dr. Chenglong Xie (postdoc 2019.09-2020.11), an associate Professor in Wenzhou Medical Universtiy in China; and Dr. Noemí Villaseca González (postdoc 2022), an Assistant Professor in University of Castilla-La Macha in Spain. Further, the Fang lab has opened the 1st course on Biology of Ageing in Norway (with Hilde Nilsen) which is turning to be a popular course. E.g., in 2023 nearly 40 students attended the course from many universities in Norway, Denmark, Sweden, Germany, and the USA (with 88.3% satisfaction).

4.3. **Clinic: propelled 5 clinical trials, with one finished with success**

Guided by their original discoveries that reduced NAD+ is a cause/high risk factor of premature ageing and neurodegenerative diseases, Dr. Fang is actively involved many translational studies, such as:

- NAD+-based clinical trial on Ataxia Telangiectasia (A-T) (led by Prof. Hilde Nilsen; ClinicalTrials.gov Identifier: NCT04870866): with very positive clinical results just published (PMID: 37899683). We show that long-term use of NR appears to be safe and well tolerated, and it improves motor coordination and eye movements in patients with A-T of all ages.

- NAD+-based clinical trial on Amyotrophic Lateral Sclerosis (ALS) (led by Prof. Ole-Bjørn Tysnes with ClinicalTrials.gov Identifier: NCT04562831)
- NAD+-based clinical trial on reducing cardiovascular side effects after chemotherapy (led by Prof. Torbjorn Omland and Dr. Evandro F. Fang, with ClinicalTrials.gov Identifier: NCT03760588)

An important milestone for our 'bench-top' to 'bedside' study was just finished recently. Led by Prof. Hilde Nilsen, we just published a phase 2 clinical trial data entitled 'Long-Term Nicotinamide Riboside Use Improves Coordination and Eye Movements in Ataxia Telangiectasia' in the leading journal Movement disorders. Ataxia telangiectasia (A-T) is a DNA repair deficient disease with premature ageing features and there is no cure. In 2016, a pre-clinical study from Prof. Vilhelm Bohr, Prof. Hilde Nilsen, and Dr. Evandro F. Fang showed that supplementation with a NAD+ precursor nicotinamide riboside (NR) reduced A-T pathologies and extended lifespan in animal models (Fang EF et al., Cell Metabolism, 2016. Download). To check whether this 'bench-top' discovery could be applicable in 'bedside', Nilsen led a 2-year NR clinical trial to treat A-T kids in Norway. The data show that NAD+ concentrations increased rapidly in peripheral blood and stabilized at a higher level than baseline. NR supplementation was well tolerated for most participants. The total scores in the neuromotor test panels, as evaluated at the 18-month time point, improved for all but one participant, primarily driven by improvements in coordination subscores and eye movements. A comparison with historical data revealed that the progression of certain neuromotor symptoms was slower than anticipated. The study concludes that Long-term use of NR appears to be safe and well tolerated, and it improves motor coordination and eye movements in patients with A-T of all ages.

Fig. 2. A summary of the NAD+-related clinical studies, including clinical trials and clinical biomarker development Fang involved in.

4.4. Collaboration with Industry

In line with the Ahus theme to collaborate with industry, the Fang lab has been actively and successfully implemented their wet lab discoveries to industry with two examples presented.

i) Based on the Fang lab ground-breaking discovery of turning up mitophagy as a therapeutic strategy in Alzheimer's disease (Fang EF et al., Nature Neuroscience 2019; commentary in Nature Reviews Drug Discovery; highlighted in Nature 2022), the Fang lab has a License agreement with the anti-ageing company Molecule AG/VITADAO for further development and commercialization of 'Inducers of mitophagy'. Prosjektnummer: 282942 (Kostnadssted 900050; direct funding NOK 2,397,750 NOK).

ii) In collaboration with one of the Norwegian biggest companies AKER (here AKER BioMarine), the Nilsen and Fang labs showed anti-ageing potential of the Norway-made Antarctic Krill oil (PMID: 36367773; also news in the Norwegian National medium NRK). This led Fang to be invited as a paid Chief Scientific and Medical Officer of NYO3 (a Norway-registered Norwegian/Chinese company): now this company is developed into one of the world's largest companies in this field.

4.5. Social impact: improved general population's understanding of ageing and dementia

This case has shown its immediate and big social impact as different areas.

- Enabled the establishment of the Norwegian Centre on Healthy Ageing Network (NO-Age, www.noage100.com): Dr Fang built the network together with Profs. Hilde Loge Nilsen, Jon Storm-Mathisen, and Linda Hildegard Bergersen. NO-Age has strong scientific impact: it is composed of 7 advisors (including the late Prof. George Martin), 43 national members, 31 international members. Among them, three are Nobel Laureates. NO-Age has organized 4 national/international meetings and more than 50 seminars over the past 4 years.

- Enabled the establishment of the Norwegian National anti-Alzheimer's disease network (NO-AD, www.noad100.com): Fang built the network together with Prof. Menno P. Witter (NTNU, Norway). The NO-AD national network has significant scientific impact: it is composed of 8 advisors, 30 national members, and 32 international members. Together with NO-Age, NO-AD has organized more than 50 seminars over the past 4 years. As most of the talks were recorded, NO-Age/AD seminars have become a popular training resource for researchers on ageing and AD.

- Disseminated the science to the broad scientific community. The discoveries were being spoken in 123 invited public talks on ageing worldwide from 2 Oct 2017: 3 (2017), 25 (2018), 40 (2019), 10 (2020), 10 (2021), 35 (2022), with 8 already scheduled in 2023.

- Organized the 1st Norway-UK meeting on ageing and dementia on18-19 Sep. 2023 (co-hosted by Prof. Lynne Cox/Oxford and Richard Siow/KCL). More than 200 students, researchers, and clinicians attended this event.

- Based on the discoveries, Fang was invited by the Norwegian national TV channel NRK to be involved in its award-winning documentary TV programme 'The Dementia Choir' (season 1 with 6 episodes): this TV programme is of a big success, as it broadly educated the general population on care, awareness, and ways to slow down the disease. Fang was involved in episode 5, bringing his laboratory discoveries on how to slow down (if we cannot stop at the moment) the progression of dementia: such as to do exercise, fasting, having healthy diet and fruits (e.g., passion fruit based on the scientific paper from the Fang lab). This programme got many awards, including the Audience Award during the Gold Route (the Norwegian 'Grammy' Award), and the human right Award by the University of Oslo.

5. Sources to corroborate the impact (indicative maximum of ten references)

- Publication of the 2-year clinical trial showing the benefit of NAD+ in treating a premature ageing disease https://pubmed.ncbi.nlm.nih.gov/37899683/
- A list of all the meetings organized by NO-Age/AD https://noad100.com/meetings-events/
- Over 50 videos were recorded as educational source https://noage100.com/videos/
- Details of the 1st Noway-UK meeting on ageing and dementia https://noage100.com/2023/08/17/the-nyo3-5th-no-age-ad-meeting-andthe-1st-norway-uk-joint-meeting-on-ageing-and-dementia/
- Web of the Fang Lab https://evandrofanglab.com/
- The Norwegian national TV channel NRK-made The Dementia Choir TV series (season 1 with 6 episodes): from 25 min in episode 5 https://tv.nrk.no/serie/demenskoret
- Interviewed by the Norwegian leading newspaper VG on anti-AD drug development progress https://mynoad100.files.wordpress.com/2022/01/vg2022_alzheimers-e28093-vg.pdf
- The 2023 Human Right Award by UiO to the Dementia Choir Season 1 https://www.uio.no/english/about/facts/awards/human-rights/

CRN – case number 1

Institution: Cancer Registry of Norway
Administrative unit: Cancer Registry of Norway
Title of case study: Cancer in immigrants
Period when the underpinning research was undertaken: 2014 and onwards
Period when staff involved in the underpinning research were employed by the submitting institution: PhDs and postdocs were employed in the period from 2014 to 2021. Several permanent employees have also been involved
Period when the impact occurred: 2017 and onwards

1. **Summary of the impact** (indicative maximum 100 words)

Our studies have contributed to the knowledge on cancer among immigrants in Norway. Substantial efforts were invested in conducting research that led to an amendment to the CRN Regulation, enabling the incorporation of information on country of birth in the registry. This regulatory modification transpired in 2018 and enabled the inclusion of immigrant-specific incidence in our annual publication, and more easily available data on country of birth for researchers. The data have also been used to enhance the understanding of incidence trends. Our research elucidated lower attendance rates for screening among immigrants, efforts to mitigate this are now being investigated further.

2. **Underpinning research** (indicative maximum 500 words)

Key research and aims:

The Cancer Registry of Norway undertook multiple research initiatives with the overarching aims of investigation **cancer incidence** (1), assessing the **stage distribution and survival** (2, 3), and examine **cancer screening attendance** (4, 5) among immigrants in Norway.

Key findings:

Cancer incidence in immigrants (1). This study encompassing 5,508,429 Norwegian-born and 850,008 immigrants residing in Norway from 1990 to 2012. The study, which included 498,336 cancer cases, revealed a lower overall cancer incidence among immigrants compared to the Norwegian-born population. Immigrants from high-income countries exhibited comparable incidence rates as the Norwegian-born. Noteworthy findings included higher incidence rates of lung cancer in men born in Eastern Europe, elevated rates of stomach cancer in Eastern European immigrants, and increased rates of liver cancer among immigrants from low-income countries.

Stage at diagnosis and survival among immigrants (2, 3). These studies were performed on a population ranging from 213 320 to 500 255 cancer cases diagnosed between 1990 and 2014. The studies identified no substantial differences in stage at cancer diagnosis between immigrants and those who were Norwegian-born, except for breast cancer where non-Western immigrants presented with more advanced stages (2). Immigrants in Norway had better survival relative to those who were Norwegian-born. Substantially better survival was observed among non-Western-born lung cancer patients and sub-Saharan African breast cancer patients. Conversely, immigrants from Eastern Europe with melanoma and prostate cancer demonstrated somewhat worse survival compared to their Norwegian-born counterparts (3).

Cancer screening attendance rates among immigrants (4, 5). The third strand of studies investigated cancer screening attendance rates among immigrants. In the study on breast cancer screening attendances in the Norwegian Breast Cancer Screening (4), involving 885 979 women aged 50–69 who had received an invitation to screening between 1996 and 2015, immigrants

displayed lower attendance rates (53.1%) than Norwegian-born women (76.1%). Notably, women born in Somalia had the lowest attendance rates in the first round (16.7%). The cervical screening study included 208 626 immigrants and 1 157 223 Norwegian-born women found lower screening attendance among immigrants across all age groups (5). Immigrants form Lithuanian had the highest non-adherence rate at 78%. All of the abovementioned studies were carried out on registry-based data.

Names of the key researchers and what positions they held at the administrative unit at the time of the research (where researchers joined or left the administrative unit during this time, these dates must also be stated).

Giske Ursin, Director of CRN, led the research project Cancer incidence among immigrants. A postdoctoral candidate **Kirsti Vik Hjerkind** was employed in the project (2014–2021).

Inger Kristin Larsen, Researcher at Department of Registration at the CRN, led the research project Stage at diagnosis and survival among immigrants. A PhD-student, **Håvard Thøgersen**, was employed for three years (2016–2019).

Solveig Hofvind, Head of Screening Section, Section of Breast Cancer Screening, and **Mari Nygård**, Head of Department, Department of Research (since 2019), led the research projects on screening attendance. **Maarit K. Leinonen** Postdoctoral fellow, Department of Research (2015–2019), and **Sameer Bhargava,** PhD student, Section of Breast Cancer Screening (2016–2019) was employed in these projects.

Other permanent employees from the CRN were also involved. They have been employed throughout the period 2012–2022, unless otherwise stated:
Bjørn Møller, Head of Department of Registration
Elisabete Weiderpass, Head of Department, Department of Research until December 2018
Trude Eid Robsahm, Researcher, Department of Research
Ronnie Babigumira, Advisor (now PhD student), Department of Research (2013–)
Stein Aaserud, Advisor, Department of Registration (2014–2022)
Kaitlyn Tsuruda, Advisor, Section of Breast Cancer Screening (2016–)
Suzanne Campell, Advisor, Department of Research
Ameli Tropé, Head of Screening Section, Section of Cervical Cancer Screening (2015–)
Gunhild Mangerud, Advisor, Section of Breast Cancer Screening

3. **References to the research** (indicative maximum of six references)

1. Hjerkind KV, Qureshi SA, Møller B, Weiderpass E, Deapen D, Kumar B, Ursin G. Ethnic differences in the incidence of cancer in Norway. Int J Cancer. 2017;140(8):1770-80. DOI: 10.1002/ijc.30598

2. Thøgersen H, Møller B, Robsahm TE, Aaserud S, Babigumira R, Larsen IK. Comparison of cancer stage distribution in the immigrant and host populations of Norway, 1990-2014 Int J Cancer. 2017;141(1):52-61. DOI: 10.1002/ijc.30713

3. Thøgersen H, Møller B, Robsahm TE, Babigumira R, Aaserud S, Larsen IK. Differences in cancer survival between immigrants in Norway and the host population. Int J Cancer. 2018;143(12):3097-105. DOI: 10.1002/ijc.31729

4. Bhargava S, Tsuruda K, Moen K, Bukholm I, Hofvind S. Lower attendance rates in immigrant versus non-immigrant women in the Norwegian Breast Cancer Screening Programme. J Med Screen. 2018;25(3):155-61. DOI: 10.1177/0969141317733771

5. Leinonen MK, Campbell S, Ursin G, Tropé A, Nygård M. Barriers to cervical cancer screening faced by immigrants: a registry-based study of 1.4 million women in Norway. Eur J Public Health. 2017;27(5):873-9. DOI: 10.1093/eurpub/ckx093

4. Details of the impact (indicative maximum 750 words)

In 2013, The Ministry of Health and Care Services in Norway published a national strategy for immigrant health. Among one of three main aim was to ensure that health and care services had access to the most resent knowledge about immigrants' health for use in the development of health services. At that time, the absence of comprehensive national data on immigrants' health was significant. Below we have outlined 6 areas that might have been influenced by our initial studies:

A foundation for knowledge on cancer in immigrants

The initial studies on immigrants and cancer in Norway included in this impact case have been collectively cited 134 times, and the findings have provided a solid knowledge foundation for our understanding of cancer in immigrants in Norway. This is evident, among other, in the national Public Health Report for 2022, where these studies, along with data from the Cancer Registry of Norway, constitute the majority of references summarizing the topic "Cancer among immigrants" (6).

Legislation changes

To meet the goals of the national strategy from 2013, it became clear that data on the country of birth must become more accessible. Substantial efforts were made to amend the Cancer Registry of Norway Regulation, in order to enable the inclusion of information about the country of birth in the registry. The regulatory modification took place in 2018.

The use of country of birth to enhance understanding of concerning incidence trends

Research revealed that immigrants in Norway had a lower cancer risk for most cancer sites compared to the host population (1). However, certain immigrant groups had a higher risk of primary liver cancer. The incidence of liver cancer had shown a worrisome increase in Norway, and the trend was suspected to be related to a growing proportion of immigrants from countries with higher risk of this specific cancer. Information on country of birth made it possible to assess the incidence trends among individuals born in Norway. The result of this analysis was somewhat surprising – there had been an increase in the incidence of primary liver cancer among the Norwegian-born population as well, and the earlier assumptions about causation were refuted (7).

The reason for low attendance in screening among immigrants needed further examinations, and new studies were conducted

Immigrant women from non-Western countries had a more advanced stage of breast cancer at diagnosis (this was not found for cervical cancer) (2). The breast cancer finding corresponded with the observed lower participation rate in immigrants to mammography screening (4). This was a worrisome discovery. Several research projects were funded by The Norwegian Cancer Society enabling us to continue working on projects to investigate barriers to participation in screening (NCS), and other closely related issues.

- **Qualitative studies** were conducted to identify and explore factors that may facilitate immigrants' access to screening (8), immigrants women's perspectives on breast cancer and screening (9).
-

- **A randomised controlled trial** was performed to explore attendance at mammographic screening among immigrants who received the invitation and information in their language of origin (Arabic, English, Polish, Somali or Urdu) and Norwegian compared to Norwegian only. However, the study did not reveal any differences in attendance between the groups (10).
-
- **Lower attendance among immigrants were also shown in a study on colorectal cancer screening (11),** and the national colorectal cancer screening programme, implemented in 2023, has tried out new methods (e.g. by distributing screening information during Friday prayer at the mosque and they will conduct a randomized study to assess the impact of verbal information on participation.

Outreach activities and collaboration

The mammography screening programme has engaged in outreach activities and collaborated with immigrant groups (e.g. Bydelsmødre "District mothers", voluntary, primarily minority women trained in parenting, health and community related issues, to bridge gaps between immigrant women and community services, addressing local challenges) and has created informational videos in several languages that were made available online in response to requests from participants and other stakeholders.

International collaborations

For several decades, the Nordic cancer registries have maintained a strong and close collaboration. Nonetheless, collaboration has been lacking around immigrants and cancer. The reasons for this limitation are not clear, though the sensitivity of country of birth information may have contributed to the hesitancy some countries have in making the data available, and therefore reducing the ability of cross-country research collaboration. It was not until 2023 that population-based studies on the incidence and mortality of cancer were published from four out of five Nordic countries (12, 13). We believe that a foundation has been established for a close collaboration on this topic in the years to come.

5. Sources to corroborate the impact (indicative maximum of ten references)

We have listed the primary sources that corroborate the impact we believe this case has contributed on:

A foundation for knowledge on cancer in immigrants

6. Spilker RI, T; Hussaini, L: Labberton, AS; Ali WA; Syse, A; Olsen, AO; Qureshi, SA; Bærug, AB; Straiton, ML; Kumar, BN; Bruun T. Folkehelserapporten. Helse blant personer med innvandrerbakgrunn. Folkehelseinstituttet: Folkehelseinstituttet; 2022 [updated 2022 Aug 26; cited 2023 Dec 08. Available from: Health in the immigrant population - NIPH (fhi.no)

Legislation changes

Place of birth was added in Forskrift om innsamling og behandling av helseopplysning i Kreftregisteret (Kreftregisterforskriften) §1-7 (Opplysninger om krefttilfeller i Kreftregisteret) pkt. 1.4. Available from: Forskrift om innsamling og behandling av helseopplysninger i Kreftregisteret (Kreftregisterforskriften) - Kapittel 3. Behandling av helseopplysninger i Kreftregisteret - Lovdata

The use of country of birth to enhance understanding of concerning incidence trends

7. Hjerkind, K. V., Larsen, I. K., Aaserud, S., Møller, B., & Ursin, G. (2020). Cancer incidence in non-immigrants and immigrants in Norway. *Acta oncologica (Stockholm, Sweden)*, *59*(11), 1275–1283. DOI: 10.1080/0284186X.2020.1817549

The reason for low attendance in screening among immigrants needed further examinations, and new studies were conducted

Qualitative studies

8. Bhargava, S., Czapka, E., Hofvind, S., Kristiansen, M., Diaz, E., & Berstad, P. (2022). Polish immigrants' access to colorectal cancer screening in Norway - a qualitative study. *BMC health services research*, *22*(1), 1332. DOI: 10.1186/s12913-022-08719-3

9. Bhargava, S., Hofvind, S., & Moen, K. (2019). Gender, letters, relatives, and God: mediating actors in mammographic screening among Pakistani women in Norway. *Acta radiologica open*, *8*(9), 2058460119875015 DOI: 10.1177/2058460119875015

Randomised controlled trial

10. Hofvind, S., Iqbal, N., Thy, J. E., Mangerud, G., Bhargava, S., Zackrisson, S., & Berstad, P. (2023). Effect of invitation letter in language of origin on screening attendance: randomised controlled trial in BreastScreen Norway. *BMJ (Clinical research ed.)*, *382*, e075465 DOI: 10.1136/bmj-2023-075465

Lower attendance among immigrants in colorectal cancer screening

11. Bhargava, S., Botteri, E., Berthelsen, M., Iqbal, N., Randel, K. R., Holme, Ø., & Berstad, P. (2023). Lower participation among immigrants in colorectal cancer screening in Norway. *Frontiers in public health*, *11*, 1254905. DOI: 10.3389/fpubh.2023.1254905

Outreach activities and collaboration

Translated information in the national mammography screening programme is available here: https://www.kreftregisteret.no/en/screening/BreastScreen_Norway/Translations/

International collaborations

12. Lamminmäki, M., Leivonen, A., Heinävaara, S., Nygård, M., Ursin, G., Campbell, S., Stefansdóttir, H., Hirvonen, E., Toikkanen, S., Vejborg, I. M. M., Njor, S. H., & Sarkeala, T. (2023). A population-based cohort study on changes in breast, lung and colorectal cancer incidence and mortality among non-Western immigrant women. *BMC cancer*, *23*(1), 665. DOI: 10.1186/s12885-023-11140-6

13. Sarkeala, T., Lamminmäki, M., Nygård, M., Njor, S. H., Virtanen, A., Leivonen, A., Hirvonen, E., Toikkanen, S., Campbell, S., Stefansdóttir, H., Ursin, G., & Heinävaara, S. (2023). Cervical, liver and stomach cancer incidence and mortality in non-Western immigrant women: a retrospective cohort study from four Nordic countries. *Acta oncologica (Stockholm, Sweden)*, *62*(9), 977–987. DOI: 10.1080/0284186X.2023.2245557

CRN - case number 2

Institution: The Cancer Registry of Norway (CRN)
Administrative unit: The Cancer Registry of Norway (CRN)
Title of case study: Accelerating cervical cancer elimination: Research-driven innovations in Prevention
Period when the underpinning research was undertaken: 2012 and onwards
Period when staff involved in the underpinning research were employed by the submitting institution: Post-docs were employed during 2015-2022. Several permanent employees have also been involved
Period when the impact occurred: 2017 and onwards

1. Summary of the impact (indicative maximum 100 words)

The establishment of a causal link between human papillomavirus (HPV) infection and cervical cancer has driven the development of new technologies for integration into existing cervical cancer prevention policies. Based on our research, the following changes have been implemented in the Norwegian screening programme, CervicalScreen Norway:

A) HPV-based screening was implemented for women over 34 years in 2017
B) screening algorithms for HPV-positives were improved using partial HPV genotyping in 2018
C) self-sampling is currently under implementation

D) Furthermore, our public-private research collaboration on long-term effectiveness and safety of HPV vaccines has had wide reaching implications, influencing decisions regarding the need of booster doses years after HPV vaccination.

2. Underpinning research (indicative maximum 500 words) **Key research and aims:**

Below we focus on studies that have had a direct impact on decisions/policies made for the CervicalScreen Norway and for HPV vaccination programmes beyond Norway.

A) **Navigating change: Gradual and controlled replacement of cytology with HPV-testing in screening for women older than 34 years of age in Norway.**
Cytology-based cervical cancer screening was pivotal in reducing cervical cancer incidence in Norway from the 1970s. From 2006 and onwards, several randomized controlled trials have demonstrated that HPV based screening is more sensitive than conventional cytology-based screening. However, the replacement of screening technology on a large scale requires significant modifications to existing infrastructure and protocols in the screening programme (including staff training, follow-up algorithms, communication). To minimize adverse effects, we performed a gradual and randomized implementation of HPV testing in CervicalScreen Norway.(1).

B) **Balancing act: How to ensure equal management for women with equal risk for cervical cancer?** Commercially available HPV assays used in screening detect 14 high-risk (hr) HPV genotypes. While these HPV-assays are more sensitive than cytology exams in screening, they cannot differentiate between clinically irrelevant transient HPV infections and persistent HPV infections that can lead to cancer. Until recently, all HPV-positive samples have been additionally tested for cellular changes to identify individuals with underlying precancers or cancers. However, referring all women with abnormal results to colposcopy and biopsy, resulted in suboptimal clinical management algorithm with low positive

predictive value (1), leading to excessive use of health care services as well as distress among women. In our effort to calibrate the follow-up algorithm, we relied on the premise that each of the 14 distinct hr HPV genotypes possesses its own unique carcinogenic potential and cervical cancer risk profile. Our study assessed the harms and benefits associated with HPV genotype specific algorithms by following up more than 3000 hrHPV positive women (2).

C) **Breaking barriers: HPV self-sampling as an alternative to physician-performed sampling.** Among the various reasons why a significant number of women do not attend cervical screening at recommended intervals, are negative past experiences related to pelvic exams, practical barriers, and, at times, a painful history of sexual abuse**.** Collecting the screening samples at home by the women themselves for HPV testing, can mitigate some of these barriers. The usefulness of HPV testing on self-collected samples for screening programmes rests on at least two assumptions: i) comparable sensitivity in detecting cervical cancer and precancers between self-sampling and physician-based sampling, and ii) increased participation in screening with self-sampling compared to physician sampling. The CRN has performed several studies to evaluate i) and ii) (3,4,)

D) **Beyond the clinical trial: HPV vaccines' prolonged impact.** in a long-term follow-up of the HPV vaccine targeting four HPV genotypes (HPV6, HPV11, HPV16, HPV18), this vaccine was found to be highly effective in preventing cervical precancers caused by these four targeted HPV types in a pivotal phase 3 study. This vaccine is used in national HPV vaccination programmes across the globe. However, the original phase 3 study, with a four-year follow-up, was insufficient to determine whether vaccination at age of 12 years provides life-long protection against HPV. In our later study the phase 3 trial was extended over 14 years, involving continued follow-up of 5493 women from Denmark, Iceland, Norway and Sweden. The aim was to evaluate the long-term effectiveness and safety through national registries, cancer screening programmes, and biobanks (5).

Names of the key researchers and what positions they held at the administrative unit at the time of the research (where researchers joined or left the administrative unit during this time, these times are stated).

Mari Nygård, Senior researcher at the Department of Research, and Head of Department since 2020, led the evaluation of the implementation of primary HPV-based screening (1), was the senior researcher in the study on improving the screening algorithm based on partial genotyping (2), PI of the self-sampling study described in (3), was heavily involved in the randomized controlled trial on self-sampling (4), and was the Norwegian PI in the long-term follow-up study of HPV vaccine (5).

Ameli Tropé, Head of Section of cervical cancer screening (2015–) led the implementation of primary HPV-based screening (1), was involved in the study on improving the screening algorithm based on partial genotyping (2), and in randomized controlled trial on self-sampling (4).

Birgit Engesæter, Senior Advisor, Section of cervical cancer screening (2015-) co-led the implementation of primary HPV-based screening(1), and improving the screening algorithm based on partial genotyping (2).
Bo Terning Hansen, Researcher, Department of Research was PI of the randomized controlled trial on self-sampling (4).
Dana Hashim, Section for cervical cancer screening (2017-2018) was the first author of (2).
Maarit Leinonen, Postdoc, Department of Research (2015-2019) was the first author of (3).
Gunvor Aasbøe, Postdoc, Department of Research (2017-2023), was the first author of (4).

Other employees from the CRN were also involved. They have been employed throughout the period 2012–2022, unless otherwise stated:
Philip E Castle, Senior Advisor (part-temporary, 2014)
Sophie Berger, Senior advisor, from 2022: Head of Section of Administration and Research Support, Department of Research
Espen Enerly, Researcher, Department of Research
Suzanne Campell, Advisor, Department of Research
Kristina Schee, Advisor, Department of Research (2013-2016)

Since 2009, research on HPV-related cancers and prevention opportunities at CRN has been conducted through the HPV Research Group, as well as by the Section of Cervical Cancer Screening.

3. References to the research (indicative maximum of six references)

1. Nygard, M, Engesaeter B, Castle PE, Berland JM, Eide ML, Iversen OE, Jonassen MC, Christiansen IK, Vintermyr OK, Tropé A. Randomized Implementation of a Primary Human Papillomavirus Testing-based Cervical Cancer Screening Protocol for Women 34 to 69 Years in Norway. Cancer Epidemiol Biomarkers Prev, 2022. 31(9): p. 1812-1822. OA https://doi.org/10.1158/1055-9965.epi-22-0340

2.Hashim, Engesæter B, Skare G, Castle P, Bjørge T, Tropé T, Nygård M. Real-world data on cervical cancer risk stratification by cytology and HPV genotype to inform the management of HPV-positive women in routine cervical screening. Br J Cancer, 2020. 122(11): p. 1715-1723. OA: https://www.nature.com/articles/s41416-020-0790-1

3. Leinonen M, Schee K, Jonassen C, Lie A, Nystrand C, Rangberg A, Furre I, Johansson M, Tropé A, Sjøborg K, Castle P, Nygård M. Safety and acceptability of human papillomavirus testing of self-collected specimens: A methodologic study of the impact of collection devices and HPV assays on sensitivity for cervical cancer and high-grade lesions. J Clin Virol, 2018. 99-100: p. 22-30. Free article: https://www.sciencedirect.com/science/article/pii/S1386653217303475?via=ihub

4. Aasbo G, Trope A, Nygard M, Christiansen IK, Baasland I, Iversen GA, Munk AC, Chriastiansen MH, Undem K, Bjørge T, Castle P, Hansen BT. HPV self-sampling among long-term non-attenders to cervical cancer screening in Norway: a pragmatic randomised controlled trial. BrJCancer,2022.**127** (10):p.1816-1826.OA: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9643532/pdf/41416_2022_Article_1954.pdf

5. Kjaer SK, Nygård M, Sundström K, Dillner J, Tryggvadottir L, Munk C, Berger S, Enerly E, Hortlund M, Ágústsson AI, Bjelkenkrantz K, Fridrich K, Guðmundsdóttir I, Sørbye SW, Bautista O, Group T, Luxenbourg A, Mershall JB, Radley D, Yang YS, Badshah C, Saah A. Final analysis of a 14-year long-term follow-up study of the effectiveness and immunogenicity of the quadrivalent human papillomavirus vaccine in women from four nordic countries. EClinicalMedicine, 2020. **23**: p. 100401. OA: https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(20)30145-0/fulltext -

4. Details of the impact (indicative maximum 750 words)

The ultimate goal of our research is to provide the best possible cervical cancer prevention options for Norwegian women, and to contribute knowledge that advances cervical cancer prevention globally. Our group is well-positioned for these tasks thanks to our existing comprehensive registry data on the cervical cancer screening programme dating back to 1991, which includes detailed information on over 14 million screening exams by more than 1.8 million women. Our flexible registry solutions enable us to assess the real-life impact of rapidly expanding pool of technologies available to enhance cervical cancer screening.

The underpinning research described in section 2 has given support for policy decisions for the cervical cancer screening programme, as well as for HPV vaccination strategies, in Norway and globally.

A) Gradual implementation of HPV-based screening in Norway for women older than 34 years of age in 2017. The 77,207 women randomized to HPV screening and 80,240 to cytology screening were followed up from 2015 to 2017, demonstrating that HPV screening was well accepted and that HPV -based screening detected 40% more cancers and 60% more pre-cancer than cytology (1). Similarly, a large study in the UK detected 50% more precancers and 30% more cancers in HPV-screening as compared to cytology (6). The UK study, along with the meta-analysis of randomised controlled studies (7) document a very low incidence of cervical precancers and cancers among HPV-negative individuals, supporting an extension of the 3-years screening interval. In summary, supported by international research, our study results provided the main scientific evidence underpinning the decision taken in 2017 to implement primary HPV-based screening to all women 34-69 years of age in Norway.

B) Partial HPV genotyping was implemented for HPV-positives in 2018. In the HPV-based screening that was implemented in 2017, all hrHPV-positive women with abnormal cytology were referred to colposcopy and biopsy which resulted in 60% higher rates for colposcopy referrals. A similar concern has been raised by cervical cancer screening programme coordinators from other countries. Our study demonstrated that separating the most carcinogenic genotypes, HPV16 and 18, from the pool of the remaining hrHPV types by partial genotyping, will stratify women according to risk for cervical cancer (in combination with cytology). This calibration of screening algorithm reduces unnecessary colposcopy referrals with biopsy for women with lower precancer or cancer risk. Our article was thoroughly discussed in an editorial by Arbyn et al., who emphasized both the importance of, and lack, of real-world studies assessing the colposcopy referral algorithms (8). This is much needed information, as the HPV-based primary screening programmes continue to evolve. Based on our research, the follow-up algorithm for HPV-positives was changed in July 2018 (2). In the historical overview of CervicalScreen Norway given in Bjørge et al, this and other changes in the screening programme is described (9).

C) Implementing self-sampling in the cervical screening programme from 2021. The CRN studies showed that (i) compared with physician-taken samples for detecting the presence of HPV DNA among women with cervical cancer and precancers, the self-sampling performed equally well. Our randomized controlled trial performed in the CervicalScreen Norway demonstrated 23% higher participation rate among long-term non-attending women who got a self-sampling kit by mail as compared to those who received a regular invitation, (ii) suggesting that self-sampling increases screening participation among those who do not attend regularly. Similar results from Sweden and Denmark were reported (10,11). Furthermore, in collaboration with a group of modelling experts at the University of Oslo and Harvard University, we assessed the cost-effectiveness and consequences of implementing self-sampling in CervicalScreen Norway. Those findings suggest that targeted self-sampling for those not attending screening likely provides a cost-effective solution (12). Supported by these studies, the CervicalScreen Norway decided in 2021 to implement self-sampling into the programme to boost participation among long-time non-attenders. In 2022, 20.5 million Norwegian kroner (NOK) were allocated over the National budget, and an additional 19.2 million NOK were allocated in 2023, for further implementation of self-sampling in the screening programme.

D) No need for a booster dose for those vaccinated with a three-dose regimen The long-term follow-up of Nordic women demonstrated 100% effectiveness during the follow-up of 14 years, with no high-grade cervical dysplasia caused by the HPV types targeted by the vaccine. The study found no evidence of waning immunity over this time period. The effectiveness results were consistent with prolonged and sustained immunity against the vaccine-related HPV types. The study has thus demonstrated that within 14 years there should be no need for a booster dose. Similar results are also available for the other HPV vaccine (13). Supported by these data, no countries have yet implemented any programme for revaccination of fully HPV-vaccinated individuals (14).

5. Sources to corroborate the impact (indicative maximum of ten references)

Navigating change: gradual and controlled replacement of cytology with HPV-testing in screening for women older than 34 years of age in Norway.

6. Rebolj M, Rimmer J, Denton K, Tidy J, Mathews C, Ellis K, Smith J, Evans C, Giles T, Frew V, Tyler X, Sargent A, Parker J, Holbrook M, Hunt K, Tidbury P, Levine T, Smith D, Patnick J, Stubbs R, Moss S, Kitchener H. Primary cervical screening with high risk human papillomavirus testing: observational study. BMJ 2019;364:l240. OA: https://www.bmj.com/content/364/bmj.l240

7. Ronco G, Dillner J, Elfström KM, Tunesi S, Snijders PJ, Arbyn M, et al. Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. Lancet, 2014. **383**(9916): p. 524-32 Link web: https://www.sciencedirect.com/science/article/pii/S0140673613622187?via=ihub

B) Balancing Act: how to ensure equal management for women with equal risk for cervical cancer?

8. Arbyn M, Yuill RS, Canfell K. Triage of HPV-positive women in Norway using cytology, HPV16/18 genotyping and HPV persistence. Br J Cancer, 2020. 122(11): p. 1577-1579. OA: https://www.nature.com/articles/s41416-020-0787-9

9. Bjørge T, Engesæter B, Skare GB, Tropé A. *CervicalScreen Norway – A screening programme in transition*. Norsk Epidemiologi, 2022. 30(1-2) DOI: https://doi.org/10.5324/nje.v30i1-2.4978

C) Implementing self-sampling in the cervical screening programme.

10. Elfström KM, Sundström K, Andersson S, Bzhalava Z, Carlsten Thor A, Gzoul Z, Öhman D, Lamin H, Eklund C, Dillner J, Törnberg S. Increasing participation in cervical screening by targeting long-term nonattenders: Randomized health services study. Int J Cancer. 2019 Dec 1;145(11):3033-3039. Fee access: https://onlinelibrary.wiley.com/doi/full/10.1002/ijc.32374

11. Lam JU, Rebolj M, Møller Ejegod D, Pedersen H, Rygaard C, Lynge E, Thirstrup Thomsen L, Krüger Kjaer S, Bonde J. Human papillomavirus self-sampling for screening nonattenders: Opt-in pilot implementation with electronic communication platforms. Int J Cancer. 2017 May 15;140(10):2212-2219. OA: https://onlinelibrary.wiley.com/doi/full/10.1002/ijc.30647

12. Burger EA, Sy S, Nygård M, Kim JJ. The Cost-Effectiveness of Cervical Self-Sampling to Improve Routine Cervical Cancer Screening: The Importance of Respondent Screening History and Compliance. Cancer Epidemiol Biomarkers Prev. 2017 Jan;26(1):95-103. Link to website: https://aacrjournals.org/cebp/article/26/1/95/71127/The-Cost-Effectiveness-of-Cervical-Self-Sampling

D) No administration of a booster dose for those vaccinated with a three-dose regimen at the age of 12

13. World Health Organization, *Human papillomavirus vaccines: WHO position paper (2022 update).* Weekly epidemiological record, 2022. **50**(97): p. 645-672. Link to website: https://www.who.int/publications/i/item/who-wer9750-645-672

14. Mariz FC, Gray P, Bender N, Eriksson T, Kann H, Apter D, Paavonen J, Pajunen E, Prager KM, Sehr P, Surcel HM, Waterboer T, Müller M, Pawlita M, Lehtinen M. Sustainability of neutralising antibodies induced by bivalent or quadrivalent HPV vaccines and correlation with efficacy: a combined follow-up analysis of data from two randomised, double-blind, multicentre, phase 3 trials. Lancet Infect Dis. 2021 Oct;21(10):1458-1468. Link: https://www.sciencedirect.com/science/article/pii/S1473309920308732?via=ihub

Diakonhjemmet Hospital, Center for Psychopharmacology [impact case #1]

Institution: Diakonhjemmet Hospital
Administrative unit: Center for Psychopharmacology
Title of case study: Pharmacogenetics of clozapine metabolism and treatment failure
Period when the underpinning research was undertaken: 2017-2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2014-present
Period when the impact occurred: 2018-2022

1. Summary of the impact

Treatment-resistant schizophrenia (TRS) is probably the most severe mental disorder. Clozapine is the drug of choice in patients with TRS, due to superior clinical effects compared to other antipsychotics. However, if the patient fails to respond to clozapine, the clinical situation and treatment prospect are worsened even more. The reasons underlying clozapine-resistance are unclear, but ultrarapid metabolism is suggested as one mechanism. Identifying potential genetic variants encoding increased metabolism of clozapine would therefore have a great impact on schizophrenia treatment and prevention of clozapine-resistance. Furthermore, discovery of genetic variants can effectively be implemented in clinical routine as pharmacogenetic test before initiating clozapine to identify patients who should receive higher doses than normal and be closely followed up by therapeutic serum concentration monitoring (TDM) to ensure that target concentrations are obtained. Discovering variants encoding ultrarapid clozapine metabolism may therefore be translated into clinical practice and change treatment approaches.

2. Underpinning research (indicative maximum 500 words)

Background:

Only one genome-wide association study (GWAS) had previously been performed, but this lacked information on smoking habits. Since smoking habits have a large impact on clozapine metabolism, lacking information on the non-genetic factor will reduce the sensitivity of discovering genome-wide significant hits. In the present study, access to smoking habits made it possible to adjust for this factor when searching for genetic variant associated with clozapine metabolism.

Methods:

A GWAS was performed on 484 patients with 10,283 steady-state serum concentrations of CLZ and N-desmethylclozapine, prescribed dosing, co-medications and known smoking habits (**part I**). The patients were included from the therapeutic drug monitoring (TDM) service at Center for Psychopharmacology (CfP). In **part II**, an enriched cohort from the same center was included to validate the effect of potential significant hits of the preceding GWAS on clozapine serum concentration and add a candidate genotype (rs2472297 *C>T* in *CYP1A*)) reported to impact clozapine metabolism in a previous study.

In **part I**, Espen Molden (PI), Robert Løvsletten Smith and Marianne K. Kringen, all from CfP, Diakonhjemmet Hospital, and Ola A. Andreassen (co-PI), Srdjan Djurovic, Lavinia Athanasiu, Srdjan Djurovic and Kevin O'Connell, all from the NORMENT Centre of Excellence at the University of Oslo, were key study group researchers.

In **part II**, Espen Molden (PI), Hasan Cagin Lenk, Robert Løvsletten Smith and Marianne K. Kringen, all from CfP, Diakonhjemmet Hospital, and Ola A. Andreassen and Kevin O'Connell, both from the

NORMENT Centre of Excellence at the University of Oslo, and Magnus Ingelman-Sundberg and Marin Jukic (Karolinske institutet in Stockholm), were key study group researchers.

Main results:

Part I: In the patient population of the GWAS, 61% were confirmed as 'smokers' and 39% as 'nonsmokers', which is in line with previous studies reporting proportion of smokers and nonsmokers in patients with schizophrenia. Before adjusting for smoking habits no genome-wide significant associations were observed. However, when including smoking habits in the independent analysis, a novel variant (rs28379954; minor *T>C* allele frequency 4.1%; 7.6% CT carriers in the population) within the gene encoding the nuclear factor 1 B-type (NFIB) was significantly associated with reduced clozapine serum concentration ($p = 1.68 \times 10\text{-}8$, beta = -0.376; explained variance 7.63%). The risk of subtherapeutic treatment with clozapine was two-fold higher in *NFIB CT* vs. *TT* carriers. For patients who were carriers of the minor *NFIB C* variant, encoding increased clozapine metabolism, and at the same time were smokers, three-fold higher clozapine doses are required to reach target concentrations.

The study (**part I**) was published in Translational Psychiatry, an open access journal within the Nature portfolio (IF 6.8).

In **Part II**, the quantitative effects of *CYP1A* rs2472297 *C>T* on clozapine serum concentration was studied in addition to *NFIB* genotype and smoking. The results showed that the *CYP1A* rs2472297 *C>T* polymorphism had a significant effect on clozapine concentration regardless of *NFIB* genotype and smoking, where the latter was new and highly relevant findings. In this second study, the results of part I were confirmed and it was further shown that by adding the *CYP1A* rs2472297 *C>T* polymorphism, the risk of subtherapeutic concentrations of clozapine was increased to 2.9-fold higher in smoking patients carrying *NFIB-C* and *CYP1A-T* versus nonsmoking noncarriers ($p < 0.0001$). This shows that the former subpopulation is at even higher risk clozapine failure unless clozapine dosing is 3- to 4-fold increased.

The study (**part II**) was published in Clinical Translational Science, an open access journal within the Wiley portfolio (IF 4.5).

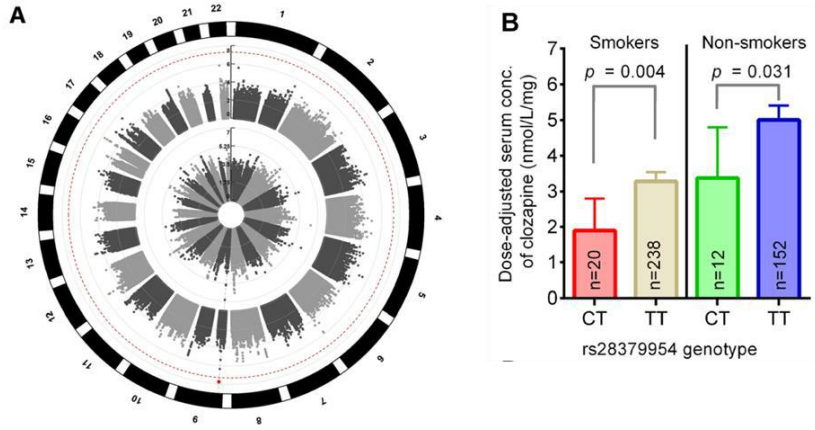
Conclusions:

Of novelty, it was found that the nuclear factor 1 B-type (*NFIB*) gene regulates drug metabolism; in this case having a significant impact on serum concentration of clozapine. In cigarette-smoking patients carrying the *NFIB C* variant, representing 5% of the population, the risk of clozapine failure is substantially increased, unless substantially higher clozapine doses are prescribed. This risk failure is even higher if carrying both the *NFIB-C* and *CYP1A-T* variants. Overall, these studies show that pharmacogenetic variability, along with smoking, is important to consider for personalized dosing of clozapine and prevention of treatment failure in patients suffering of treatment-resistant schizophrenia.

This impact case aligns with administrative unit's strategy of identifying and quantifying factors of importance for personalized medicine of patients with serious psychiatric disorders.

Follow up studies:

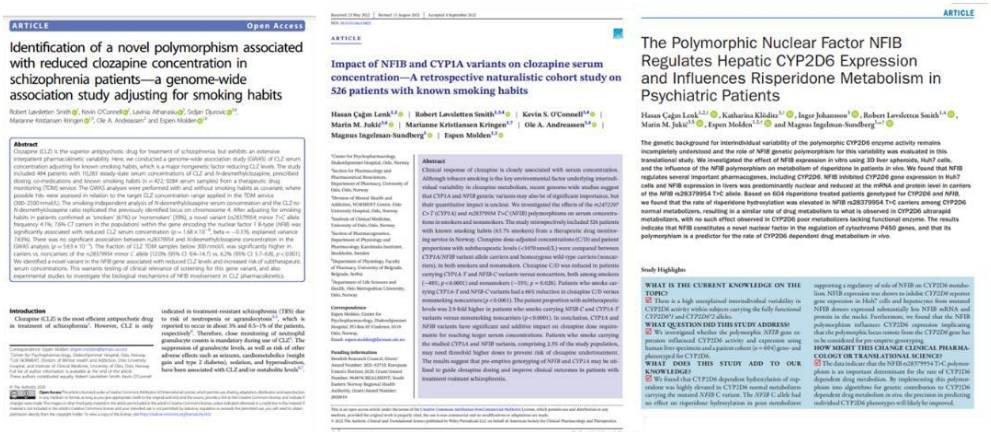
Future studies should investigate if preemptive, genotype-guided dosing of clozapine can improve treatment response in patients with resistant schizophrenia.



Circular Manhattan plot showing the identification of the genome-wide significant hit in the *NFIB* gene (left; red dot) and its effect on clozapine serum concentration, in relation to smoking (right).

3. References to the research

1. Identification of a novel polymorphism associated with reduced clozapine concentration in schizophrenia patients-a genome-wide association study adjusting for smoking habits Transl Psychiatry. 2020 Jun 19;10(1):198. doi: 10.1038/s41398-020-00888-1.
   This paper reports results from the genome-wide association study identifying a novel variant in the *NFIB* gene associated with increased clozapine metabolism and risk of underdosing and treatment failure
2. Impact of NFIB and CYP1A variants on clozapine serum concentration—A retrospective naturalistic cohort study on 526 patients with known smoking habits. Clin Transl Sci. 2023 Jan;16(1):62-72. doi: 10.1111/cts.13422
   This paper reports results from the study verifying the effects of NFIB and CYP1A genotypes, along with smoking habits, in reducing serum concentration of clozapine
3. The Polymorphic Nuclear Factor NFIB Regulates Hepatic CYP2D6 Expression and Influences Risperidone Metabolism in Psychiatric Patients. Clin Pharmacol Ther. 2022 May;111(5):1165-1174. doi: 10.1002/cpt.2571.
   This paper reports on results of *in vitro* studies showing that NFIB regulates drug metabolism via several enzymes, and hence probably dose requirements om many drugs other than clozapine. This supports the high relevance of this impact case.



4. Details of the impact

This the studies of this case provide evidence that pharmacogenetic variability is of substantial importance for the metabolism and risk of clozapine undertreatment in patients with resistant schizophrenia, which is among most severe psychiatric diagnoses. Patients suffering of treatment-resistant schizophrenia have failed on multiple antipsychotics before qualifying for clozapine use, a drug restricted due this condition due to superior effect but also most serious toxicity profile.

After initiating clozapine treatment, it is critical with symptom control as soon as possible, because treatment switch usually occurs in relation to a psychotic episode, where rapid response is very important. In addition, when treatment is effective, this usually motivates the patients to continue treatment. We have in large studies showed that the nonadherence rates of antipsychotic drugs are high but is significantly lower with clozapine than other antipsychotics (PMID 33221147). Thus, effective treatment indeed seems to reduce nonadherence in this patient population.

As the present impact case show, pharmacogenetics has a significant impact on dose requirements of clozapine to reach target concentrations. Several studies have shown that serum concentration should be above 350 ng/ml to obtain sufficient symptom reduction (PMID 34461790). In the two real-world studies included in this case, the risk of subtherapeutic concentrations, i.e. below 350 ng/ml, was 2-3-fold higher among smoking patients who carry the minor *NFIB C* allele compared non-smoking noncarriers. AS much as 5% of the patients with schizophrenia belong to the first group and require at least twice the dose as usually recommended of clozapine when starting treatment. For the psychiatrists to be confident in prescribing twice the dose of clozapine, they probably will request information to support this decision. A pharmacogenetic analysis can give the psychiatrist incentives to clozapine treatment at higher doses than recommended.

This impact case illustrates the importance of having access to information about multiple factors that affect individual variability in dose requirements. Here, we had access to smoking habits in addition to genotypes, age and gender. Without smoking habits, we would not have been able to detect the NFIB polymorphism's association to clozapine concentration. Factors that were not specifically focused on in the studies are drug-drug interactions. It is well known that e.g. concomitant use of the SSRIs fluvoxamine is potent inhibitor of clozapine metabolism (PMID 34461790).

In the clinical situation of personalized dosing, which is the main topic of the research in our group, the studies shows that access to multiple factors are required to predict dose recommendations on to individual patients with sufficient precision. This also illustrates the power of our large TDM database in research project in personalized medicine. In addition to information on multiple factors, access to multiple concentration measurements per patient imply that the statical analyses also become very robust.

An aspect with this case, which perhaps is the most important from a translational point of view, may the discovery that NFIB, a transcription factor involved in tissue differentiation, also regulates drug metabolism. This has never been reported before and in collaboration with Magnus Ingelman-Sundberg's group at the Karolinska institutet, it was shown that NFIB is involved in the regulation of other drug-metabolizing enzymes as well (ref. #3 above). Most importantly, it was found that NFIB regulates activity of the enzyme CYP2D6, which is responsible for the metabolism of many drugs, including antidepressants and antipsychotics. This finding may be significant for treatment of patients with psychiatric disorders and may open new avenues for identifying new mechanisms underlying the unexplained, hereditable variability in drug metabolism. Overall, this case from our research therefore illustrates the value of translational projects, as they both have

scientific and clinical beneficiaries. Furthermore, it is important to acknowledge our collaborating partners at UiO and KI, who played key roles in making this a successful research project.

Although not directly related to the present project, it is worth mentioning that the GWAS data from was pooled into a huge international population with schizophrenia aiming to identify gene variants associated with the risk of developing the disease. This collaborative study has resulted in two publications, one in Nature Genetics (2018) and one in Nature (2022), where Espen Molden, PI from Center for Psychopharmacology, is co-author. These publications are not relevant for the research at Center for Psychopharmacology, but they show the impact and relevance of the big data from this service that can be applied in innovative and novel research projects.

5. Sources to corroborate the impact

1. https://www.pharmgkb.org/clinicalAnnotation/1451356180. Clinical Annotation for rs28379954 (NFIB); clozapine; Schizophrenia (level 3 Metabolism/PK) in PharmGkb, which is one of the most important pharmacogenetic databases.
2. https://twitter.com/BousmanChad/status/1503205931231834113. Chad Bousman, a pioneer in pharmacogenetic research of mental disorders tweets that '*More evidence showing NFIB variant (rs28379954) regulates CYP450 enzymes. This time a 2-fold increase in risperidone metabolism among CYP2D6 normal metabolizers, similar to the rate of drug metabolism observed in CYP2D6 ultrarapid metabolizers*.'
3. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9804310/ A review article on substrates of different drug-metabolizing enzymes mentions NFIB as an important factor regulating enzyme activities.

Diakonhjemmet Hospital, Center for Psychopharmacology [Impact case #2]

Institution: Diakonhjemmet Hospital
Administrative unit: Center for Psychopharmacology
Title of case study: Impact of *CYP2C19* genotype on escitalopram metabolism, dosing, and antidepressant drug switch
Period when the underpinning research was undertaken: 2017-present
Period when staff involved in the underpinning research were employed by the submitting institution: 2007-present
Period when the impact occurred: 2018- present

2. Summary of the impact

Major depression is the most common mental disorder with a lifetime prevalence of 10-15%. Antidepressant drugs are often used in treatment of major depression with selective serotonin reuptake inhibitors (SSRIs) on top of the prescription list. Among SSRIs escitalopram is the most used one world-wide. However, as for other antidepressants, the individual variability in clinical response to SSRIs is extensive. The causality is complex and probably a mixture of biological heterogeneity of depression, pharmacokinetics (e.g. metabolism), pharmacodynamics (e.g. target protein expression or binding), placebo, and nonadherence. This complexity makes it difficult to study factors determining variability in response. However, during drug development the treatment response is dose dependent. Thus, as dose determines concentration, factors associated with variability in concentration, such as cytochrome P450 (CYP) metabolism, should be relevant for patient differences in effect and tolerability. Studies investigating associations between CYP genotypes and clinical response are therefore rational, but high degree of conflicting findings, probably due to complex causalities, prohibit implementation of CYP genotype-guided dosing of escitalopram and other SSRIs clinical practice. To overcome the inconsistency in results, large studies are required in real-world settings where the heterogeneity is high. For escitalopram it is well known that CYP2C19 genotype is the main factor causing variability in concentration. The clinical and societal impacts of conducting a conclusive study regarding the future role of genotype-guided dosing in escitalopram treatment are therefore high. Of the same reason, the potential benefits of identifying new variant increasing the precision of genotype-phenotype translations are substantial. Overall, these issues set the scene for studies on treatment outcomes in relation to escitalopram concentration, and to discover new variants predicting escitalopram metabolism. Discovery of genetic variants can effectively be implemented in clinical routine pharmacogenetic test panels, thereby improving the panels' relevance which further enhances impact of the project.

2. Underpinning research (indicative maximum 500 words)

Background:

It was known that escitalopram is metabolized by the polymorphic enzyme CYP2C19, but to which extent this had an impact on dosing and switch to other antidepressants in a real-world setting would provide evidence for the clinical relevance of this pharmacokinetic feature. Previous studies trying to link escitalopram and treatment outcome were small and underpowered, so larger studies were required to assess whether *CYP2C19* genotyping could be used as a tool to improve clinical response of this most use SSRI world-wide. A study to clarify thus the issue could be performed on a large population of *CYP2C19*-genotyped patients who also had been performed therapeutic drug monitoring (TDM) analyses of escitalopram. Furthermore, many patients genotyped as 'normal metabolizers' exhibit phenotypically ultra rapid CYP2C19 metabolism of escitalopram. With biobanked blood samples from patients with data on escitalopram concentration and metabolism, next generation sequencing (NGS) can identify possible novel variant encoding ultra rapid CYP2C9 metabolism.

Methods:

Part I. A study on 2,087 CYP2C19-genotyped patients with a total of 4,228 escitalopram serum concentration measurements were included from the TDM database at Center for Psychopharmacology (CfP). Information on drug dosing was available from the TDM requisition forms. For each patients the TDM profiles (histories) were reviewed based on information the database. This approach enabled identification of drug switch event, i.e. TDM of escitalopram being replaced by later TDM of another antidepressant drug (within 12 months). By coupling escitalopram concentrations, doses, and switch rates to CYP2C19 genotypes, a retrospective, real life study was performed. Tore Haslemo and Espen Molden (PI) (both Diakonhjemmet Hospital), and Magnus Ingelman-Sundberg and Marin Jukic (Karolinske institutet in Stockholm), were key study group researchers.

Part II. By NGS analyses of 24 patients showing very low serum concentrations of escitalopram at normal dosing, a study searching for unknown variants encoding rapid CYP2C19 metabolism was performed. Magnus Ingelman-Sundberg and Marin Jukic, researchers at the Karolinske institutet in Stockholm, were collaborators on this study as well. Marianne K. Kringen (PI), Line Bråthen and Espen Molden, all from CfP at Diakonhjemmet Hospital, and Magnus Ingelman-Sundberg and Marin Jukic, both from Karolinske institutet in Stockholm, were key study group researchers.

Main results:

Part I: Escitalopram serum concentrations were significantly increased 3.3-fold and 1.6-fold in patients genotype-predicted with absent ('poor metabolizers', PM) and intermediate metabolism (IM), respectively, compared patients interpreted as CYP2C19*1/*1 carriers (normal metabolizer, NM). For patients carrying the *CYP2C19*17* gain-of-function allele (ultrapid metabolizers, UM) had 10-15% lower escitalopram serum concentrations than CYP2C19 NMs. Switches from escitalopram to another antidepressant within 1 year were 3.3 and 3.0 times more frequent among the CYP2C19 PMs and CYP1C19 UMs, respectively. Daily dose of escitalopram was 30% lower in CYP2C19 PMs vs. NMs, whereas average doses were similar in UMs and NMs. Regarding dosing in PM vs. NM, a 70% lower dose would have been required in PMs to obtain the same concentration as in NMs.

The study (**part I**) was published open access in American Journal of Psychiatry (IF 19.2) in 2018.

In **Part II**, NGS analyses of 24 patients previously genotyped as *CYP2C19*1/*1* by a routine panel with stably low serum concentrations of escitalopram over time (< 25 nM/10 mg) showed found three new haplotypes of the CYP2C locus (*CYP2C:TG*, *CYP2C:TA*, and *CYP2C:CG*). The *CYP2C:CG* and *CYP2C:TA* haplotypes had no significant impact on escitalopram concentration, but . homozygous *CYP2C:TG* carriers showed a 24.8% lower escitalopram concentration compared with noncarriers. The increased metabolism encoded by this haplotype was consistent for different diplotypes.

The study (**part II**) was published in Clinical Pharmacology and Therapeutics (IF 7.1) in 2021.

Conclusions:

In a large, naturalistic cohort of escitalopram-treated patients, *CYP2C19* genotype was shown as a significant determinant of escitalopram concentration and dose requirements, and was also significantly associated with drug switch, as a surrogate measure of unsuccessful treatment probably reflecting side effects (PMs) or lacking effect (UMs). These findings provide evidence for

genotype-guided treatment of escitalopram with reduced dosing in CYP2C19 PMs to avoid drug switching. The causative relationship between escitalopram concentration and switch rate among CYP2C19 UMs is a bit unexpected, but still warrants for closer monitoring and higher dosing in this subgrup. The novel *CYP2C:TG* haplotype has the same effect on escitalopram metabolism as *CYP2C19*17*, and thus is expected to be associated increased switch rates as well, unless higher doses of escitalopram are prescribed in *CYP2C:TG* carriers. Overall, the impact case support that *CYP2C19* genotyped-guided dose predictions van be utilized for personalized medicine of escitalopram to prevent treatment switch.

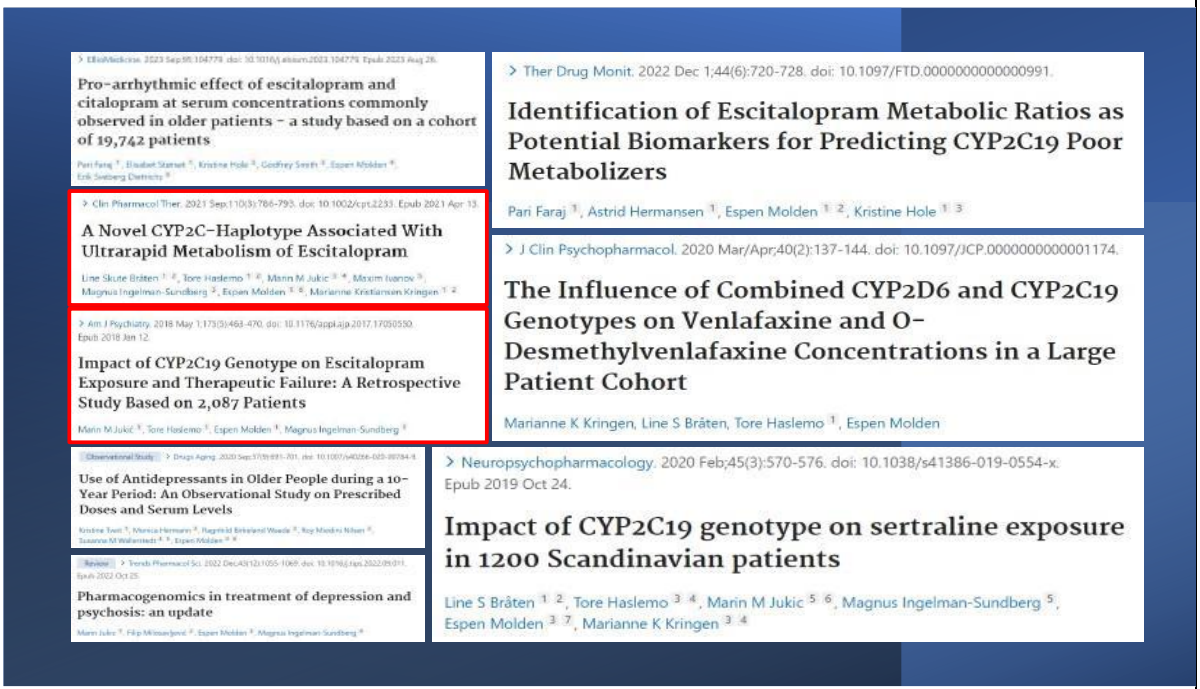
This impact case aligns with administrative unit's strategy of identifying and quantifying factors of importance for personalized dosing of patients with serious psychiatric disorders.

Follow up studies:

A follow study from Center for Psychopharmacology has already been performed, where impact of the *CYP2C:TG* haplotype on metabolism of sertraline, another SSRI also metabolized by CYP2C19, was investigated. The findings of this study showed that *CYP2C:TG* also encodes increased metabolism of sertraline to a similar extent as for escitalopram. Thus, the study confirmed that *CYP2C:TG* should be considered included in standard routine genotyping panels for personalized dosing of drugs metabolized by CYP2C19.

Future studies should investigate if preemptive, genotype-guided dosing of escitalopram and sertraline can prevent drug switch and increase treatment persistence with a prospective, randomized, controlled study design. In addition, it would be valuable to study the effects of the *CYP2C:TG* haplotype on metabolism of other CYP2C19 substrates than escitalopram and sertraline.

The findings of this impact cases align with the research strategy at Center for Psychopharmacology, where the importance of *CYP* pharmacogenetics on metabolism and effect of antidepressants has been investigated in many studies (c.f. Figure).



Papers on the pharmacogenetic impact on CYP metabolism and concentration/response of antidepressant drugs from studies conducted by the research group at Center for Psychopharmacology. Red frames indicate papers comprising the current impact case.

3. References to the research

4. Impact of CYP2C19 Genotype on Escitalopram Exposure and Therapeutic Failure: A Retrospective Study Based on 2,087 Patients. Am J Psychiatry 2018 May 1;175(5):463-470. doi: 10.1176/appi.ajp.2017.17050550
   This paper reports results from study showing a significant impact of *CYP2C19* genotype on concentration and drug switch rate of escitalopram to other antidepressants, which provide evidence that CYP2C19 metabolism is a factor associated with outcome of escitalopram treatment.
5. A Novel CYP2C-Haplotype Associated With Ultrarapid Metabolism of Escitalopram. Clin Pharmacol Ther. 2021 Sep;110(3):786-793. doi: 10.1002/cpt.2233.
   This paper reports results from a study identifying a novel *CYP2C* haplotype associated with increased metabolism of escitalopram, which considering the previous study may indicate increased risk of failure among patients carrying this haplotype.
6. Impact of the novel CYP2C:TG haplotype and CYP2B6 variants on sertraline exposure in a large patient population. Clin Transl Sci. 2022 Sep;15(9):2135-2145.doi: 10.1111/cts.13347
   This paper reports results from a study on sertraline metabolism and concentration in relation to presence of the *CYP2C:TG* haplotype, but also *CYP2B6* genotype. The study supports the *CYP2C:TG* haplotype encodes increased CYP2C19 metabolism.

4. Details of the impact

The studies of this case show that CYP2C19 metabolism determines escitalopram concentration with subsequent impact on the clinical outcome in treatment of patients with depression. A significant association between CYP2C19 genotype and rate of drug switch is relevant from a clinical point of view since treatment discontinuation is frequent in treatment of depression, especially in the early phase, which possibly is most important. While side effects may occur in the initiation phase, there is a time lag before treatment effect on depressive symptoms is obtained. Thus, if CYP2C19 genotyping and dose can reduce the risk of side effects during early phase and ensure good clinical effect after a couple of weeks of treatment, this will provide great benefits for the patients and their respective psychiatrists/general practitioners by increasing the chance of successful outcomes.

There is little doubt that knowledge from this research case, providing evidence for the clinical benefits of genotype-guided, personalized dosing of escitalopram (and sertraline), can have a substantial on health among patients suffering of depression, which is the common of all mental disorders. It remains to see whether the study will be a 'game-changer' towards increased use of pharmacogenetic testing pre-emptively to be ahead of problem, but from the significantly increased numbers of routine genotyping suggest that physicians have become more aware of this tool for decision-making when prescribing antidepressants. Many will always ask for more evidence, but from a pragmatic point of view it can be interpreted that dose dependent effects

found in clinical trial imply sufficient evidence for CYP genotyping as a tool for improved dosing, sinde genotype determines the 'biological dose' (i.e. serum concentration).

An important aspect with findings of this project, is that the frequencies of CYP2C19 variants vary a lot across different ethnic groups. For example in East Asians, the prevalence of CYP2C19 PMs is 15-30%, while the same proportion in White Europeans is 2-3%. As there are no differences in recommended doses of escitalopram between East Asian and European countries, the population risk of dose dependent side effects will be much higher among East Asians who are treated with escitalopram, and probably also sertraline. The ethnic aspect of pharmacogenetics is indeed something that should be studied more to succeed in implementing genotype-guided dose predictions in treatment with antidepressants and other psychiatric drugs for all patients.

5. Sources to corroborate the impact

4. Editorial in Am J Psych by Julia Stingl. https://pubmed.ncbi.nlm.nih.gov/29712478/. Selected article for an editorial comment discussing the clinical impact of the study findings and how they can be implemented in clinical practice.
5. Norwegian Ministry of Healthy, annual report from the Regional Health Trusts: https://www.helse-vest.no/499f84/siteassets/documents/planar-og-rapportar/documents/nasjonal-forsknings-og-innovasjonsrapport/forskning-og-innovasjon-til-pasientens-beste-2017.pdf. Presentation in the national report from the regional health trust to the ministry of health, where the 2018-study on escitalopram from Center for Psychopharmacology was selected as one of 10 national projects to the report.
6. Aftenposten: https://www.aftenposten.no/norge/i/3j4Jj9/100000-nordmenn-bruker-denne-pillen-mot-depresjon-naa-har-forskerne-funnet-svar-paa-hvorfor-behandlingen-svikter. An article in Aftenposten presenting main findings of the 2018-study on escitalopram.

Diakonhjemmet Hospital, Division of Rheumatology and Research – case #1

Institution: Diakonhjemmet Hospital
Administrative unit: Division of Rheumatology and Research
Title of case study: The ARCTIC trial – treatment strategies in rheumatoid arthritis
Period when the underpinning research was undertaken: 2010-2022
Period when staff involved were employed by the submitting institution: 2010-present
Period when the impact occurred: 2015-2022

1. Summary of the impact

The ARCTIC trial was a multicentre, randomised controlled trial (RCT) assessing whether a treatment strategy incorporating structured ultrasound assessment led to improved outcomes in rheumatoid arthritis (RA), compared with a conventional approach. Additionally, the study provided a unique opportunity to investigate the impact of modern treatment recommendations in an inception cohort of treatment-naïve early RA patients. The ARCTIC REWIND trial was designed in a continuum of the ARCTIC trial, assessing tapering and withdrawal of disease-modifying antirheumatic drugs in patients reaching remission. Results from the ARCTIC and ARCTIC REWIND trials have led to practice changing results, informing current treatment of patients with RA.

2. Underpinning research

Should the evaluation of patients with early RA include structured ultrasound?

The ARCTIC trial was conducted in Norway 2010-2015, and included 238 patients fulfilling 2010 criteria for RA (1). Participants were randomized to an ultrasound tight control strategy (targeting clinical and imaging remission) or a conventional tight control strategy (targeting clinical remission). Both groups followed the same drug escalation algorithm with 13 visits over two years. The primary endpoint was the proportion of patients with clinical remission, no swollen joints, and non-progression of radiographic joint damage between 16 and 24 months. Results revealed no significant difference in primary endpoint achievement between the two groups. Secondary outcomes, including disease activity, physical function, joint damage, and adverse events, were similar. We concluded that systematic use of ultrasound in the follow-up of early RA patients is not justified based on the study's results. The findings informed current recommendations and emphasize the importance of randomized trials to assess the clinical application of medical technology.

Seronegative and seropositive RA

Seronegative RA has been considered to represent a less severe disease subset than seropositive RA. We showed that after the implementation of 2010 classification criteria for RA, which put strong emphasis on serological status, seronegative patients have higher inflammatory activity compared to seropositive patients at time of diagnosis (2). Disease activity, remission rates and radiographic progression were similar in patients with seronegative and seropositive RA after 2 years of follow-up (3). However, treatment response was slower in seronegative than in seropositive patients, although all patients were treated according to the same algorithm.

Impact of ultrasound on intra-articular injections

We further assessed the value of ultrasound in relation to intra-articular glucocorticoid injections (4). We found that the efficacy of glucocorticoid injections varies according to ultrasound findings at the time of injection, supporting the use of ultrasound as a tool to select joints that will benefit from intra-articular injections. However, ultrasound needle guidance of injections was not superior to palpation guidance.

Predictive value of MRI and ultrasound

In this substudy we investigated the predictive value of inflammation detected by MRI or ultrasound in patients with early RA (5). We found that imaging-detected inflammation, both at

diagnosis and in remission, is associated with elements of future disease development. However, the lack of a significant effect on prediction models indicates limited value of systematic MRI and ultrasound in clinical management of early RA.

The value of calprotectin in rheumatoid arthritis

Calprotectin is a potential inflammatory marker that could contribute to the understanding of inflammatory burden in rheumatoid arthritis. This project assessed calprotectin in the ARCTIC cohort, with results indicating that calprotectin did not add important clinical information (6).

Understanding of rheumatoid arthritis remission

Remission is the preferred treatment target in rheumatoid arthritis, and several different remission criteria have been developed. Data from ARCTIC have been used to provide novel understanding of how achieving different remission definitions is associated with future joint damage and physical function (7)

Tapering and discontinuation of treatment in rheumatoid arthritis remission

The ARCTIC REWIND trial was designed in a continuum of ARCTIC, as a multicenter, randomized trial, assessing the impact of tapering conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) on the risk of flares in rheumatoid arthritis patients in sustained remission (8). 160 patients with RA on stable csDMARD therapy were randomly assigned between 2013-2018 to half-dose or stable-dose csDMARDs. Results showed half-dose csDMARDs did not demonstrate non-inferiority for disease flares over 12 months compared to stable-dose therapy. Flares occurred in 25% of the half-dose group versus 6% in the stable-dose group. The study concluded that half-dose therapy is not supported for RA patients in remission on csDMARDs.

The ARCTIC REWIND project additionally included a separate study on tapering of TNF inhibitors (a type of biologic treatment) in the same patient group, but this study was published in 2023 and thus not included in this overview.

Details of staff conducting the underpinning research from the admin unit:

Key researchers (name)	Roles(s):	Period employed:
Espen A. Haavardsholm	PI ARCTIC (2010-), ARCTIC REWIND (2013-2020)	2012-present
Siri Lillegraven	Project lead (2013-) and PI (2020-) of ARCTIC REWIND	2012-present
Anna-Birgitte Aga	Local PI and PhD-fellow ARCTIC, thesis 2016, postdoc ARCTIC and ARCTIC REWIND	2012-present
Lena Nordberg	PhD-fellow ARCTIC, thesis 2019, postdoc ARCTIC	2015-present
Ulf Sundin	PhD-fellow ARCTIC, thesis 2021	2018-present
Nina Sundlisæter	Local PI and PhD-fellow ARCTIC REWIND, thesis 2020, postdoc ARCTIC REWIND	2016-present
Tore K. Kvien	Medical lead ARCTIC/ARCTIC	2012-present
Joe Sexton	Biostatistician	2014-present

3. References to the research

1) **Haavardsholm EA, Aga AB, Olsen IC, Lillegraven S, Hammer HB, Uhlig T**, Fremstad H, Madland TM, Lexberg ÅS, Haukeland H, Rødevand E, Høili C, Stray H, Noraas A, Hansen IJ, Bakland G, **Nordberg LB,** van der Heijde D**, Kvien TK.** Ultrasound in management of rheumatoid arthritis: ARCTIC randomised controlled strategy trial. 2016 DOI: 10.1136/bmj.i4205. *The main publication of the ARCTIC trial concluded that systematic ultrasound use in early RA follow-up, is not justified when compared to conventional follow-up.*

2) **Nordberg LB, Lillegraven S, Lie E, Aga AB, Olsen IC, Hammer HB, Uhlig T, Jonsson MK, van der Heijde D, Kvien TK, Haavardsholm EA**; and the ARCTIC working group Patients with seronegative RA have more inflammatory activity compared with patients with seropositive RA in an inception cohort of DMARD-naïve patients classified according to the 2010 ACR/EULAR criteria. 2017 DOI: 10.1136/annrheumdis-2015-208873 *The implementation of 2010 RA*

classification criteria revealed higher inflammatory activity in seronegative patients at diagnosis, challenging the perception of seronegative RA as less severe.

3) **Nordberg LB, Lillegraven S, Aga AB, Sexton J, Olsen IC, Lie E, Berner Hammer H, Uhlig T, van der Heijde D, Kvien TK, Haavardsholm EA** Comparing the disease course of patients with seronegative and seropositive rheumatoid arthritis fulfilling the 2010 ACR/EULAR classification criteria in a treat-to-target setting: 2-year data from the ARCTIC trial. 2018 DOI: 10.1136/rmdopen-2018-000752. *The study showed similar disease courses but slower treatment responses in seronegative patients compared to seropositive patients.*

4) **Nordberg LB, Lillegraven S, Aga AB, Sexton J, Lie E, Hammer HB, Olsen IC, Uhlig T, van der Heijde D, Kvien TK, Haavardsholm EA** The Impact of Ultrasound on the Use and Efficacy of Intraarticular Glucocorticoid Injections in Early Rheumatoid Arthritis: Secondary Analyses From a Randomized Trial Examining the Benefit of Ultrasound in a Clinical Tight Control Regimen. 2018 DOI: 10.1002/art.40494. *The ARCTIC substudy demonstrated that ultrasound aids in selecting joints for glucocorticoid injections, aligning treatment with individual joint needs. However, ultrasound guidance did not outperform palpation guidance.*

5) **Sundin U, Sundlisater NP, Aga AB, Sexton J, Nordberg LB, Hammer HB, van der Heijde D, Kvien TK, Haavardsholm EA, Lillegraven S**; the ARCTIC Study Group. Value of MRI and ultrasound for prediction of therapeutic response and erosive progression in patients with early rheumatoid arthritis managed by an aggressive treat-to-target strategy. 2021 DOI: 10.1136/rmdopen-2020-001525*The investigation into the predictive value of imaging-detected inflammation highlighted associations with future disease development. Yet, the limited effect on prediction models questioned the widespread use of systematic MRI and ultrasound in early RA management.*

6) **Jonsson MK, Sundlisæter NP**, Nordal HH, **Hammer HB, Aga AB, Olsen IC**, Brokstad KA, **van der Heijde D, Kvien TK**, Fevang BS, **Lillegraven S, Haavardsholm EA**. Calprotectin as a marker of inflammation in patients with early rheumatoid arthritis. 2017 DOI: 10.1136/annrheumdis-2017-211695 *The study examined the potential role of calprotectin in early rheumatoid arthritis, and concluded that no clinical benefit was added.*

7) **Paulshus Sundlisæter N, Aga AB, Olsen IC, Hammer HB, Uhlig T, van der Heijde D, Kvien TK, Lillegraven S, Haavardsholm EA**; ARCTIC study group. Clinical and ultrasound remission after 6 months of treat-to-target therapy in early rheumatoid arthritis: associations to future good radiographic and physical outcomes. 2018DOI: 10.1136/annrheumdis-2017-212830 *This report assessed how different definitions of remission were able to identify patients with good future radiographic and functional outcome, with support to current remission criteria.*

8) **Lillegraven S, Paulshus Sundlisæter N, Aga AB, Sexton J,** Olsen IC, Fremstad H, Spada C, Madland TM, Høili CA, Bakland G, Lexberg Å, Hansen IJW, Hansen IM, Haukeland H, Ljoså MA, **Moholt E, Uhlig T**, Solomon DH, **van der Heijde D, Kvien TK, Haavardsholm EA**. Effect of Half-Dose vs Stable-Dose Conventional Synthetic Disease-Modifying Antirheumatic Drugs on Disease Flares in Patients With Rheumatoid Arthritis in Remission: The ARCTIC REWIND Randomized Clinical Trial. 2021 DOI: 10.1001/jama.2021.4542

In the continuation trial ARCTIC REWIND, tapering conventional synthetic disease-modifying drugs (csDMARDs) for RA patients in sustained remission was assessed. Results indicated that half-dose csDMARD therapy lacked non-inferiority for preventing flares over 12 months, advising against its use.

4. Details of the impact

Underpinning Research, nature and extent of the impact

Ultrasound in the management of RA: The ARCTIC trial, conducted in Norway from 2010 to 2015, aimed to assess the impact of a treatment strategy based on structured ultrasound assessment on rheumatoid arthritis (RA) outcomes. The trial, involving 238 patients, concluded that systematic ultrasound use in early RA follow-up, according to current recommendations, is not justified. Subsequent substudies refined the understanding of seronegative and seropositive RA, the value of ultrasound in intra-articular injections, and the predictive value of MRI and ultrasound.

Seronegative and Seropositive RA: The implementation of 2010 RA classification criteria revealed higher inflammatory activity in seronegative patients at diagnosis, challenging the perception of seronegative RA as less severe. The study also showed similar disease courses but slower treatment responses in seronegative patients.

Ultrasound in Intra-Articular Injections: The ARCTIC substudy demonstrated that ultrasound aids in selecting joints for glucocorticoid injections, aligning treatment with individual joint needs. However, ultrasound guidance did not outperform palpation guidance.

Predictive Value of MRI and Ultrasound: The investigation into the predictive value of imaging-detected inflammation highlighted associations with future disease development. Yet, the limited effect on prediction models questioned the widespread use of systematic MRI and ultrasound in early RA management.

ARCTIC REWIND trial: In the continuation trial ARCTIC REWIND, tapering conventional synthetic disease-modifying drugs (csDMARDs) for RA patients in sustained remission was assessed. Results indicated that half-dose csDMARD therapy lacked non-inferiority for preventing flares over 12 months, advising against this approach.

Process Leading to Impact:

The impact stemmed from two rigorous randomized controlled trials exploring various aspects of RA management. In addition, a large number of substudies have contributed nuanced insights, influencing perceptions of seronegative RA severity, optimizing intra-articular injections, and challenging the widespread adoption of extensive imaging in RA care. Both trials were designed, financed, coordinated, conducted, reported and disseminated by the administrative unit, but included both national and international collaborators. The involvement of almost all Norwegian rheumatology departments in the two trials established this research as a national effort, and secured that the results were translated into clinical practice. The international advisors and collaborators contributed to the study design, ensuring that the results also would be of relevance to an international audience. The primary results from both trials were reported as oral presentations at the main international congresses within rheumatology, the ACR and EULAR congresses, and were published in generic medical journal with a high international impact, the ARCTIC trial in BMJ in 2016, and the ARCTIC REWIND trial in JAMA in 2021 (and additionally after the relevant period, in 2023). The 2021 JAMA publication was accompanied by an editorial especially focusing on the clinical relevance, further highlighting the results.

The research has been conducted by a dedicated research group. Within the time period, eight PhD students have worked on data from the trials, with important contributions to the dissemination of the results through numerous presentations nationally and internationally and about 35 publications in leading international journals up until today.

Beneficiaries:

Clinical Practitioners: Rheumatologists and healthcare professionals in Norway and beyond have benefitted from refined and knowledge based treatment approaches based on the ARCTIC and ARCTIC REWIND trials, as well as the substudies.

Patients with RA: Enhanced understanding of RA subtypes and optimized treatment strategies directly benefit patients, ensuring tailored and effective care with improved outcomes.

Healthcare Systems: RA is a chronic disease, which for most patients require lifelong treatment. A sustainable organisation of care for the patient group is thus necessary to ensure optimal use of healthcare resources. It is highly relevant that the examinations performed at each patient visit should contribute important information. The ARCTIC trial showed that an extensive structured ultrasound examination was not necessary to detect inflammation, and thus would not be necessary as part of standard care. These results contribute to more cost-effective and efficient healthcare practices.

Nature of the Impact:

Clinical Guidelines: The ARCTIC and ARCTIC REWIND trial findings have influenced the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) guidelines for

managing RA, promoting a more focused and efficient approach. In addition, the Norwegian recommendations for managing RA have largely been developed based on the insights gained from the management strategies employed in the ARCTIC trial.

Point-of-Care ultrasound: The adoption of ultrasound at the point of care for joint assessment is now widespread. Clinicians can rely on clinical skills without the need for extensive and costly ultrasound examinations, but apply ultrasound for focused assessment, in the diagnostic work-up or for selecting joints for i.a. injections.

Evidence of Impact:

Guideline adoption: The incorporation of ARCTIC trial results into ACR and EULAR guidelines, as well as Norwegian recommendations, serves as a tangible indicator of its impact on clinical practices.

Healthcare efficiency: Reduced reliance on extensive ultrasound examinations is evidence of improved healthcare efficiency, benefiting both practitioners and patients.

In summary, the ARCTIC trial and its substudies as well as the ARCTIC REWIND trial have significantly impacted the management of RA, influencing guidelines, refining treatment strategies, and promoting more efficient healthcare practices. These findings have had a far-reaching and positive effect on clinical practitioners, patients, and healthcare systems.

5. Sources to corroborate the impact

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9) **Lillegraven S, Haavardsholm EA.** Subclinical Treatment Targets in Rheumatology: Lessons from Randomized Clinical Trials in Rheumatoid Arthritis. 2019 DOI: 10.1016/j.rdc.2019.07.007
10) Cush J. ARTIC REWIND - Don't Half DMARD Therapy, RheumNow, 06-05-2021.

Diakonhjemmet Hospital, Division of Rheumatology and Research – case #2

Institution: Diakonhjemmet Hospital
Administrative unit: Division of Rheumatology and Research
Title of case study: The ESpA-study – paving the way for high intensity aerobic exercise in patients with inflammatory joint diseases
Period when the underpinning research was undertaken: 2012-2022
Period when staff involved were employed by the submitting institution: 2012-present
Period when the impact occurred: 2014-2022

1. Summary of the impact

Inflammatory joint diseases (IJDs) are characterized by systemic inflammation, joint pain, fatigue and dysfunction, often alongside an array of comorbidities. Exercise recommendations have traditionally favored gentle exercises. However, given the elevated risk of cardiovascular diseases (CVD) following IJDs, cardiorespiratory exercise has emerged as a potential disease modifying treatment alternative, capable of modulating both inflammatory and CVD pathways. Through the ESpA and ExeHeart trials, we have unraveled the effect, feasibility and tolerability of high intensity aerobic exercise in reducing disease activity and CVD risk in patients with IJD. This have paved way for a paradigm shift in physiotherapy strategies.

2. Underpinning research

2012-2017:

Studies preparing for the ESpA-study (presented below)

1: Physical fitness in patients with axial spondyloarthritis (axSpA) was explored in a cross-sectional study (2012). Key findings: axSpA patients had significantly lower VO^2 peak than matched healthy controls, disease activity was inversely associated with VO^2 peak in patients and cardiorespiratory fitness was associated with favorable levels of CV risk factors in patients and controls (2013). Higher levels of circulating inflammatory cytokines and cytokine receptors were found in patients than in controls (2014).

2: Pilot-study (preparing for the ESpA-study): significant treatment effects were seen on disease activity, arterial stiffness, VO^2 peak (ml/kg/min) and trunk fat. No adverse events occurred. Conclusions: high intensity exercise improved disease activity and reduced CV risk factors in patients with active axSpA. Finding should be confirmed in a full-scale RCT.

3: A systematic review with meta-analyses was conducted, investigating effects of cardiorespiratory and strength exercises on disease activity for patients with IJDs (2017), confirming potential beneficial effects of exercise.
Key research insight: the initial studies strengthened the rationale for further investigation of disease modifying effects of aerobic exercise in IJD.

2019-2022: The ESpA-study

Large multicenter RCT including 100 patients with axSpA. Key findings: significant, beneficial effects of high intensity interval training (HIIT) on disease activity, inflammation, physical function and CV-health (2019). A qualitative study was performed to capture participants' experiences with HIIT. Key findings: rapid bodily effects strengthened the respondents' self-efficacy and faith in their own bodies.
Research insight: The results of the ESpA-study debunked concerns that high intensity exercise might exacerbate disease activity in patients with axSpA.

2020-2022

The ExeHeart study was based on logistics and results of the ESpA-study but had a broader scope and included all IJDs. Study aims were to examine the effects of HIIT on cardiorespiratory fitness, CVD risk and disease activity in patients with IJDs (protocol 2022), to implement HIIT in primary health care and to test the validity of fitness calculators (studies published 2022-2023).

Key contextual information

The overall aim of the ESpA and ExeHeart studies was to develop more effective non-pharmacological treatment for patients with IJD, targeting both inflammatory and CVD pathways. The studies were carried out with solid methods. Patient research partners have significantly influenced all phases of the research. The results have informed international treatment recommendations (EULAR2018), facilitating dissemination of the results.

An advanced test-laboratory is established at Diakonhjemmet Hospital, resulting in a paradigm shift in clinical practice for many patient-groups. Several hospital departments, including the Norwegian National Unit for Rehabilitation for Rheumatic Patients with Special Needs, now offer thorough test of cardiorespiratory fitness and the ESpA-treatment model. Implementation into primary health care was explored in the ExeHeart study. Cardiorespiratory fitness calculators have been validated for use in clinical practice. An article was recently published, although it falls outside the assessment period. The dissemination of research insights and findings is ensured by the senior researchers' extensive teaching at all educational levels.

Details of staff conducting the underpinning research from the admin unit:

Key researchers (name):	Roles(s):	Period employed:
Hanne Dagfinrud	Project lead (ESpA)	2012-present
Silje H Sveaas	PhD fellow (underpinning research ESpA), Postdoc (ESpA), PI (ESpA)	2012-2019
Anne Therese Tveter	Project lead (ExeHeart)	2020-present
Kristine Norden	PhD fellow (ExeHeart)	2020-present
Camilla Fongen	Research assistant	2012-present
Anne Grete Semb	Research group	2012-present
Sella Provan	Research group	2012-present
Inger Jorid Berg	Research group	2012-present
Joe Sexton	Statistician, research group	2020-present
Gerd J Aanerud	Patient research partner	2012-2015
Thalita Blanck	Patient research partner	2012-2017

3. References to the research

1) **Sveaas SH, Berg IJ, Provan SA, Semb AG, Hagen KB**, Vøllestad N**, Fongen C, Olsen IC**, Michalsen A, Ueland T, Aukrust P**, Kvien TK, Dagfinrud H**. Efficacy of high intensity exercise on disease activity and cardiovascular risk in active axial spondyloarthritis: a randomized controlled pilot study. 2014 DOI: 10.1371/journal.pone.0108688 *Single-blinded pilot-RCT, including 24 patients, verified the logistics and feasibility of HIIT in patients with active SpA. Significant treatment effects were found for disease activity, physical fitness and cardiovascular risk factors. No adverse events.*
2) **Sveaas SH, Smedslund G, Hagen KB, Dagfinrud H**. Effect of cardiorespiratory and strength exercises on disease activity in patients with inflammatory rheumatic diseases: a systematic review and meta-analysis. 2017 DOI: 10.1136/bjsports-2016-097149 *The systematic review and meta-analysis included 26 RCTs with a total of 1286 patients, providing solid evidence for beneficial effects of exercise programs (dosed according to recommendations for improving fitness) on disease activity, pain and erythrocyte sedimentation rate.*
3) **Sveaas SH**, Bilberg A**, Berg IJ, Provan S, Rollefstad S, Semb AG, Hagen KB**, Johansen MW, Pedersen E, **Dagfinrud H**. High intensity exercise for 3 months reduces disease activity in axial spondyloarthritis (axSpA): a multicentre randomised trial of 100 patients. 2020 DOI:10.1136/bjsports-2018-099943 *Multicenter RCT, including 100 patients. In addition to significant effects of high intensity interval training (HIIT) on disease activity, inflammation, physical function and CV-health, the study was also strengthened by high adherence, no adverse events*
4) Bilberg A, **Sveaas SH, Dagfinrud H**, Mannerkorpi K. How Do Patients With Axial Spondyloarthritis Experience High-Intensity Exercise? 2020 DOI: 10.1002/acr2.11128*Interviews of participants in ESpA-trial, analyzed with qualitative content analysis, including both manifest content and interpretations of underlying latent meaning. Respondents experienced that HIIT*

provided rapid bodily effects that strengthened their faith in their own bodies, enhanced their motivation, exercise self-efficacy and adherence to the exercise program.

5) **Sveaas SH, Dagfinrud H, Berg IJ, Provan SA,** Johansen MW, Pedersen E, Bilberg A. High-Intensity Exercise Improves Fatigue, Sleep, and Mood in Patients With Axial Spondyloarthritis: Secondary Analysis of a Randomized Controlled Trial 2020 DOI: 10.1093/ptj/pzaa086 *Secondary analyses of the ESpA-trial, showing that high intensity interval training had beneficial effect on fatigue, sleep, mood and general health.*
6) **Nordén KR, Dagfinrud H, Semb AG,** Hisdal J, **Viktil KK, Sexton J, Fongen C, Skandsen J, Blanck T**, Metsios GS, **Tveter AT**. Effect of high-intensity exercise on cardiorespiratory fitness, cardiovascular disease risk and disease activity in patients with inflammatory joint disease: protocol for the ExeHeart randomised controlled trial 2022 DOI: 10.1136/bmjopen-2021-058634. *Protocol article. The results of the ExeHeart study published January 2023*

4. Details of the impact

Spondyloarthitis (SpA) is an inflammatory rheumatic joint disease (IJD) manifesting in young adulthood, typically reaching its most active phase during formative years when education, work life and family are established. Treatment recommendations encompass relevant medication and self-management strategies. Considering the aim to protect joints, alleviate pain, and accommodate the fact that patients with IJD are often afflicted by fatigue, best clinical practice has been regarded gentle, non-exhaustive stretching and mobility exercises.

However, recent research has shown that systemic inflammation increases the risk of cardiovascular diseases (CVD). Given that SpA starts early in life and follows a chronic course, it is important to mitigate the negative effects of the disease while simultaneously reducing the risk of CVD. This was the basis for our investigation into whether non-pharmacological interventions could be better utilized, aiming to offer exercise methods that serve a broader purpose than solely maintaining or improving joint mobility.

Cardiorespiratory training, especially in the form of high-intensity aerobic exercise (HIIT), is established as an effective method for improving CV health. Such training methods have traditionally been deemed unsuitable for patients with IJD, as it has been assumed that the intensive form would exacerbate disease activity (expressed as a combination of pain, stiffness and inflammation).

With the goal of offering the most optimal, disease modifying non-pharmacological treatment for patients with IJD, our research focus since 2012 has been to examine the effects, tolerance, feasibility and experience of HIIT. A knowledge base was established through a systematic review and meta-analysis focusing on the effects of cardiorespiratory and strength exercises on disease activity in patients with IJD (2017). The meta-analysis comprised 26 randomized controlled trials (RCTs) with a total of nearly 1300 patients, randomized to training (dosed according to recommendations for improving fitness) or control. The results showed overall positive treatment effects, and importantly, the typical clinical features such as pain, stiffness, and fatigue did not worsen. The results informed treatment recommendations formulated by EULAR (European League Against Rheumatism) and constituted a crucial support pillar for the further work in our research group.

The meta-analysis was, however, based on interventions with moderate intensity, and with the evidence for importance of intensity for CV effects, we wanted to test the effect, feasibility and tolerance of HIIT in patients with active SpA. We conducted a pilot RCT (2014), showing that the training modality was feasible and yielded promising results. This laid the groundwork for a full-scale RCT including 100 SpA patients (ESpA-study). The main results (2020) showed that the training modality had expected effects on heart health, in addition to the crucial finding that patients with active inflammatory disease could complete the training and benefit from the positive effects without worsening disease activity (pain, stiffness, fatigue, inflammation).

However, a concern from both clinicians and patients has been that patients with SpA might not perceive HIIT as an acceptable form of exercise. To gain insight into participants' experiences, we

conducted a qualitative study based on interviews with 14 study-participants (2020). Among the most important results were that supervised HIIT was perceived as a challenging, but positive experience, with rapid bodily effects that strengthened respondents' motivation and self-efficacy for exercise and strengthened their adherence to the program.

As a further step in extending knowledge about exercise as treatment for IJD, the ExeHeart study was initiated in 2020. The study aims were to investigate the effects of HIIT on fitness, CVD risk, and disease activity in all IJDs (spondyloarthritis, rheumatoid arthritis, psoriatic arthritis). Additionally, we want to examine the feasibility of implementing HIIT in primary health care and to provide evidence for validity of simple calculators to estimate oxygen uptake by means of algorithms, for use in clinical practice. Physiotherapists in primary healthcare were trained to carry out the intervention in the ExeHeart study.

Through groundbreaking research in the ESpA and ExeHeart-studies, we have established the effect and tolerability of HIIT in improving disease activity and CVD risk in patients with IJD. The findings have facilitated a paradigm shift in physiotherapy strategies, and more optimal, effective and self-managed treatment alternatives can be offered patients with lifelong inflammatory rheumatic diseases.
The ESpA and ExeHeart studies have been conducted with high methodological quality and have yielded clear results. Patient representatives have significantly influenced all phases of this research, from planning to dissemination. The findings and experiences from the studies have been disseminated through various channels; lectures and articles in patient organizations and magazines, websites, social media, podcasts, daily and weekly press and health care students at all educational levels**.**

5. Sources to corroborate the impact

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2) Rausch Osthoff AK, Niedermann K, Braun J, Adams J, Brodin N, **Dagfinrud H,** Duruoz T, Esbensen BA, Günther KP, Hurkmans E, Juhl CB, Kennedy N, Kiltz U, Knittle K, Nurmohamed M, Pais S, Severijns G, Swinnen TW, Pitsillidou IA, Warburton L, Yankov Z, Vliet Vlieland TPM. 2018 EULAR recommendations for physical activity in people with inflammatory arthritis and osteoarthritis 2018 DOI: 10.1136/annrheumdis-2018-213585
3) van der Heijde D, Ramiro S, Landewé R, Baraliakos X, Van den Bosch F, Sepriano A, Regel A, Ciurea A, **Dagfinrud H**, Dougados M, van Gaalen F, Géher P, van der Horst-Bruinsma I, Inman RD, Jongkees M, Kiltz U, Kvien TK, Machado PM, Marzo-Ortega H, Molto A, Navarro-Compàn V, Ozgocmen S, Pimentel-Santos FM, Reveille J, Rudwaleit M, Sieper J, Sampaio-Barros P, Wiek D, Braun J. 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. 2017 DOI: 10.1136/annrheumdis-2016-210770.
4) Participating in a Delphi study informing a global strategy to improve musculoskeletal health, conducted by Global Alliance for Musculoskeletal Health (G-MUSC), University of Sydney, Australia. Towards a global strategy to improve musculoskeletal health. 2021

Podcast:

5) Spondyloartritt m/ Hanne Dagfinrud (Norwegian), PAIN – a podcast about musculoskeletal pain
6) Cold winter (Norwegian), The Norweigan Rheumatism Association

Webinar:

7) Correct training and diet (Norwegian), The Norweigan Rheumatism Association
8) Exercise with spondylarthritis (Norwegian), The Spondyloarthritis Patient Organisation (SPAFO)

Diakonhjemmet Hospital, Division of Rheumatology and Research – case #3

Institution: Diakonhjemmet Hospital
Administrative unit: Division of Rheumatology and Research
Title of case study: NOR- SWITCH – driving the switch from originator to biosimilar infliximab
Period when the underpinning research was undertaken: 2014-2020
Period when staff involved in the underpinning research were employed by the submitting institution: 2014-2022
Period when the impact occurred: 2017-2022
Summary of the impact Due to the high costs associated with biological medicines, healthcare systems in many countries have been unable to adopt such treatment for patients with immune mediated inflammatory diseases. The NOR-SWITCH study opened the doors to biosimilar medicines, about which there were previously much skepticism. The fact that the study had many participants, was fully funded through Norway's government and had no ties to the pharmaceutical industry helped give the study credibility. In countries with a weak economy, the patients have an equally great need for biological medicines, but cannot afford them. The acceptance of biosimilars, which the NOR-SWITCH study helped bring about, is now changing that.

2. Underpinning research

The NOR-SWITCH study examined switching from originator infliximab (a tumor necrosis factor inhibitor) to biosimilar CT-P13 regarding efficacy, safety, and immunogenicity. The study was funded by the Norwegian government.

The NOR-SWITCH trial was a randomised, non-inferiority, double-blind, phase 4 trial with 52 weeks follow-up. Adult patients on stable treatment with infliximab originator treated for at least 6 months were eligible. Patients in 40 Norwegian study centres were randomised 1:1 to either continued infliximab originator or switch to CT-P13 treatment, with unchanged dosing regimen. Patients, assessors, and patient care providers were masked to treatment allocation. The primary endpoint was disease worsening during 52-week follow-up.

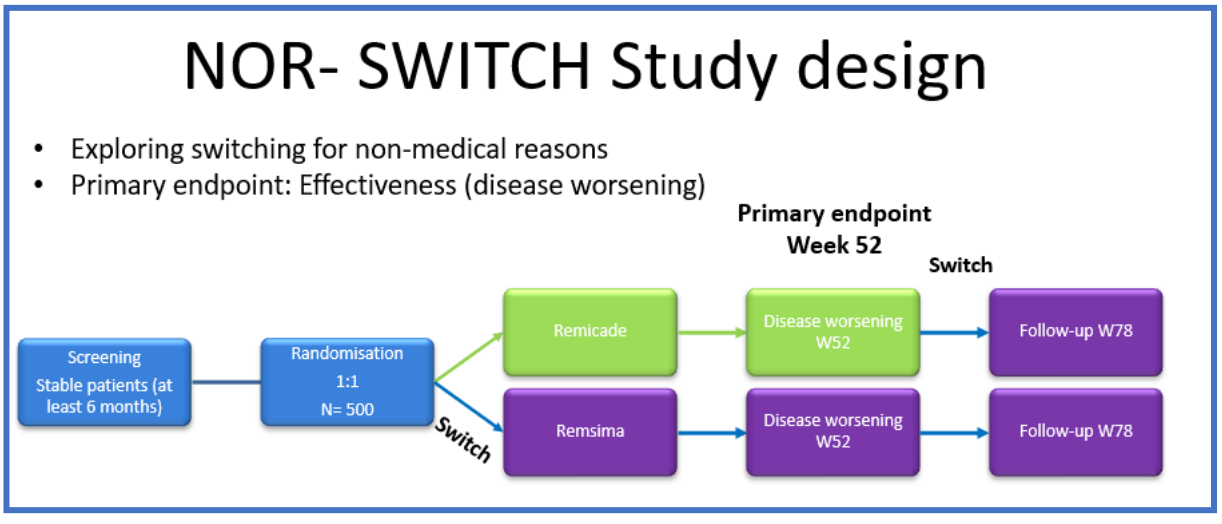

Figure 1 NOR-SWITCH study design

Findings Between Oct 24, 2014, and July 8, 2015, 482 patients were randomised, 32% of patients had Crohn's disease, 19% ulcerative colitis, 19% spondyloarthritis, 16% rheumatoid arthritis, 6% psoriatic arthritis, and 7% chronic plaque psoriasis. 408 patients were included in the per-protocol dataset. Disease worsening occurred in 26% of patients in the originator group and 30% of patients in the CT-P13 group (per-protocol set; adjusted treatment difference –4·4%, 95% CI –12·7 to 3·9). Frequency of adverse events was similar between groups (serious adverse events, 24 [10%] for infliximab originator *vs* 21 [9%] for CT-P13; for overall adverse events, 168 [70%] *vs* 164 [68%]). Similarity was also observed for secondary efficacy endpoints and for variables reflecting immunogenicity (drugs levels, formation of anti-drug antibodies).

Interpretation Switching from infliximab originator to CT-P13 was not inferior to continued treatment with originator according to a prespecified 15% non-inferiority margin. The study was not powered to show non-inferiority in individual diseases.

The NOR-SWITCH extension trial assessed efficacy, safety and immunogenicity in patients on CT-P13 throughout the 78-week study period (maintenance group) versus patients switched to CT-P13 at week 52 (switch group). Primary outcome was disease worsening during follow-up. and included 380 of the 438 patients who completed the main study: 197 in the maintenance group and 183 in the switch group.

Baseline characteristics were similar in the two groups at the time of switching (week 52). Disease worsening occurred in 32 (1.8%) patients in the maintenance group vs. 20 (11.6%) in the switch group (per-protocol set). Adjusted risk difference was 5.9% (95% CI -1.1 to 12.9). Frequency of adverse events, anti-drug antibodies, changes in generic disease variables and disease-specific composite measures were comparable between arms.

The NOR-SWITCH extension showed no difference in safety and efficacy between patients who maintained CT-P13 and patients who switched from originator infliximab to CT-P13, supporting that switching from originator infliximab to CT-P13 is safe and efficacious.

Details of staff conducting the underpinning research from the admin unit:

Key researchers (name)	Roles(s):	Period employed:
Tore K Kvien	PI NOR- SWITCH	2014-present
Guro L Goll	Study coordinator for rheumatology	2014-present
Espen A. Haavardsholm	Study methodologist	2014-present
Inge C. Olsen	Study statistician	2014-2018

3. References to the research

1. Jørgensen KK, **Olsen IC, Goll GL**, Lorentzen M, Bolstad N, **Haavardsholm EA**, Lundin KEA, Mørk C, Jahnsen J, **Kvien TK**; NOR-SWITCH study group. Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial. Lancet 2017 DOI: 10.1016/S0140-6736(17)30068-5 *This paper reports on the efficacy and safety of switching from originator to biosimilar infliximab across inflammatory and reach the important conclusion that such a switch was not inferior to continued treatment with the originator compound.*

2. **Goll GL**, Jørgensen KK, **Sexton J, Olsen IC,** Bolstad N, **Haavardsholm EA**, Lundin KEA, Tveit KS, Lorentzen M, Berset IP, Fevang BTS, Kalstad S, Ryggen K, Warren DJ, Klaasen RA, Asak Ø, Baigh S, Blomgren IM, Brenna Ø, Bruun TJ, Dvergsnes K, Frigstad SO, Hansen IM, Hatten ISH, Huppertz-Hauss G, Henriksen M, Hoie SS, Krogh J, Midtgard IP, Mielnik P, Moum B, Noraberg G, Poyan A, Prestegård U, Rashid HU, Strand EK, Skjetne K, Seeberg KA, Torp R, Ystrøm CM, Vold C, Zettel CC, Waksvik K, Gulbrandsen B, Hagfors J, Mørk C, Jahnsen J, **Kvien TK.** Long-term efficacy and safety of biosimilar infliximab (CT-P13) after switching from originator infliximab: open-label extension of the NOR-SWITCH trial. 2019 DOI: 10.1111/joim.12880. *In this extension of the main study, we report results on efficacy and safety 26 weeks and 78 weeks after switching from originator to biosimilar infliximab*

3. Jørgensen KK, **Goll GL, Sexton J,** Bolstad N, Olsen IC, Asak Ø, Berset IP, Blomgren IM, Dvergsnes K, Florholmen J, Frigstad SO, Henriksen M, Hagfors J, Huppertz-Hauss G, **Haavardsholm EA**, Klaasen RA, Moum B, Noraberg G, Prestegård U, Rydning JH, Sagatun L, Seeberg KA, Torp R, Vold C, Warren DJ, Ystrøm CM, Lundin KEA, **Kvien TK**, Jahnsen J. Efficacy and Safety of CT-P13 in Inflammatory Bowel Disease after Switching from Originator Infliximab: Exploratory Analyses from the NOR-SWITCH Main and Extension Trials. 2020 DOI: 10.1007/s40259-020-00438-7. *This paper gives a detailed analysis of study outcomes from the gastroenterology patients participating in the NOR-SWITCH trial*

4. Veselý R, Richardson P. The switch to infliximab biosimilars. Lancet 2017 DOI: 10.1016/S0140-6736(17)31258-8 *In this Lancet comment, the authors discuss how the NOR-SWITCH study may put one of the most controversial aspects of biosimilar use to rest, and switching from originator to biosimilars would likely become usual practice.*

5. **Uhlig T, Goll GL.** Reviewing the evidence for biosimilars: key insights, lessons learned and future horizons. 2017 DOI: 10.1093/rheumatology/kex276. *In this review, the authors place the results from the NOR-SWITCH study into a broader context, discussing how these study results could impact the use of biosimilars within rheumatology*

4. Details of the impact

TNF inhibitors (TNFi) have improved treatment of Crohn's disease, ulcerative colitis, spondyloarthritis, rheumatoid arthritis, psoriatic arthritis, and chronic plaque psoriasis. TNFi came to the market around 1999–2000. These drugs were originally very expensive (annual costs between 10,000–20,000 US dollars) which limited their use in most countries.

One opportunity to lower this cost and improve access was the availability of biosimilar TNFi. Since biological drugs are complex molecules, identical copies cannot be produced. Hence, copies of originator TNF inhibitors are not true generics, but rather biosimilars – with identical amino acid sequence, but different in terms of glycosylation, 3D folding and probably also in other details. The European regulatory agencies developed guidelines early for approval of biosimilars. Such biosimilars have been available in Europe for infliximab since 2013, etanercept 2016, and adalimumab 2018. These biosimilar TNFi deliver more affordable treatment options and potentially much improved patient access.

The implementation of biosimilars has varied widely in Europe and around the world. There has especially been strong skepticism against switching patients from an originator on which they were doing well, to a biosimilar that by definition could not be identical to the originator.

The NOR-SWITCH study was the first randomized, double-blinded study to directly compare biosimilar TNF inhibitor to the reference drug, at a time when the introduction of more affordable biosimilar medicines caused much discussion. On the one hand, biosimilar agents provide an opportunity to give excellent medical treatment to patients who could not afford that treatment previously. On the other hand, switching a patient who is doing well to a different but similar treatment was controversial. The study was government funded in the National budget for 2014 without any links to the pharmaceutical industry, a fact that was also highly significant.

Results from the study have been disseminated though scientific publications in highly rated journals; abstracts presentations at international congresses within gastroenterology, dermatology and rheumatology; press releases, newspapers and other news outlets; patient organisations; publications from the regional health authorities; and the Norwegian Medical Association.

Study results were first presented at the UEGW meeting in Vienna October 2016. The venue was fully packed by colleagues, who also waited for the results outside the auditorium. One month later, the results were presented for a large audience as a late breaking poster at the American Congress of Rheumatology in November 2016. The study was then accepted as a full article in *The Lancet* and published May 2017. The PI was invited by the editor of the Lancet to submit this article based on the large interest and potentially strong impact globally of this study. The publication in one of the world's most prestigious journals is in itself an indication of how this study was judged to be of global impact. The regional health authorities of Norway selected NOR-SWITCH as one of the most significant studies of 2016 (reference 1). The authors of the NOR-SWITCH study have later been asked to write several

comments on their work and on biosimilars in general in a number of scientific journals. Further, several comments have been written about the study from authors with no connection to the study (reference 2). According to google scholar, the study has now been referenced 880 times as of 17.12.23.

The results from the NOR-SWITCH study have been highlighted and discussed by news outlets centered on medical news, where the societal impact of showing non-inferiority of biosimilars compared to costly originators has been a recurrent theme (4-7)

Beneficiaries from this study have been patients with inflammatory joint and bowel diseases and psoriasis, because acceptance of biosimilar medicines means more competition and lower prices, which in turn makes these medicines more accessible for patients. Study results showing the same efficacy and the same safety data for patients switching to a biosimilar as for those continuing the originator drug, have been reassuring to both patients and clinicians, who can then confidently alter medical treatment to a more affordable option.

Beneficiaries have also been health care systems and payers, who are able to treat more patients with TNF inhibitors at no increased cost, when prices are lower.

Beneficiaries have also included manufacturers of biosimilar medicines generally, as the study helped boost confidence in this class of medicines generally.

The impact of biosimilars and the subsequent increased competition has been very clear in Scandinavia, and has been noted also in important European and American journals (8,9). The Nor-SWITCH study was important in informing the 2018 recommendations of an international task force on the use of biosimilars and published in the journal of EULAR, the European organization for rheumatological societies in Europe (10).

5. Sources to corroborate the impact

1) Research and innovation for the benefit of the patient, National report from the Secondary Health Care System in Norway, 2016. Cheaper medication means more patients get the best treatment. Page 34-35. (Norwegian only)
2) Kay J, Winthrop K. Biosimilar switching — "To set a form upon desired change". 2017 DOI: 10.1038/nrrheum.2017.79
3) Kay J. A 'wind of change' to biosimilars: The NOR-SWITCH trial and its extension. 2019 DOI: 10.1111/joim.12896
4) **Kvien TK, Goll GL**. Biosimilars: Improve access to treatment and reduced cost. 2021 Page 20-21. Open Access Government
5) Marshall J, Fegan B. CARE PERSPECTIVES NOR-SWITCH TRIAL. 2017
6) NOR-SWITCH study finds biosimilar infliximab not inferior to originator. 2016 Generics and biosimilar initiative
7) Cush J. Caution Optimism for Biosimilars in Rheumatology. 2017 RheumNow
8) **Goll GL, Kvien TK.** Improving patient access to biosimilar tumor necrosis factor inhibitors in immune-mediated inflammatory disease: lessons learned from Norway. 2023 DOI: 10.1080/14712598.2023.2273938
9) **Goll GL, Kvien TK.** An Opportunity Missed: Biosimilars in the United States. 2020 DOI: 10.1002/art.41280
10) Kay J, Schoels MM, Dörner T, Emery P, **Kvien TK**, Smolen JS, Breedveld FC. Consensus-based recommendations for the use of biosimilars to treat rheumatological diseases. 2018 DOI: 10.1136/annrheumdis-2017-211937.

Diakonhjemmet Hospital, Division of Rheumatology and Research – case #4

Institution: Diakonhjemmet Hospital
Administrative unit: Division of Rheumatology and Research
Title of case study: The NOR-DRUM trials – proactive therapeutic monitoring of tumor necrosis factor inhibitors in patients with immune-mediated inflammatory diseases
Period when the underpinning research was undertaken: 2016-present
Period when staff involved were employed by the submitting institution: 2016-present
Period when the impact occurred: 2021-2022
Summary of the impact Biologic drugs with TNF inhibitors (TNFi) being the cornerstone therapies, have improved outcomes of inflammatory diseases, but many patients do not respond to treatment or lose response over time. Response to TNFi is related to serum drug levels and formation of anti-drug antibodies, which vary significantly among patients given the same dose. Thus, prescribing a standard dose in all patients may lead to both under- and overtreatment of patients. Guidance of treatment decisions by measuring serum drug concentrations, therapeutic drug monitoring (TDM), may optimize therapy with TNFi and other biologic drugs. The randomized NOR-DRUM trials were the first to investigate TDM effectiveness across all indications for the TNFi infliximab during induction and maintenance treatment. By showing a benefit of proactive TDM, results from these trials are already leading to a change clinical practice.
2. Underpinning research (indicative maximum 500 words) The NOR-DRUM trials were the first randomized clinical trials to compare the effectiveness of proactive TDM to standard infliximab therapy across patients with immune-mediated inflammatory diseases. The NOR-DRUM A trial assessed the use of TDM during induction treatment, while the NOR-DRUM B trial assessed TDM during maintenance treatment. Both trials were randomized, parallel-group, open-label clinical trials, carried out in 21 Norwegian hospitals (3). **Main results:** The NOR-DRUM A trial, recruiting patients from March 1, 2017, to January 10, 2019, was published in JAMA May 2021 (1). Including 411 adults with rheumatoid arthritis, spondyloarthritis, psoriatic arthritis, ulcerative colitis, Crohn's disease, or psoriasis initiating infliximab therapy, it showed that proactive TDM compared to standard therapy did not improve treatment outcomes during induction of infliximab therapy, with a comparable proportion of patients (51 vs 53%) achieving remission at week 30 in the TDM and standard therapy group. However, the study did suggest a benefit of proactive TDM during induction in patients at a high risk of anti-drug antibody formation, as the proportion of patients in remission was higher in the TDM group (56%) than the standard therapy group (35%) among those who developed anti-drug antibodies (70 patients, 15%). Also, the results suggested that regular measurements of anti-drug-antibodies may prevent infusion reactions, as significantly fewer infusion reactions were seen in the TDM group (n = 5) than in the standard therapy group (n = 16). The NOR-DRUM B trial, with patients recruited from June 7, 2017, to December 12, 2019, was published in JAMA December 2021 (2). Here, focus was on the effectiveness of proactive TDM in the maintenance phase of infliximab therapy and included 458 patients with rheumatoid arthritis, spondyloarthritis, psoriatic arthritis, ulcerative colitis, Crohn's disease, or psoriasis receiving infliximab therapy. The conclusion was that proactive TDM was more effective than treatment without TDM in maintaining disease control. The primary endpoint of sustained disease control without disease worsening was observed in 167 (73.6%) patients in the TDM group, and 127 (55.9%) patients in the standard therapy group. The adjusted difference was 17.6% (95% confidence interval 9.0–26.2%; $p < 0.001$) favoring TDM. Of note, drug consumption was similar in both groups meaning that TDM did not increase drug consumption over all. **Main conclusions** from the NOR-DRUM A and B trials are that TDM is more effective than standard therapy in sustaining disease control without disease worsening in patients on infliximab

maintenance therapy. During induction, TDM did not significantly improve remission rates over the first 30 weeks after treatment initiation. However, also during induction there may be subgroups of patients who benefit clinically from TDM.

Follow-up studies have investigated risk factors for making anti-drug antibodies to identify subgroups who will particularly benefit from TDM and other measures to mitigate the risk of anti-drug antibody formation. Anti-drug antibodies are common (10-20% of patients) and neutralize the drug and blocking its therapeutic effects. Among risk factors identified from the NOR-DRUM trials, certain HLA genes were shown to be particularly important. Also, the consequences of ADAb formation have been investigated and they have been found to be highly detrimental to patient health (4-6).

Details of staff conducting the underpinning research from the admin unit:

Key researchers (name)	Roles(s):	Period employed:
Espen A. Haavardsholm	PI	2016-present
Silje W. Syversen	Project lead	2016-present
Guro Løvik Goll	Clinical coordinator, rheumatology	2016-present
Tore K. Kvien	Medical lead	2016-present
Joe Sexton	Biostatistician	2016-present
Inge Olsen	Biostatistician	2016-2017
Marthe K. Brun	PhD-fellow	2019-present

3. References to the research

1) **Syversen SW, Goll GL,** Jørgensen KK, Sandanger Ø, Sexton J, Olsen IC, Gehin JE, Warren DJ, **Brun MK,** Klaasen RA, Karlsen LN, Noraberg G, Zettel C, Ljoså MKA, Haugen AJ, Njålla RJ, Bruun TJ, Seeberg KA, Michelsen B, Strand EK, Skorpe S, Blomgren IM, Bragnes YH, Dotterud CK, Thune T, Ystrøm CM, Torp R, Mielnik P, Mørk C, **Kvien TK,** Jahnsen J, Bolstad N, **Haavardsholm EA.** Effect of Therapeutic Drug Monitoring vs Standard Therapy During Maintenance Infliximab Therapy on Disease Control in Patients With Immune-Mediated Inflammatory Diseases: A Randomized Clinical Trial. 2021 DOI:10.1001/jama.2021.4172 *This paper reports results from the NOR-DRUM A trial, where results did not show any increase in the proportion of patients achieving remission at week 30, i.e. the early loading phase of infliximab treatment.*

2) **Syversen SW**, Jørgensen KK, **Goll GL, Brun MK,** Sandanger Ø, Bjørlykke KH, **Sexton J**, Olsen IC, Gehin JE, Warren DJ, Klaasen RA, Noraberg G, Bruun TJ, Dotterud CK, Ljoså MKA, Haugen AJ, Njålla RJ, Zettel C, Ystrøm CM, Bragnes YH, Skorpe S, Thune T, Seeberg KA, **Michelsen B**, Blomgren IM, Strand EK, Mielnik P, Torp R, Mørk C, **Kvien TK**, Jahnsen J, Bolstad N, **Haavardsholm EA.** Effect of Therapeutic Drug Monitoring vs Standard Therapy During Maintenance Infliximab Therapy on Disease Control in Patients With Immune-Mediated Inflammatory Diseases: A Randomized Clinical Trial. 2021 DOI: 10.1001/jama.2021.21316 *This paper reports results from the NOR-DRUM B trial, demonstrating a clear benefit of TDM in order to achieve sustained remission in patients on maintenance infliximab therapy*

3) **Syversen SW**, **Goll GL,** Jørgensen KK, Olsen IC, Sandanger Ø, Gehin JE, Warren DJ, **Sexton J,** Mørk C, Jahnsen J, **Kvien TK**, Bolstad N, **Haavardsholm EA.** Therapeutic drug monitoring of infliximab compared to standard clinical treatment with infliximab: study protocol for a randomised, controlled, open, parallel-group, phase IV study (the NOR-DRUM study). 2020 DOI: 10.1186/s13063-019-3734-4. *This paper outlines the trial design and study protocol for the NOR-DRUM A and B trials including details of the TDM algorithm used.*

4) **Brun MK, Goll GL**, Jørgensen KK, **Sexton J**, Gehin JE, Sandanger Ø, Olsen IC, Klaasen RA, Warren DJ, Mørk C, **Kvien TK**, Jahnsen J, Bolstad N, **Haavardsholm EA, Syversen SW.** Risk factors for anti-drug antibody formation to infliximab: Secondary analyses of a randomised controlled trial. 2022 DOI: 10.1111/joim.13495. *This paper investigates risk factors for anti-drug antibody formation, enabling the identification of patients at higher risk for treatment failure*

5) **Brun MK,** Bjørlykke KH, Viken MK, Stenvik GE, Klaasen RA, Gehin JE, Warren DJ, **Sexton J**, Sandanger Ø, **Kvien TK,** Mørk C, **Haavardsholm EA,** Jahnsen J, **Goll GL,** Lie BA, Bolstad N, Jørgensen KK, **Syversen SW.** HLA-DQ2 is associated with anti-drug antibody formation to

infliximab in patients with immune-mediated inflammatory diseases. 2023 DOI: 10.1111/joim.13616 *Here, the authors report on the most comprehensive analysis to date on genetic risk factors in the HLA region for propensity to anti-drug antibody formation*

6) **Brun MK** Gehin JE, Bjørlykke KH, Warren DJ, Klaasen RA, **Sexton J,** Sandanger Ø, **Kvien TK,** Mørk C, Jahnsen J, Bolstad N, Jørgensen KK, **Haavardsholm EA, Goll GL, Syversen SW.** Clinical consequences of infliximab immunogenicity and the impact of proactive therapeutic drug monitoring: exploratory analyses of the NOR-DRUM trials 2024 (*In press). This paper was recently accepted in Lancet Rheumatology, investigating the occurence and clinical consequences of ADAb development in the individual patient. Also, how the use of TDM helps alleviate the negative consequences of ADAb formation*

4. Details of the impact

Beneficiaries:

Clinical Practitioners: Rheumatologists and healthcare professionals will benefit from refined treatment approaches based on the NOR-DRUM trials and their substudies.

The most significant impact of the NOR-DRUM studies has been the realization among healthcare professionals that TDM may provide individualized, optimized treatment with existing drugs for large patient groups.

Focus has been put on drug immunogenicity, manifested as the formation of anti-drug antibodies as a major clinical problem which in part can be overcome by prediction and early identification by TDM. Anti-drug antibodies influence the pharmacokinetics of the drug, are associated with reduced clinical efficacy, and an increased risk of adverse events, and are a key reason why serum drug levels vary among patients even when the same dose is given.

Patients with RA: Individualised treatment strategies optimizing therapy by preventing flares and infusion reactions directly benefit a large patient group using this common therapy. Optimal use of expensive therapies means better patient treatment results and likely also better access to these treatments.

Healthcare Systems: Efficiency gains, particularly in avoiding unnecessary use of non-effective therapy, contribute to more cost-effective and efficient healthcare practices.

Nature of the Impact:

Publications, viewpoints, talks and (social) media: Results from the NOR-DRUM studies have been disseminated though scientific publications in highly rated journals; abstract presentations at international congresses within gastroenterology, dermatology and rheumatology; press releases, newspapers and other news outlets; and through patient organizations. The trials have received great attention nationally and internationally. Publication in one of the world's most prestigious journals is in itself a mark of how significant the NOR-DRUM studies were judged to be. Further, the regional health authorities of Norway selected NOR-DRUM as one of the most significant Norwegian studies of 2021 (1). Several commentary articles have been written about the studies from authors with no connection to the study group (2-4). The study results have been discussed on well-known web sites centered on medical news for rheumatology professionals (5) and have been highlighted in literature reviews that will underpin future treatment recommendations (6,7)

Further research: The NOR-DRUM trials were central for the development of a large project from the European SQUEEZE consortium, which in total received more than NOK 100 million in funding from the EU through the Horizon Europe 2022 call. The funds are earmarked research on improving treatment of rheumatoid arthritis, where personalized treatment with biologic drugs is an important focus. Within this consortium, the researchers behind NOR-DRUM will join forces with international centers to conduct a TDM study on subcutaneous TNFi. Hence, the Horizon Europe 2022 funding enables the study of similar treatment strategies for other TNF inhibitors used to treat patients with rheumatoid arthritis in Europe.

Following the original publications, members of the NOR-DRUM study group have been invited to write comments and reviews on the topic of TDM (8,9).

Clinical Guidelines: The NOR-DRUM trials were published in 2021, and the positive results of proactive TDM have not yet been incorporated into guidelines yet. Results from NOR-DRUM B are central to current work on a Rapid recommendation for TDM due to be published by BMJ in collaboration with the MAGIC foundation in early 2024. At the same time a Norwegian guideline based on BMJ recommendation will be launched. The NOR-DRUM trail and its genetic substudy has been included in the SLR underlying the next American gastroenterology association recommendation on TDM. The results from NOR-DRUM are anticipated to highly influence the updated EULAR points to consider for therapeutic drug monitoring of biopharmaceuticals in inflammatory rheumatic and musculoskeletal diseases (10).

The NOR-DRUM trials were conducted at 21 Norwegian hospitals ensuring rapid implementation of new knowledge nationally.

In summary, the NOR-DRUM trails and its substudies have already, and will continue to significantly impact the management of immune-mediated inflammatory diseases, influencing guidelines and treatment strategies and ensuring new large research efforts within this field.

5. Sources to corroborate the impact

1) Wallace ZS, Sparks JA. Therapeutic Drug Monitoring for Immune-Mediated Inflammatory Diseases 2021 DOI: 10.1001/jama.2021.21315.
2) Javor E, Hauser G, Skelin M Therapeutic Drug Monitoring vs Standard Therapy During Maintenance Infliximab Therapy and Control of Immune-Mediated Inflammatory Diseases. 2022 DOI: 10.1001/jama.2022.2935
3) Vande Casteele N. Therapeutic Drug Monitoring vs Standard Therapy During Maintenance Infliximab Therapy and Control of Immune-Mediated Inflammatory Diseases. 2022 DOI: 10.1001/jama.2022.2932
4) Cush J. Monitoring Infliximab Drug Levels Improves Efficacy | RheumNow. 03-11-21
5) Nguyen NH, Solitano V, Vuyyuru SK, MacDonald JK, **Syversen SW**, Jørgensen KK, Crowley E, Ma C, Jairath V, Singh Proactive Therapeutic Drug Monitoring Versus Conventional Management for Inflammatory Bowel Diseases: A Systematic Review and Meta-Analysis. S.Gastroenterology. 2022 Oct;163(4):937-949.e2. doi: 10.1053/j.gastro.2022.06.052.
6) Solitano V, Facciorusso A, McGovern DPB, Nguyen T, Colman RJ, Zou L, Boland BS, **Syversen SW**, Jørgensen KK, Ma C, Armuzzi A, Wilson A, Jairath V, Singh S. HLA-DQA1*05 Genotype and Immunogenicity to Tumor Necrosis Factor-α Antagonists: A Systematic Review and Meta-analysis. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2023 DOI: 10.1016/j.cgh.2023.03.044.
7) **Syversen SW,** Gehin JE, **Goll GL**, Bolstad N, **Haavardsholm EA, Lillegraven S**. Therapeutic Drug Monitoring: A Tool to Optimize Treatment of Inflammatory Joint Diseases 2023 DOI:10.1002/art.42764.
8) Gehin JE, **Goll GL, Brun MK**, Jani M, Bolstad N, **Syversen SW**. Assessing Immunogenicity of Biologic Drugs in Inflammatory Joint Diseases: Progress Towards Personalized Medicine. 2022 DOI: 10.1007/s40259-022-00559-1.
9) Krieckaert CL, van Tubergen A, Gehin JE, Hernández-Breijo B, Le Mélédo G, Balsa A, Böhm P, Cucnik S, Elkayam O, Goll GL, Hooijberg F, Jani M, Kiely PD, McCarthy N, Mulleman D, Navarro-Compán V, Payne K, Perry ME, Plasencia-Rodriguez C, Stones SR, **Syversen SW,** de Vries A, Ward KM, Wolbink **G,** Isaacs JD. EULAR points to consider for therapeutic drug monitoring of biopharmaceuticals in inflammatory rheumatic and musculoskeletal diseases Online May 2022 DOI: 10.1136/annrheumdis-2022-222155
10) New treatment strategies for inflammatory diseases, National report from the specialist health service 2021 Page 16-17 (Norwegian only)

Møre and Romsdal Hospital Trust, impact case 1

Institution: Møre and Romsdal Hospital Trust
Administrative unit: Møre and Romsdal Hospital Trust
Title of case study: Bergen 4-day treatment
Period when the underpinning research was undertaken: 2018-2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2014-
Period when the impact occurred: 2018-2022

1. Summary of the impact (indicative maximum 100 words)

The integration of research and clinical practice for the Bergen 4-Day OCD Treatment (B4DT) at Helse Møre og Romsdal Hospital Trust, enabled by collaboration with the Bergen Center for Brain Plasticity, has connected with leading global researchers. This partnership has significantly advanced mental health care, especially for OCD and anxiety disorders, by cutting therapy time from months to four days. B4DT has improved patient outcomes, increased treatment accessibility and efficiency, and its widespread adoption underscores its effectiveness and broad benefits to patients and mental health services.

2. Underpinning research (indicative maximum 500 words)

The Bergen 4-Day OCD Treatment (B4DT) represents a paradigm shift in treating Obsessive-Compulsive Disorder (OCD), demonstrating exceptional efficacy in a markedly short period. This contrasts sharply with traditional therapies, which typically require months to produce results. Since 2018, B4DT has been integrated into routine care for treating OCD, social phobia, and panic disorder. It employs intensive four-day therapy sessions, a departure from traditional, prolonged treatment models.

The development and execution of B4DT spanned several years, underscored by various studies and clinical trials, including partnerships in larger studies and specific implementation research in Møre og Romsdal. The team comprised six therapists, including three PhD candidates conducting research on the treatment format, and an external PhD candidate.

This research's impact is substantial, introducing an efficient and effective new treatment approach for OCD and anxiety disorders. It not only significantly cuts down treatment time but also potentially enhances patient outcomes and access to effective treatments. Furthermore, this approach uniquely combines clinical trials with research on predictors and biological mechanisms, broadening the understanding and potential applications of B4DT in mental health care.

The research has been facilitated through a decade of close collaboration with the Bergen Center for Brain Plasticity, led by Professor Bjarne Hansen and where the leader of the research group, Kristen Hagen, works as co-director.

Kristen Hagen: Reserch group leader and professor (associated) (2014-)
Kristian Tjelle: Clinical psychologist/PhD candidate (2016-)
Håvard Berg Opstad: Clinical psychologist/PhD Candidate (2016-)
Thorstein Olsen Eide: Clinical Psycholoist/PhD candidate (2018-)

Gunvor Launes: MD/PhD candidate (2018-)

3. References to the research (indicative maximum of six references)

Iversen, H. M., Eide, T. O., Harvold, M., Solem, S., Kvale, G., Hansen, B., & Hagen, K. (2022). The Bergen 4-day treatment for panic disorder: replication and implementation in a new clinic. BMC Psychiatry, 22(1), 728. DOI: 10.1186/s12888-022-04380-6

Tjelle, K., Opstad, H. B., Solem, S., Launes, G., Hansen, B., Kvale, G., & Hagen, K. (2021). Treatment Adherence as Predictor of Outcome in Concentrated Exposure Treatment for Obsessive-Compulsive Disorder. Frontiers in Psychiatry, 12. DOI: 10.3389/fpsyt.2021.667167

Hagen, K., Nordahl, H., Launes, G., Kvale, G., Öst, L. G., Hystad, S., et al. (2021). Does Concentrated Exposure Treatment for Obsessive-Compulsive Disorder Improve Insomnia Symptoms? Results From a Randomized Controlled Trial. Frontiers in Psychiatry, 12, 625631. https://doi.org/10.3389/fpsyt.2021.625631

Hansen, B., Hagen, K., Öst, L. G., Solem, S., & Kvale, G. (2018). The Bergen 4-Day OCD Treatment Delivered in a Group Setting: 12-Month Follow-Up. Frontiers in Psychology, 9, 639. doi:10.3389/fpsyg.2018.00639.

Kvale, G., Hansen, B., Hagen, K., Abramowitz, Børtveit, T., Crase, M., Franklin, M. E., Haseth, S., Himle, J.A., Hystad, S., Kristensen, U.B., Launes, G., Lund, A., Solem, S., Öst, L-G (2020) Effect of D-Cycloserine on the Effect of Concentrated Exposure and Response Prevention in Difficult-to-Treat Obsessive-Compulsive Disorder: A Randomized Clinical Trial. *JAMA Network Open* 3(8):e2013249 DOI: 10.1001/jamanetworkopen.2020.13249

Thorsen, A. L., de Wit, S. J., Hagland, P., Ousdal, O. T., Hansen, B., Hagen, K., ... & van den Heuvel, O. A. (2020). Stable inhibition-related inferior frontal hypoactivation and fronto-limbic hyperconnectivity in obsessive–compulsive disorder after concentrated exposure therapy. NeuroImage: Clinical, 28, 102460. DOI:10.1016/j.nicl.2020.102460

4. Details of the impact (indicative maximum 750 words)

The research underpinning the Bergen 4-Day OCD Treatment (B4DT), primarily driven by the collaborative efforts with the Bergen Center for Brain Plasticity, has made a distinct and material contribution to mental health care, particularly in the treatment of Obsessive-Compulsive Disorder (OCD), social phobia, and panic disorder.

Process and Means of Impact

- Dissemination: The research findings were widely disseminated through scientific publications, conferences, and workshops, ensuring that the innovative treatment approach reached a broad spectrum of healthcare professionals.
- Influence: The efficacy and efficiency of B4DT captured the attention of clinicians and healthcare systems, leading to its adoption as a routine care model in various clinical settings.
- Application: The intensive four-day treatment protocol, diverging from traditional prolonged therapies, was implemented in clinical practices, demonstrating its practical applicability and effectiveness.

Contribution of the Administrative Unit

- The research team's work was part of a larger body of research on OCD treatments. However, the specific contribution of the administrative unit was pivotal in developing the condensed treatment format of B4DT, which significantly differed from existing methods.
- Collaborations with other institutions and researchers were integral to the study, but the administrative unit's unique contribution was in the clinical application and evaluation of B4DT in real-world settings.

Beneficiaries

- Patients with OCD, social phobia, and panic disorder have directly benefited from the shortened treatment duration and improved outcomes.
- Mental health practitioners and healthcare systems benefited by having an effective, time-efficient treatment option, enabling them to treat more patients and reduce waiting times.
- The broader mental health community, including researchers and clinicians, gained valuable insights into alternative treatment methodologies for anxiety disorders.

Nature of the Impact

- Patients have experienced significant improvements in their conditions in a shorter time frame, enhancing their quality of life and reducing the long-term burden of chronic mental health issues.
- Healthcare providers have adopted a more efficient treatment model, leading to optimized resource utilization and potential cost savings.

Evidence and Extent of Impact

- Clinical studies and trials have shown the effectiveness of B4DT in reducing symptoms of OCD and related disorders.
- The adoption of B4DT in various healthcare settings and its inclusion in treatment guidelines serve as indicators of its impact on mental health care practices.
- Patient testimonials and case studies provide qualitative evidence of the treatment's positive effects on individuals' lives.

Timeline of Impacts

- The implementation of B4DT as a routine care model began in 2018 in Møre og Romsdal Hospital Trust, following years of research and clinical trials.
- Since then, ongoing evaluations and studies have continued to demonstrate its impact, with significant real-world applications observed in subsequent years.

5. Sources to corroborate the impact (indicative maximum of ten references)

Prizes:

- **https://www.dagensmedisin.no/angst-eksponeringsterapi-helse-more-og-romsdal/innforte-fire-dager-intensiv-eksponeringsterapi-svaert-vellykket/577285**
- **https://www.rbnett.no/nyheter/i/WRW7Wr/eksporterer-supermetode-mot-angst-og-tvangslidelser**
- **https://psykologisk.no/2023/08/ny-studie-panikkangst-kan-behandles-pa-fire-dager/**
- **https://www.vg.no/forbruker/helse/i/Q70L3R/angst-denne-behandlingen-hjelper**
- **https://www.rbnett.no/nyheter/i/MoBxMR/lena-tok-livet-tilbake-med-4-dagerskur-mot-panikkangst**
- **https://www.aftonbladet.se/halsa/a/8J8nOA/ny-behandling-mot-angest-hjalper-pa-fyra-dagar**
- **https://www.tk.no/behandler-panikklidelser-pa-fire-dager/s/5-51-1401041**
- Norsk angst-forsker hentet hjem pris under internasjonal forskningskonferanse (psykologisk.no)
- Time Magazine: Time Magazine, 50 most influential in health 2018
- **https://forskning.no/angst-forskningsradet-ntb/angstbehandling-far-forskningspris/2118034**

Møre and Romsdal Hospital Trust, impact case 2

Institution: Møre and Romsdal Hospital Trust
Administrative unit: Møre and Romsdal Hospital Trust
Title of case study: The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation
Period when the underpinning research was undertaken: 2014 - 2016
Period when staff involved in the underpinning research were employed by the submitting institution: 1999 to date
Period when the impact occurred: 2016 - 2024

1. Summary of the impact

The work has improved and systematized the knowledge about the use of antirheumatic medication in pregnant women with inflammatory rheumatic diseases, and how it may affect the health of the mother, fetus and child. The publication EULAR points to consider has been essential for and contributed to the development of public policies and health services provided for this group of women in Norway, Europe, and outside Europe. It has resulted in a tighter follow up and better disease control, using compatible medication during pregnancy and lactation, with a positive impact on health and quality of life for the individual woman.

2. Underpinning research

The European alliance of associations of rheumatology (EULAR) is a non-profit organisation representing people with rheumatic and musculoskeletal diseases, health professionals in rheumatology, rheumatologists and scientific societies of rheumatology of all European nations. EULAR task forces are gathered to share expertise and develop recommendations or points to consider on classification, response criteria, diagnostic approaches and management of different rheumatic diseases.

Research concerning pregnant women and medication use is a demanding task, as both the level and quality of evidence is often low. The findings therefore needed to be interpreted and conveyed by competent clinicians and patients. The current case was developed by a task force initiated by Professor Monika Østensen. Her affiliations at that time were the National Service for Pregnancy and Rheumatic Diseases, Department of Rheumatology, Trondheim University Hospital, Trondheim, Norway, and Department of Neuroscience, Norwegian University of Science and Technology (NTNU), Trondheim, Norway.

A systemic literature search (SLR) was performed, and pregnancy exposure data from several registries was reviewed, for the period 2008 – April 1st 2015, with an additional search for some medications 2006 – 2008. The data search included 31 anti-inflammatory medications, resulting in more than 6000 references on antirheumatic drugs during pregnancy and lactation, of which a total of 319 publications were eligible for analysis. This was the work of the research fellow (Carina Gøtestam Skorpen), the convenor (Professor Monika Østensen) and a research librarian at the NTNU. The results of the SLR were presented to the task force consisting of 20 members from 10 European countries and the USA, and statements on the compatibility of antirheumatic drugs during pregnancy and lactation were developed. Four overarching principles and 11 points to consider for use of antirheumatic drugs during pregnancy and lactation were defined. An expert consensus was reached to help clinicians in the treatment of pregnant women with rheumatic diseases aiming at inactive disease and at the same time avoid exposure to teratogenic treatment. The experts also stated how they would use the medications in clinical practice.

Carina Götestam Skorpen was appointed part time as a research fellow for the case study, at the time affiliated to the National Service for Pregnancy and Rheumatic Diseases, Department of Rheumatology, Trondheim University Hospital, Trondheim, Norway, and Department of

Neuroscience, NTNU, Trondheim, Norway, and Department of Rheumatology, Ålesund Hospital, Ålesund, Norway. She worked part time as a rheumatologist at Department of Rheumatology in Ålesund and started her PhD parallel to this case study.

3. References to the research

The publication for this case study:

Götestam Skorpen C, Hoeltzenbein M, Tincani A, et al. The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. Ann Rheum Dis 2016;75:795–810.

The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation - PubMed (nih.gov)

Two earlier publications were the first to document and discuss the use and safety of anti-rheumatic medication in pregnant women with inflammatory rheumatic diseases. A consensus workshop on antirheumatic drugs during pregnancy and lactation held in connection with the 4th International Conference on Sex Hormones, Pregnancy and Rheumatic Diseases, in September 2004. Because of an increasing use of biological agents in women of fertile age, the information from the consensus paper in 2006 was later updated for the years 2006 and 2007.

Østensen M, Khamashta M, Lockshin M et al Anti-inflammatory and immunosuppressive drugs and reproduction. Arthritis Res Ther 2006;8:209. https://doi.org/10.1186/ar1957

Østensen M, Lockshin M, Doria A et al. Update on safety during pregnancy of biological agents and some immunosuppressive anti-rheumatic drugs. Rheumatology (Oxford) 2008;47(Suppl 3):iii28–31 https://doi.org/10.1093/rheumatology/ken168

4. Details of the impact

An abstract with the outline of the case study was submitted to the EULAR conference in June 2014, and presented as a poster.
The recommendation was first published on February 17th 2016 in Annals of the Rheumatic diseases (ARD), which is the leading rheumatology journal from EULAR, publishing original research, reviews and recommendations.
There is increasing awareness in the community of rheumatology, but also in other medical specialities and the patients including patient organisations about this matter.

In Norway, the recommendation was implemented in the digital national guidelines authored by the National Service for Pregnancy and Rheumatic Diseases, freely available and regularly updated online. NKSR – Helsepersonnel – Veileder i svangerskap og revmatiske sykdommer
Pregnant women with rheumatic diseases have tighter follow up, and the recommendations are also implemented in the national guidelines of The Norwegian Society of Gynecology and Obstetrics.
Revmatisk inflammatorisk sykdom (artrittsykdommer, bindevevssykdommer og vaskulitter) (legeforeningen.no)

RevNatus is a Norwegian nationwide pregnancy register for women with rheumatic diseases. They are followed in every trimester and the first year after birth as recommended, resulting in inactive or low disease activity and improving outcomes. Disease activity, medication use and pregnancy outcomes are recorded, and contribute to new prospective data important for research purposes. A core data set for pregnancy registries in rheumatology was proposed in the points to consider and has later been prepared and is implemented in RevNatus and other European registries. This facilitates collaboration across borders, and a European Network of Pregnancy Registers in Rheumatology (EuNeP) has been formed, including registers from France, Switzerland, Germany and Norway, with a potential to include new registers from other European countries.

The EULAR points to consider is now in the process of update, to include research from the period of 2015 until 2022. A new taskforce has been formed, this time with 3 research fellows, a convenor and 20 experts from Europe and the USA.

Health care providers, patients, their spouses and offspring benefit from the increased knowledge about medication in pregnancy. Disease activity is better controlled, pregnancies are often planned and the pregnancy outcomes are improving for mother and child.

4. Sources to corroborate the impact

Andreoli L, Chighizola CB, Iaccarino L et al. Immunology of pregnancy and reproductive health in autoimmune rheumatic diseases. Update from the 11th International Conference on Reproduction, Pregnancy and Rheumatic Diseases. Autoimmun Rev. 2023 Mar;22(3):103259. https://doi.org/10.1016/j.autrev.2022.103259. Epub 2022 Dec 20. PMID: 36549355

Ramoni VL , Häfeli C, Costedoat-Chalumeau N, Chambers C, Dolhain R, Govoni M, Levy R, Götestam Skorpen C, Tincani A, Förger F. Changes to expert opinion in the use of antirheumatic drugs before and during pregnancy five years after EULAR: points to consider. Rheumatology (Oxford). 2022 Nov 2;61(11)

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Russell M,Dey M, Flint J et al. British Society for Rheumatology guideline on prescribing drugs in pregnancy and breastfeeding: immunomodulatory anti-rheumatic drugs and corticosteroids Rheumatology, 62(4), e48-e88 - November 2022 https://doi.org/10.1093/rheumatology/keac551

Meissner Y, Fischer-Betz R, Andreoli L, et al. EULAR recommendations for a core data set for pregnancy registries in rheumatology. Ann Rheum Dis 2021;80:49–56. http://dx.doi.org/10.1136/

Lisa R. Sammaritano L, Bermas B, Chakravarty E et al. 2020 American College of Rheumatology Guideline for the Management of Reproductive Health in Rheumatic and Musculoskeletal Diseases. First published: 23 February 2020 https://doi.org/10.1002/art.41191

Meissner Y, Strangfeld A, Costedoat-Chalumeau N et al. European Network of Pregnancy Registers in Rheumatology (EuNeP)—an overview of procedures and data collectionArthritis Research & Therapy (2019) 21:241 https://doi.org/10.1186/s13075-019-2019-3

Andreoli L, Bertsias GK, Agmon-Levin N, et al. EULAR recommendations for women's health and the management of family planning, assisted reproduction, pregnancy and menopause in patients with systemic lupus erythematosus and/or antiphospholipid syndrome Ann Rheum Dis 2017;76:476–485.

EULAR recommendations for women's health and the management of family planning, assisted reproduction, pregnancy and menopause in patients with systemic lupus erythematosus and/or antiphospholipid syndrome - PubMed (nih.gov)

Møre and Romsdal Hospital Trust, impact case 3

Institution: Møre and Romsdal Hospital Trust
Administrative unit: Møre and Romsdal Hospital Trust
Title of case study: Clinical research unit
Period when the underpinning research was undertaken: 2013-2016
Period when staff involved in the underpinning research were employed by the submitting institution: 2002 - ongoing
Period when the impact occurred:2017 – ongoing

1. Summary of the impact (indicative maximum 100 words)

The development of a Clinical research unit (CRU-HMR stage I) that enables a professional and continuous support to researchers and clinical researchers. The research support includes trained research staff, basic laboratory and biobank services, technical equipment, and treatment areas. One might call a CRU an "outpatient clinic for research", and the support is not only to the researcher, but also to the industry and very much the participants in studies – the patients.

2. Underpinning research (indicative maximum 500 words)

In 2013 division of medicine, HMR, started out trying to organize research within the division. When asking clinicians and dedicated researchers at the departments, the lack of time due to no practical support stood out as a main challenge. Research had to be done in between tasks or on the researchers' own time. This made it very difficult to do research and clinical studies, a general and increasing challenge. In 2013 there were still few clinicians with formal research education and experience, and who actively did research within the division, some clinicians did clinical studies together with the pharmaceutical industry. Division of medicine acknowledged the issue, "lack of support. Senior consultant Dag Arne Lihaug Hoff MD, PhD, was appointed to the task from the head of division of medicine, Torstein Hole MD, Assoc. Prof. Dr. Hoff, a gastroenterologist and researcher, had personal experience using support from a CRU, from studies done at Haukeland University hospital, Bergen, Norway. Because research support was a general concern at the hospital trust, the "CRU-Biobank" project was expanded to include support the entire hospital trust. This CRU should support academic-clinical and clinical research with staff and room. After some years of planning, implementation of biobank, activities were added to the project plan. This was in close collaboration with the regional Biobank1®.To develop a CRU, division of medicine applied (a competitive process) for funding on several occasions during the years 2013-2016, both locally and regionally, and succeeded. It did not at all add extra costs to the institutions' budgets. The "CRU-Biobank project was founded by the R&D department in the phases of planning, the Central Norway Regional Health Authority (RHA) founded the in-hospital area re-construction and the Liaison Committee between the RHA and the Norwegian University of Science and Technology (NTNU) founded the operational phase 2017-2020. In October 2017 part I of the CRU was ready, staff employed i.e. 1.5 positions as study nurse, 1 position as medical laboratory scientist and 0.7 position as consultant / head of the unit. Furthermore a full laboratory for handling every aspect of taking, allocation and storing at minus 20-150 degrees Celsius of different body fluids. Treatment area and meeting area.

Dag Arne Lihaug Hoff MD, PhD, in addition to being a clinician and researcher, has had different positions at the administrative unit; research advisor 2013-17, 2017 – ongoing head of clinical research unit (CRU-HMR).

3. References to the research (indicative maximum of six references)

The CRU had during planning of the unit a goal to go live with clinical research project prior to the completeness of the facilities build. Therefore, after staff was employed in 2016/17 we planned and launched one regional study in November 2016, started the planning of another national project which was launched June 2017 both still ongoing (see the self-assessment research group "Imed-HMR" project 1 and 2). The last project, which ended 2020/21, "*Documentation of physical effects and qualities of marine protein hydrolysates in sport and sarcopenia" short MPH-BIA. A Research council of Norway founded project, #*266684. The CRU was a major partner in this two-center study, two PhD students, four clinical trials at the CRU, six publications and two PhD thesis.

Thesis:

Hanna Fjeldheim Dale 2020 – **Co-supervisor Dag Arne Lihaug Hoff**
"Health effects of supplementation with cod protein hydrolysate: Impact on glucose metabolism and appetite in healthy subjects and gut health in irritable bowel syndrome"
https://hdl.handle.net/1956/21611

Caroline Jensen 2021 – **Supervisor Dag Arne Lihaug Hoff**
"Supplementation with cod protein hydrolysate: Intervention studies in healthy adults and adults with metabolic syndrome"
https://hdl.handle.net/11250/2734286

Journal publications (four of six in the project):

The Effect of Supplementation with Low Doses of a Cod Protein Hydrolysate on Satiety Hormones and Inflammatory Biomarkers in Adults with Metabolic Syndrome: A Randomized, Double-Blind Study. Caroline Jensen , Hanna Fjeldheim Dale , Trygve Hausken, Jan Gunnar Hatlebakk, Ingeborg Brønstad, Gülen Arslan Lied, **Dag Arne Lihaug Hoff**
Nutrients 2020, *12*(11), 3421; https://doi.org/10.3390/nu12113421

Supplementation with Low Doses of a Cod Protein Hydrolysate on Glucose Regulation and Lipid Metabolism in Adults with Metabolic Syndrome: A Randomized, Double-Blind Study
Caroline Jensen , Hanna Fjeldheim Dale , Trygve Hausken, Jan Gunnar Hatlebakk, Ingeborg Brønstad, Gülen Arslan Lied, **Dag Arne Lihaug Hoff**
Nutrients 2020, *12*(7), 1991; https://doi.org/10.3390/nu12071991

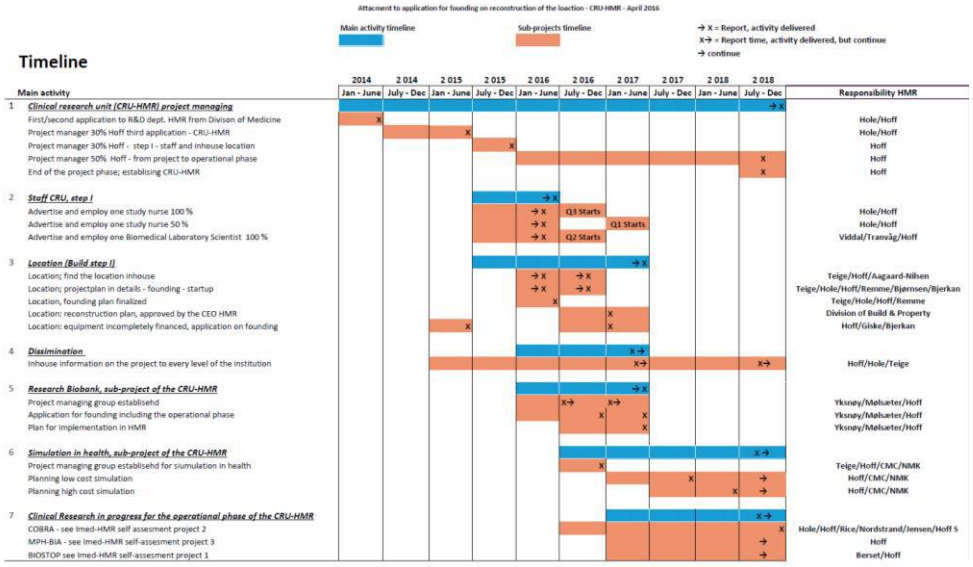
Acute effect of a cod protein hydrolysate on postprandial acylated ghrelin concentration and sensations associated with appetite in healthy subjects: a double-blind crossover trial
Hanna F. Dale, Caroline Jensen, Trygve Hausken, Einar Lied, Jan G. Hatlebakk, Ingeborg Brønstad, **Dag Arne L. Hoff** and Gülen A. Lied
Food Nutr Res. 2019 Oct 22:63. DOI: 10.29219/fnr.v63.3507. eCollection 2019.

Effect of a cod protein hydrolysate on postprandial glucose metabolism in healthy subjects: a double-blind cross-over trial. Hanna F. Dale, Caroline Jensen, Trygve Hausken, Einar Lied, Jan G. Hatlebakk, Ingeborg Brønstad, **Dag Arne L. Hoff** and Gülen A. Lied
J Nutr Sci. 2018 Nov 28:7:e33. DOI: 10.1017/jns.2018.23. eCollection 2018.

4. Details of the impact (indicative maximum 750 words)

I report some of the reasons this CRU-HMR impacts research: Important to the patient, professional and improved patients care in research. Give patients an opportunity to be a part of research located near their home. Improved data collection due to trained research staff, vital to results. Improved support to the clinicians i.e. the only way clinicians can be able to combined clinical work and research. Educating and part of the innovative medicine, important to the clinicians. Collaboration with pharmaceutical industry give patient's access to new drugs several years before others and for some the only way to cure. This list is not exhaustive.

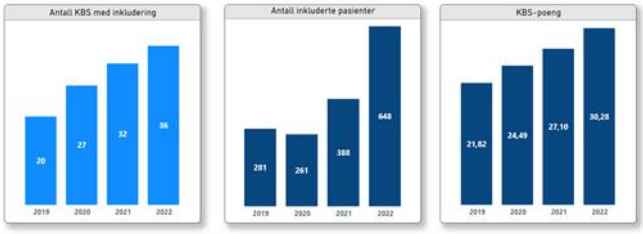
As illustrated by the Gantt Chart, the project included several activities and effort to finalize.



Detailed data on development of the CRU-HMR

During the years in the operational phase, there has been a gradual expanding activity when it comes to research studies/projects, employment of more staff and initiation step II of the build at Ålesund Hospital, and build III will be in the new hospital Nordmøre & Romsdal, operational from Q2 2025. In 2022, we employed several new study nurses at different departments (oncology at Ålesund hospital, gastroenterology/neurology at Molde hospital and in orthopaedics in Kristiansund hospital, as well as medical laboratory scientist at Molde hospital). These study nurses will support not only the specialties in speak, but also if need other specialities. The action plan is to increase research support at different locations throughout the hospital trust, but the staff will be affiliated with the CRU, to give them colleagues, network, someone to discuss work related issues with on a daily basis (if needed!).

One example of research is reported above; the MPH-BIA project. Another project (see details in another of the impact cases) the BAROBS (Bariatric surgery observation study)-project (part I ended, and part 2 ongoing), the CRU-HMR has been vital. It's a major reason why the Ålesund part of the projects runs well and can deliver complete data. The BAROBS-project has published six articles, data have been used in revision of guidelines and used in several master thesis, some of them published in international journals. If we address another important issue to the CRU-HMR, clinical studies in collaboration with pharmaceutical or med. tech industry it also runs well exemplified by the figure of national reported activity data – an area of national importance.



Clinical studies, only studies with the yearly inclusion of new patients who get treatment

5. Sources to corroborate the impact (indicative maximum of ten references)

Jan Gunnar Hatlebakk, Professor in gastroenterology, Haukeland University hospital, Bergen
Knut Lundin, Professor in clinical medicine, Oslo University Hospital and University, Oslo
Petter Holger Johnsen, Researcher, MD, University Hospital North Norway, Harstad
Jorunn Sandvik, assoc.professor NTNU, gastro surgeon Ålesund Hospital, Ålesund
Frederik Emil Juel, Researcher, MD, University of Oslo, Bærum Hospital, Bærum
Magnus Strømmen, Researcher, PhD, Centre of Obesity and innovation, St. Olav University hospital, Trondheim

Website for CRU-HMR: Clinical Research Unit and Biobank1 - Helse Møre og Romsdal (helse-mr.no)

Some current clinical trials running with the help of CRU-HMR:

- Study Details | Anti-tumor Necrosis Factor in Patients With Ulcerative Colitis in Clinical Remission: to Continue or Not? | ClinicalTrials.gov
- Project #2494579 - Behandling av irritabel tarm syndrom med tarmflora fra frisk donor. REFIT2 - en norsk multisenter fase III studie - Cristin
- Study Details | Efficacy and Safety Study of HRO350 in Patients With Mild-to-moderate Psoriasis (the 'HeROPA' Study). | ClinicalTrials.gov
- CetoSkin: Effekten av fiskeolje på atopisk eksem - Helse Møre og Romsdal (helse-mr.no)

Other sources: (only available in norwegian)

- 2017 Interview in Sunnmørsposten newspaper: Using millions on healthreserach at Ålesund Hospital
- Kan nyutviklet fiskeolje ha positiv effekt på atopisk eksem? - Møreforsking AS (moreforsk.no)
- Fagdag for celle-, dyre- og kliniske studier - Blue Legasea
- Omfattande forskingsprosjekt starta i dag - Helse Møre og Romsdal (helse-mr.no)

Møre and Romsdal Hospital Trust, impact case 4

Institution: Møre and Romsdal Hospital Trust
Administrative unit: Møre and Romsdal Hospital Trust
Title of case study: BAROBS Bariatric surgery observation study
Period when the underpinning research was undertaken: 2017-ongoing
Period when staff involved in the underpinning research were employed by the submitting institution: 2017- ongoing
Period when the impact occurred: 2020-ongoing

Summary of the impact (indicative maximum 100 words)

Observational studies on long-term (five and 10 years) follow-up after bariatric surgery have changed the recommendation for standard follow-up from five to 10 years in the national quality register for bariatric surgery. Results have been used in updating Nordic guidelines for vitamin and mineral supplements after bariatric surgery, and in revision of regional standardized paths for treatment of severe obesity.
The results from these studies are also valuable for patients considering bariatric surgery, and for health personnel advising these patients.

2. Underpinning research (indicative maximum 500 words)

Bariatric surgery as treatment for severe obesity was established as a regional program in 2004, and local quality registries were started at the three hospitals in the Central Norway Regional Health Authority offering this treatment: Namsos Hospital, St. Olavs Hospital Trondheim University Hospital, and Ålesund Hospital.
In the period 2004 to 2015, 2300 patients underwent a gastric bypass or a sleeve gastrectomy for severe obesity at these three hospitals.
Data from the local quality register from Ålesund was used in consultant in surgery Jorunn Sandvik's PhD project "Long-term results after surgical treatment for severe obesity" in the period 2017-2020. This project included all patients who had gastric bypass at Ålesund Hospital with more than five years postoperative follow up.

One of the main findings was that half of the patients had been in need for medical imaging and 18% of the patients were in need of abdominal surgery after the gastric bypass operation, either because of suspected internal herniation or gallstone disease.
It was also found that self-rated health and quality of life were improved in more than two thirds of the patients five years after surgery. Only 8% had a decline in self-rated health five years after surgery. This knowledge has been useful for patients considering bariatric surgery.
The third paper in the PhD-project revealed that one third of the patients had been in need of treatment with intravenous iron during the five first years after surgery, due to iron deficiency with and without anaemia. These findings changed the strategy for treatment for iron deficiency after gastric bypass surgery, with easier access to intravenous iron treatment in the hospitals in the region, as well as on a national level.

As a continuation of Sandvik's PhD project, a regional study on the result of bariatric surgery after more than ten years, started in 2018. The aim of the Bariatric surgery observation study (BAROBS)

was to evaluate the durability of weight loss and improvement in comorbidities a decade after surgery, as well as to reveal the degree of new morbidity caused by the treatment. An evaluation of the patient education program before and after the operation, and patient satisfaction were also included.

The first data collection in BAROBS took place from August 2018 to June 2020, and included clinical measurements and investigations, questionnaires, blood tests, and interviews. The three hospitals participated as equal partners in the steering committee, and in the practical work. BAROBS is lead from the Regional Centre for Obesity Research at St Olavs Hospital where Sandvik has a part-time position as project leader. The other members of the steering committee from Ålesund are Kirsti Kverndokk Bjerkan and Dag Arne Lihaug Hoff. The clinical research unit at Ålesund Hospital has been responsible for the BAROBS data collection in Ålesund.

Kirsti Kverndokk Bjerkan, who is a clinical dietitian, is, as a PhD-student in the period 2020-2024 been exploring the effect of participation in patient education program on weight loss and lifestyle. She has also evaluated the patients' compliance to recommendations on vitamin and mineral supplements. Whether these recommendations have been sufficient to avoid deficiencies have also been explored.
The results of Bjerkan's work have been used in a revision on Nordic guidelines on supplements after bariatric surgery in 2023.

As part of the BAROBS-project Siren Nymo in Helse Nord-Trøndelag has had a post doc position from 2019, exploring the differences between patients with optimal and sub optimal weight loss after surgery.

From April 2023 Åsne Ask Hyldmo started a PhD-project exploring reasons for and possible solution on abdominal pain after bariatric surgery which might affect one third of those who have gastric bypass surgery.

- Jorunn Sandvik, MD, PhD, clinical position as consultant in Surgery, Ålesund, and part time (30%) position as researcher at the research unit in Helse Møre og Romsdal and Regional centre for obesity research at St.Olav's hospital, Trondheim. From February 2023 associate professor at NTNU
- Kirsti Kverndokk Bjerkan, MSc, Clinical dietitian at Ålesund hospital and PhD student at Volda University College from September 2020. Member of the steering committee for BAROBS
- Dag Arne Lihaug Hoff, MD, PhD. Consultant in gastroenterology at Ålesund hospital and leader for the clinical research unit in Helse Møre and Romsdal. He is also member of the steering committee of BAROBS.
- Torstein Hole, MD, PhD, professor at NTNU and consultant in cardiology at Ålesund hospital. He has been researcher and supervisor for medical students using BAROBS-data for their thesis.
- Kjetil Roth, MD, PhD, consultant in pulmonary diseases has been researcher and supervisor medical students using BAROBS-data.

3. References to the research (indicative maximum of six references)

- Sandvik J, Hole T, Klöckner CA, Kulseng BE, Wibe A. High-Frequency of Computer Tomography and Surgery for Abdominal Pain After Roux-en-Y Gastric Bypass. Obes Surg. 2018 Sep;28(9):2609-2616. doi: 10.1007/s11695-018-3223-y. PMID: 29619755.
- Sandvik J, Hole T, Klöckner CA, Kulseng BE, Wibe A. Intravenous Iron Treatment in the Prevention of Iron Deficiency and Anaemia After Roux-en-Y Gastric Bypass. Obes Surg. 2020 May;30(5):1745-1752. doi: 10.1007/s11695-020-04396-5. PMID: 31955373; PMCID: PMC7228960.
- Bjerkan KK, Sandvik J, Nymo S, Græslie H, Johnsen G, Mårvik R, Hyldmo ÅA, Kulseng BE, Høydal KL, Hoff DAL. The Long-Term Impact of Postoperative Educational Programs on Weight Loss After Roux-en-Y Gastric Bypass. Obes Surg. 2022 Sep;32(9):3005-3012. doi: 10.1007/s11695-022-06187-6. Epub 2022 Jul 6. PMID: 35790673; PMCID: PMC9392699.
- Bjerkan KK, Sandvik J, Nymo S, Græslie H, Johnsen G, Mårvik R, Hyldmo ÅA, Kulseng BE, Sommerseth S, Høydal KL, Hoff DAL. Vitamin and Mineral Deficiency 12 Years After Roux-en-Y Gastric Bypass a Cross-Sectional Multicenter Study. Obes Surg. 2023 Oct;33(10):3178-3185. doi: 10.1007/s11695-023-06787-w. Epub 2023 Aug 27. PMID: 37635164; PMCID: PMC10514116.
- Nymo S, Børresen Skjølsvold O, Aukan M, Finlayson G, Græslie H, Mårvik R, Kulseng B, Sandvik J, Martins C. Suboptimal Weight Loss 13 Years After Roux-en-Y Gastric Bypass: Is Hedonic Hunger, Eating Behaviour and Food Reward to Blame? Obes Surg. 2022 Jul;32(7):2263-2271. doi: 10.1007/s11695-022-06075-z. Epub 2022 May 4. PMID: 35505168; PMCID: PMC9276719.
- Belgau I, Johnsen G, Græslie H, Mårvik R, Nymo S, Bjerkan K, Hyldmo Å, Klöckner C, Kulseng B, Hoff D, Sandvik J. Frequency of cholelithiasis in need of surgical or endoscopic treatment a decade or more after Roux-en-Y gastric bypass. Surg Endosc. 2023 Feb;37(2):1349-1356. doi: 10.1007/s00464-022-09676-y. Epub 2022 Oct 6. PMID: 36203112; PMCID: PMC9944031.

4. Details of the impact (indicative maximum 750 words)

Data from BAROBS has been available for medical students and master students for their thesis. By the end of 2023 four master students and 20 medical students have written their thesis on a wide range of topics related to obesity and bariatric surgery. Some of the theses have been published in international journals. These students have had supervisors from other clinics in addition to the BAROBS study group, e.g. specialists in gynaecology, orthopaedic surgery, neurology, gastroenterology, public health, endocrinology, cardiology, and others.

In 2023 a second wave of Data collection, BAROBS2, started, inviting patients who had bariatric surgery at the three participating hospitals from 2010 to 2015.

5. Sources to corroborate the impact (indicative maximum of ten references)

The referenced Nordic guidelines for vitamin and mineral supplements after bariatric surgery have not yet been published.

Helse Bergen – Haukeland University Hospital – Impact case #1

Institution: Haukeland University Hospital
Administrative unit: Department of Microbiology
Title of case study: The impact of molecular testing on diagnostics and management of acute lower respiratory tract infections
Period when the underpinning research was undertaken: 2019-2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2019-2022
Period when the impact occurred: 2019-2022

1. Summary of the impact

Molecular testing of representative samples from patients with lower respiratory tract infections provides faster and more accurate microbial results than standard-of-care testing. Implementation of molecular testing in clinical practice can optimize patient treatment and reduce antibiotic overuse, especially in settings with high prevalence of antibiotic resistant microbes.

2. Underpinning research

Most patients with community acquired pneumonia – a leading cause of hospital admissions and death – do not receive an etiological diagnosis. Treatment is therefore based om clinical presentation and empirical guidelines. Recent developments in molecular methods can potentially increase rapidity of pathogen detection, facilitate pathogen directed treatment, reduce unnecessary antibiotic use, and improve patient outcome. Accordingly, the Department of Microbiology has streamlined an infrastructure for rapid handling of samples received from the hospital, including transportation, sample preparation, analysis for pathogens and electronic delivery of analysis reports directly to the patient information system.

There is limited scientific evidence as to the diagnostic value of rapid testing in clinical settings. To investigate the effects of rapid molecular testing of sputum from patients with lower respiratory tract infections, we therefore conducted a pragmatic, parallel-arm single-blinded, single-centre, randomised controlled superiority trial (1). The research was a collaborative effort between researchers and staff at Haukeland University Hospital (Department of Microbiology and the Emergency Care Clinic), and the University of Bergen. Funding was obtained from the Research Council of Norway (NORCAP; 288718) (principal funder), the Trond Mohn Foundation (COVID-19 CAPNOR; TMS2020TMT07 and RESPNOR; BFS2019TMT06), the University of Bergen (UoB), and Haukeland University Hospital (HUS).

Although the results of the randomised controlled trial (RCT) have not yet been published, several substudies performed between 2019 and 2022 have ascertained that routine deployment of PCR testing for pathogens provides faster and more targeted microbial treatment for patients with suspected community acquired pneumonia than time-consuming laboratory-based diagnostics (2-6). Additionally, we have recently conducted a study supporting host transcriptional signatures in peripheral blood samples as a potential tool for

guiding clinical decision-making and enhancing antibiotic stewardship in community-acquired pneumonia (7).

Research was conducted by members of the Bergen Integrated Diagnostic Stewardship cluster (BIDS), Dept. of Clinical Science, University of Bergen. Key researchers were:
Dagfinn L. Markussen, Senior consultant, Phd-candidate, HUS, UoB
Sondre Serigstad, Consultant, Phd, HUS, UoB
Christian Ritz, Professor, University of Southern Denmark, Copenhagen, Denmark
Siri T Knoop, Consultant, Phd, HUS
Marit H Ebbesen, Senior consultant, Phd, HUS
Daniel Faurholt-Jepsen, Senior consultant, Phd, Rigshospitalet, Denmark
Lars Heggelund, Professor, senior consultant, Drammen Hospital, UoB
C. H. (Henri) van Werkhoven, Associate Professor, University Medical Center Utrecht, The Netherlands
Tristan W Clark, Professor, University of Southampton, UK
Rune O Bjørneklett, Professor, senior consultant, HUS, UoB
Øyvind Kommedal, Senior consultant, Phd, HUS
Elling Ulvestad, Professor, Head of Department, UoB, HUS
Harleen M.S. Grewal, Professor, senior consultant, leader of BIDS, UoB, HUS

3. References to the research

1. Serigstad S, Ritz C, Faurholt-Jepsen D, Markussen D, Ebbesen MH, Kommedal Ø, Bjørneklett RO, Heggelund L, Clark TW, van Werkhoven CH, Knoop ST, Ulvestad E, Grewal HMS; CAPNOR study group. Impact of rapid molecular testing on diagnosis, treatment and management of community-acquired pneumonia in Norway: a pragmatic randomised controlled trial (CAPNOR). Trials 2022;23:622 Impact of rapid molecular testing on diagnosis, treatment and management of community-acquired pneumonia in Norway: a pragmatic randomised controlled trial (CAPNOR) - PubMed (nih.gov)

2. Markussen DL, Grewal HMS, Knoop ST, Serigstad S, Kommedal Ø, Ebbesen M, Ulvestad E, Bjørneklett R; CAPNOR Study Group. Comparison of rapid molecular testing methods for detecting respiratory viruses in emergency care: a prospective study. Infect Dis 2022;54:247-254. Comparison of rapid molecular testing methods for detecting respiratory viruses in emergency care: a prospective study - PubMed (nih.gov)

3. Serigstad S, Markussen D, Grewal HMS, Ebbesen M, Kommedal Ø, Heggelund L, van Werkhoven CH, Faurholt-Jepsen D, Clark TW, Ritz C, Ulvestad E, Bjørneklett R, Knoop ST; CAPNOR Study Group. Rapid syndromic PCR testing in patients with respiratory tract infections reduces time to results and improves microbial yield. Sci Rep 2022;12:326. Rapid syndromic PCR testing in patients with respiratory tract infections reduces time to results and improves microbial yield - PubMed (nih.gov)

4. Serigstad S, Markussen DL, Ritz C, Ebbesen MH, Knoop ST, Kommedal Ø, Heggelund L, Ulvestad E, Bjørneklett RO, Grewal HMS; CAPNOR study group. The changing spectrum of

microbial aetiology of respiratory tract infections in hospitalized patients before and during the COVID-19 pandemic. BMC Infect Dis 2022;22:763. The changing spectrum of microbial aetiology of respiratory tract infections in hospitalized patients before and during the COVID-19 pandemic - PubMed (nih.gov)

5. Serigstad S, Knoop ST, Markussen DL, Ulvestad E, Bjørneklett RO, Ebbesen MH, Kommedal Ø, Grewal HMS. Diagnostic utility of oropharyngeal swabs as an alternative to lower respiratory tract samples for PCR-based syndromic testing in patients with community-acquired pneumonia. J Clin Microbiol. 2023;61(9):e0050523. Diagnostic utility of oropharyngeal swabs as an alternative to lower respiratory tract samples for PCR-based syndromic testing in patients with community-acquired pneumonia - PubMed (nih.gov)

6. Markussen DL, Ebbesen M, Serigstad S, Knoop ST, Ritz C, Bjørneklett R, Kommedal Ø, Jenum S, Ulvestad E, Grewal HMS. The diagnostic utility of microscopic quality assessment of sputum samples in the era of rapid syndromic PCR testing. Microbiol Spectr 2023 :e0300223. doi: 10.1128/spectrum.03002-23. The diagnostic utility of microscopic quality assessment of sputum samples in the era of rapid syndromic PCR testing - PubMed (nih.gov)

7. Sivakumaran D, Jenum S, Vaz M, Selvam S, Ottenhoff THM, Haks MC, Malherbe ST, Doherty TM, Ritz C, Grewal HMS. Combining host-derived biomarkers with patient characteristics improves signature performance in predicting tuberculosis treatment outcomes. Commun Biol 2020;3:359. Combining host-derived biomarkers with patient characteristics improves signature performance in predicting tuberculosis treatment outcomes - PubMed (nih.gov)

4. Details of the impact

Management of severe infectious diseases necessitates rapid investigation and ascertainment of microbial pathogens and their resistance characteristics. The slowness of traditional approaches – which take at least 48 hours for identification and susceptibility testing of bacterial pathogens – drives prolongation of potentially inappropriate therapies and thereby the evolution of antimicrobial resistance.

The last couple of years has seen a gradual increase in available techniques for rapid diagnostics of pathogens and their susceptibility patterns. Such developments may fundamentally change microbiological approaches towards pathogen identification and susceptibility testing.

Application of the novel techniques is costly in terms of equipment, consumables, and infrastructure organisation. Cost-effectiveness analyses focusing on the direct benefits for patients are therefore required, for example in the form of rigorous intervention studies.

The investigations leading up to the RCT have provided information relating to performance of the novel techniques in a real-life clinical setting. Further elaboration of data from the RCT will likely provide information relating to costs in implementing molecular technologies for acute respiratory infections for the laboratory and the clinic. The RCT was, however, not designed to elaborate

whether patients receiving rapid molecular testing fared better than patients receiving traditional diagnostics.

5. Sources to corroborate the impact

D'Onofrio V, Salimans L, Bedenić B, Cartuyvels R, Barišić I, Gyssens IC. The clinical Impact of rapid molecular microbiological diagnostics for pathogen and resistance gene identification in patients with sepsis: A systematic review. Open Forum Infect Dis. 2020.
The Clinical Impact of Rapid Molecular Microbiological Diagnostics for Pathogen and Resistance Gene Identification in Patients With Sepsis: A Systematic Review - PubMed (nih.gov)

Hitchcock MM, Gomez CA, Pozdol J, Banaei N. Effective Approaches to Diagnostic Stewardship of Syndromic Molecular Panels. J Appl Lab Med 2024; 9:104-115.
Effective Approaches to Diagnostic Stewardship of Syndromic Molecular Panels - PubMed (nih.gov)

Pickens CI, Gao CA, Morales-Nebreda L, Wunderink RG. Microbiology of Severe Community-Acquired Pneumonia and the Role of Rapid Molecular Techniques. Semin Respir Crit Care Med. 2024 Microbiology of Severe Community-Acquired Pneumonia and the Role of Rapid Molecular Techniques - PubMed (nih.gov)

Helse Bergen – Haukeland University Hospital – Impact case #2

Institution: Haukeland University Hospital
Administrative unit: Dep. of Radiology (in collaboration with Dep. of Gynaecology)
Title of case study: Precision Imaging in Gynaecologic Cancer
Period when the underpinning research was undertaken: 2016-2023
Period when staff involved in the underpinning research were employed by the submitting institution: 2016-2023
Period when the impact occurred: 2016-2023

1. Summary of the impact (indicative maximum 100 words)
This section should briefly state what specific impact is being described in the case study.

Gynaecologic cancer patients diagnosed and treated at Haukeland University Hospital (HUS) are routinely offered advanced imaging by pelvic magnetic resonance imaging (MRI) and positron emission tomography-computed tomography (PET-CT) in parallel with histologic/molecular tumour profiling. A platform for artificial intelligence guided automated tumour profiling in combination with other imaging- and tissue markers has been developed. This will be utilized for further refining pretreatment staging, prognostication and monitoring of therapeutic response in gynaecologic cancers. Importantly, the implementation of imaging guided tailored treatment schemes (minimally invasive- or extended therapy) according to risk profiles, is essential for providing best standard of patient care.

2. Underpinning research (indicative maximum 500 words)

1.) The value of preoperative imaging (mostly MRI and PET-CT) for pretherapeutic staging and prognostication in endometrial cancer and cervical cancer has during 2013-23 been described in large well-annotated cohorts at HUS, and the findings have implications for imaging guidelines and the delivery of best practice in gynaecologic cancer patient care. In endometrial cancer, PET-CT has been shown to yield better accuracy than MRI for predicting lymph node metastases (Fasmer et al., Eur. Radiol. 2020); however, using selective PET in patients with high-risk MRI findings only, may represent a safe alternative to PET and MRI in all (Fasmer et al., Eur Radiol. 2023). Furthermore, preoperative pelvic MRI yields important staging information and imaging markers that may guide choice of surgical procedure (Dyvik et al., Insights Imaging 2022). In cervical cancer, interobserver reproducibility for MRI based 2018 staging parameters is good and tumour size yields strong prognostic power (Wagner-Larsen et al., Eur Radiol. 2022, Lura et al., Insights Imaging 2022). Pelvic MRI is also essential for establishing correct tumour stage pretherapeutically, guiding choice of primary treatment (primary surgery or chemoradiation with curative intent) in cervical cancer (Wagner-Larsen et al., Eur Radiol. 2022).

Key researchers involved in this initiative: Prof. Ingfrid Haldorsen (PI), senior researcher Erlend Hodneland, postdoc Kristine Fasmer, MD/PhD student Kari Wagner-Larsen, MD/PhD student Njål Lura, MD/PhD student Julie Dybvik, MD/PhD student Ankush Gulati and PhD student Jostein Sæterstøl.

2.) We have during 2018-23 developed a machine learning platform for accurate automated tumour segmentations from MRI in uterine endometrial- and cervical cancer (Hodneland et al., Scientific Reports 2021; Cancers 2022) that enables automated radiomic tumour profiling enabling better prognostication in endometrial cancer (Høivik et al., Comm. Biol.

2021; Fasmer et al., JMRI 2021) and in cervical cancer (Wagner-Larsen et al., Cancer Medicine 2023).

The artificial intelligence (AI) guided machine learning platform was awarded Innovation support of 1 MNOK from Helse-Vest Regional Health in 2024-25 (technical PI: senior researcher Erlend Hodneland) for further development and potential implementation into the standard routine clinical work-flow.

Key researchers involved in this initiative: Prof. Ingfrid Haldorsen (PI), senior researcher Erlend Hodneland, postdoc Kristine Fasmer, PhD Sathiesh Kaliyugarasan, MD/PhD student Kari Wagner-Larsen, MD/PhD student Njål Lura, MD/PhD student Julie Dybvik, MD/PhD student Ankush Gulati and PhD student Jostein Sæterstøl.

3.) The research group has during 2016-23 developed an organoid endometrial cancer mouse model (Berg et al., Commun Med 2021) where preclinical MRI- and PET-CT findings mirror imaging findings in human endometrial cancers (Espedal et al., J Transl Med 2021). This preclinical model is now utilized for further testing of novel therapies.

Key researchers involved in this initiative: Prof. Ingfrid Haldorsen (PI), Prof. Camilla Krakstad (UiB), postdoc Heidi Espedal (2018-22), postdoc Hege Berg.

-

3. References to the research (listing **six references** only out of)

1.)
- Author(s): Fasmer KE, Gulati A, Dybvik JA, Wagner-Larsen KS, Lura N, Salvesen Ø, Forsse D, Trovik J, Pijnenborg JMA, Krakstad C, Haldorsen IS
- Title: Preoperative pelvic MRI and 2-[18F]FDG PET/CT for lymph node staging and prognostication in endometrial cancer-time to revisit current imaging guidelines?
- Year of publication: 2023
- Eur Radiol. 2023, 33:221-232. **Level 2 (high-impact publication)**
- doi: 10.1007/s00330-022-08949-3.

2.)
- Author(s): Wagner-Larsen KS, Lura N, Salvesen ØO, Halle MK, Forsse D, Trovik J, Smit N, Krakstad C, Haldorsen IS
- Title: Interobserver agreement and prognostic impact for MRI--based 2018 FIGO staging parameters in uterine cervical cancer
- Year of publication: 2022
- Eur Radiol 2022, 32, 6444-6455. **Level 2 (high-impact publication)**
- doi:10.1007/s00330-022-08666-x.

3.)
- Author(s): Espedal H, Berg HF, Fonnes T, Fasmer KE, Krakstad C, Haldorsen IS
- Title: Feasibility and utility of MRI and dynamic 18F-FDG-PET in an orthotopic organoid-based patient-derived mouse model of endometrial cancer
- Year of publication: 2021
- Journal of Translational Medicine 2021, 406. **Level 2 (high-impact publication)**
- DOI: 10.1186/s12967-021-03086-9

4.)
- Author (s): Høivik EA, Hodneland E, Dybvik JA, Wagner-Larsen KS; Fasmer KE, Berg HF, Halle MK, Haldorsen IS, Krakstad C

- Title A radiogenomics application for prognostic profiling of endometrial cancer
- Year of publication: 2021
- Commun Biol. 2021
- doi: 10.1038/s42003-021-02894-5

5.)
- Author(s) : Hodneland E, Dybvik JA, Wagner-Larsen KS, Šoltészová V, Munthe-Kaas AZ, Fasmer KE, Krakstad C, Lundervold A, Lundervold AS, Salvesen Ø, Erickson BJ, Haldorsen IS
- Title Automated segmentation of endometrial cancer on MR images using deep learning
- Year of publication: 2021
- Scientific Reports, 2021
- doi: 10.1038/s41598-020-80068-9

6.)
- Author(s): Fasmer KE, Hodneland E, Dybvik JA, Wagner-Larsen K, Trovik J, Salvesen Ø, Krakstad C, Haldorsen IS
- Title: Whole-Volume Tumor MRI Radiomics for Prognostic Modeling in Endometrial Cancer
- Year of publication 2021
- J Magn Reson Imaging 2021, 53:928-937 **Level 2 (high-impact publication)**
- DOI: 10.1002/jmri.27444

4. Details of the impact (indicative maximum 750 words)

The impact of this project is manyfold:

1.) **Machine learning algorithms have been incorporated into the research PACS system at HUS** (led by Assoc. Profs. Erlend Hodneland, Hauke Bartsch, Alexander Lundervold at UiB/HVL/MMIV). This will be further developed to allow *prospective utilization of a work-flow integrated machine learning platform* (as a part of our funded NRC project) on MRI and PET data for assessing whether *this yields diagnostic-, prognostic- and therapeutic decision support in a routine clinical setting in gynaecologic cancers*. Furthermore, the imaging platform will be extended to allow sharing of imaging data and machine learning algorithms across collaborating sites which will facilitate external validation and testing in independent patient cohorts, supporting translation and potential implementation into the clinic.

2.) **We have developed a machine learning platform for radiogenomic tumour profiling** *where we extract radiomic MRI- and PET-CT profiles in combination with corresponding molecular-, transcriptomic- and genomic tumour profiles in gynaecologic cancer***.** This involves analyses of radiomic tumour features from tumour segmentations by expert radiologists and from the machine learning model in combination with results from molecular-, transcriptomic-, and genomic profiling (conducted and led by Bergen Gynaecologic Cancer Research Group).

3.) **We have established a preclinical organoid orthotopic endometrial cancer mouse model** *that is used for testing of therapeutic response during targeted therapies*. Changes in primary tumour volumes, metastatic spread, and in radiomic MRI tumour profiles during tumour growth in non-treated and treated mice are studied, with the aim to unravel early markers of therapeutic response. Importantly, the preclinical imaging findings mirror characteristic imaging findings in human endometrial cancer, and thus this imaging model

represents an excellent translational platform for the development and testing of novel therapies.

4.) **We are positioned to systematically assess diagnostic performance metrics of advanced PET-CT- and MRI markers and their clinical benefit** *for pretherapeutic staging and disease monitoring in endometrial- and cervical cancer* in large well-annotated patient cohorts (n~900 endometrial cancers; n~700 cervical cancers at HUS). The results will be discussed and presented in the context of current international treatment and staging guidelines that incorporate imaging findings into stage allocations and treatment stratifications.

Collaboration with international clinical gynaecologists/radiologists who collect imaging data on gynaecologic cancer patients will be continued, in order to ensure validation of relevant findings in external patient cohorts.

5.) **The developed research infrastructure at Mohn Medical Imaging and Visualization Centre (MMIV) will be instrumental for successful translation into better patient care.** The research facilities at MMIV provide infrastructure for running extensive machine learning studies. The high-quality offices allow hosting visiting local or international researchers/students for periods of time and accommodate up to ~40 researchers simultaneously. By being co-localized at MMIV with access to a large lunch and meeting room, all researchers are invited to regular research meetings for the different research groups and to join social lunches on a daily basis with all researchers at MMIV. The co-localization has been a great asset to our research community and has resulted in students and researchers at MMIV being overall very content.

See MMIV report 2022-23 for more information about MMIV: mmiv-annual-report-08062023-forweb.pdf

5. Sources to corroborate the impact: with references to ***public visibility/press coverage*** during 2019-23 demonstrating impact of the research.

1.) **Patients diagnosed with gynaecologic cancer are routinely offered advanced diagnostic imaging guiding treatment decisions with overall high patient satisfaction:**
Dagen etter kreftoperasjonen kunne Tordis dra hjem. Da var hun ferdigbehandlet. (bt.no)

2.) **Automated tumour segmentations in uterine cancer allow tumour profiling relevant for patient care.**
Forskning: Utvikler ny behandling for livmorkreft - VG

3.) **Imaging derived tumor markers predict survival in uterine cervical cancer**
Primary Mean Tumor ADC Values May Predict Survival | RSNA 2022

4.) **MRI refines pretherapeutic staging in uterine cervical cancer**
MRI Effective for Pre-Therapeutic Staging and Tailoring | RSNA 2020

5.) **AI guided radiogenomic tumor profiling in uterine cancer allows prediction of patients with high-risk disease**
Kunstig intelligens skal oppdaga kreft – NRK Vestland

6.) **Automated tumor segmentations is possible in gynecologic cancer**
AI-revolusjonen Snart kan Julie slippe «drittjobbene» (tv2.no)

7.) AI- guided diagnostics will transform health care

Håper dette kan hjelpe mot de dødeligste hjernegåtene (tv2.no)
Slik kan kunstig intelligens endre bildemedisinen (dagensmedisin.no)

Radiologiprofessor: - Å kombinere kunstig intelligens og genanalyse er det neste store innen kreftdiagnostisering (healthtalk.no)

Helse Bergen - Haukeland **University Hospital - Impact case** # 3

Institution: Haukeland University Hospital
Administrative unit: Division of Psychiatry
Title of case study: Personalized antipsychotic drug treatment
Period when the underpinning research was undertaken: 2012-2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2012-2022
Period when the impact occurred: 2019-2023

1. Summary of the impact (indicative maximum 100 words)

We have documented differential effectiveness between antipsychotic medications and different response patterns in patients with schizophrenia-spectrum disorder and that men and women respond differently to particular antipsychotics. We have found that childhood trauma may influence antipsychotic effectiveness but substance use does not. Use of antipsychotics compared to periods with non-use seems to strongly reduce all-cause mortality risk.

2. Underpinning research (indicative maximum 500 words)

Schizophrenia spectrum disorders are among the most severe and costly mental illnesses, with life-long episodic symptoms of psychosis (hallucinations and delusions) and functional decline in the majority of cases. Antipsychotic drugs remain the only effective pharmacological treatment, but little is still known about group level differential effectiveness between first line drugs in every-day clinical practice. Furthermore, it is largely unknown which individuals will have the optimal benefit/ harm ratio for any particular drug, as substantial, unpredictable inter-individual differences between patients exist for both wanted effects and side effects. Antipsychotic treatment of schizophrenia generally follows a trial-and-error approach with few if any qualifiers for choice of any first-line drug. The chosen antipsychotic drug should be used for 4-6 (8) weeks to evaluate its effectiveness. In the event of problematic side effects or insufficient beneficial effects, change to another antipsychotic drug is recommended followed by the same procedure of evaluation of the next drug. After two mistrials, change to clozapine, the only superior antipsychotic drug in treatment-resistant cases, is indicated. As a result of this tedious process, identifying optimal antipsychotic drug may be delayed by several months in the individual patient.

To address key shortcomings in the evidence base we designed the RCN-funded Bergen-Stavanger-Innsbruck-Trondheim Study (BeSt InTro) (Oct. 2011-Dec. 2017) to produce data with potentially major impact on clinical decision making and to compliment treatment guidelines. BeSt InTro is a pragmatic, randomized, controlled effectiveness study comparing amisulpride, aripiprazole and olanzapine, three first-line antipsychotic drugs. The study had a one-year follow-up, and was designed and conducted independently of pharmaceutical industry. A total of 144 participants were randomized, and through BeSt InTro we have found

1) clinically important differential effectiveness between the antipsychotic medications for reducing symptoms of psychosis at group level (Johnsen, 2020 (Lancet Psychiatry));
2) that men and women responded very differently to amisulpride and amulpride was less effective and had more side effects compared to in men (Hoekstra, 2021, NPJ Schizophrenia)),;
3) that concomittant substance abuse or dependence do not, contrary to common beliefs, influence effectiveness or side effects of antipsychotic drugs (Alisauskiene, 2023 (General Hospital Psychiatry);
4) that childhood trauma may influence antipsychotic effectiveness with delayed response to antipsychotic drugs (Mørkved, 2022 (Schizophrenia Research)).

Another venue of research in the group has addressed the controversial issue of how use versus non-use of antipsychotic drugs impact outcomes related to premature mortality in persons with

schizophrenia. Based on the common side effects of antipsychotic drugs related to weight gain and adverse impact on serum lipids and glucose, it has been expected that antipsychotics increase mortality risk. In a total cohort (N=696) of all patients with schizophrenia discharged after an acute hospital admission and followed for up to 10 years, we found that periods with non-use of antipsychotic drugs compared to periods with use of were associated with almost three times higher risk of deatht (Strømme, 2021 (Schizophrenia Research)), meaning use of antipsychotic drugs reduced the risk of premature death substantially. This finding has direct relevance to clinical decision making in psychosis treatment.

Erik Johnsen, Head Psychiatrist, senior researcher/ professor
Rune A. Kroken, Psychiatrist, senior researcher/ associate professor
Else-Marie Løberg, Specialist in clinical psychology, senior researcher/ professor
Vidar M. Steen, Head of department, senior researcher/ professor, consultant, MD.

3. References to the research (indicative maximum of six references)

Johnsen E, Kroken RA, Loberg EM, Rettenbacher M, Joa I, Larsen TK, et al. Amisulpride, aripiprazole, and olanzapine in patients with schizophrenia-spectrum disorders (BeSt InTro): a pragmatic, rater-blind, semi-randomised trial. The Lancet Psychiatry 2020;7(11):945-54.

Hoekstra S, Bartz-Johannessen C, Sinkeviciute I, Reitan SK, Kroken RA, Loberg EM, et al. Sex differences in antipsychotic efficacy and side effects in schizophrenia spectrum disorder: results from the BeSt InTro study. NPJ Schizophr. 2021;7(1):39.

Alisauskiene R, Johnsen E, Gjestad R, Kroken RA, Kjelby E, Sinkeviciute I, et al. Does drug use affect the efficacy of amisulpride, aripiprazole and olanzapine in patients with schizophrenia spectrum disorders? Results from a pragmatic, randomised study. Gen Hosp Psychiatry. 2023;83:185-93.

Morkved N, Johnsen E, Kroken RA, Winje D, Larsen TK, Thimm JC, et al. Impact of childhood trauma on antipsychotic effectiveness in schizophrenia spectrum disorders: A prospective, pragmatic, semi-randomized trial. Schizophr Res. 2022;246:49-59.

Stromme MF, Mellesdal LS, Bartz-Johannesen C, Kroken RA, Krogenes M, Mehlum L, et al. Mortality and non-use of antipsychotic drugs after acute admission in schizophrenia: A prospective total-cohort study. Schizophr Res. 2021;235:29-35.

4. Details of the impact (indicative maximum 750 words)

Current treatment guidelines generally recommend starting an antipsychotic drug in the presence of psychosis but offers little guidance regarding choice of particular drug except to base choices on the different side effect profiles of first-line agents. We compared three first-line antipsychotic drugs (amisulpride, aripiprazole and olanzapine) and found that amisulpride had reduced psychosis symptoms statistically significantly more than aripiprazole and olanzapine after 52 weeks of follow-up, the primary outcome. The magnitude of the difference between amisulpride and the other agents corresponds to a moderate effect size which is usually regarded as being clinically significant. The findings were disseminated in national media (NRK 19.10.2020) and in the Psychiatric News of the American Psychiatric Association (16.11.2020), quoting Professor Stephen Marder at University of California: “The advantages of amisulpride were substantial. I’m hopeful that studies like this may encourage industries to sponsor amisulpride studies in the United States”.

Furthermore, side effect differences were much smaller than what have been found in previous short-term studies. As an example, weight gain, one of the most problematic side effects of antipsychotic drugs, was of comparable magnitude for all study drugs after 52 weeks, which contrasts findings of large differences between drugs. The added value of the BeSt InTro study includes having a longer follow-up, a pragmatic design with a patient sample more representative of patients in clinical practice than most randomized controlled trials of efficacy. Taken together,

our research may substantiate a revision of current guidance that focuses primarily on drug choice being based side effect differences whereas our research identified substantial effectiveness differences and minor tolerability differences.
Next, we investigated whether gender differences existed for drug effects, as this is only rarely researched. To our surprise, we found that the superior effectiveness of amisulpride was restricted to men only. Further, women using amisulpride had substantially more hyperprolactinemia than men. This is highly relevant clinically, as recent findings indicate that prolactin-elevating antipsychotic drugs seem to be associated with increased risk of breast cancer in women. The study also contributed to the Evidence-Based Recommendations for the Pharmacological Treatment of Women With Schizophrenia Spectrum Disorder (21.10.2023). Taken together, lack of superior efficacy and possible increased cancer risk mean that amisulpride should not be a first-line agent in women.
Concomitant illicit drug abuse or dependence is frequent in people with schizophrenia, and many claims have been made on how illicit substances might counteract the beneficial effects of antipsychotic drugs or worsen side effects. Previous results from our group found no support for any of these claims as highlighted by Nasjonal kompetansetjeneste for samtidig rusmisbruk og psykisk lidelse (NKROP) (22.11.2019 and 30.09.2021), and further confirmed by results from the BeSt InTro study, meaning that similar antipsychotic drug response is to be expected in both populations with and without illicit substance abuse in addition to schizophrenia.
Childhood trauma has been established as an important risk factor for later development of schizophrenia, and some argue that its presence reduces the beneficial effects of antipsychotic drugs. We found no support for reduced effectiveness compared to those without history of trauma, but that response to treatment may be delayed in the trauma group (Nasjonal kompetansetjeneste for samtidig rusmisbruk og psykisk lidelse 07.10.2022). This is important information, as in patients with a history of adverse life events a longer expectancy may be indicated for signs of response to avoid unnecessary premature termination.
Finally, we have demonstrated that, in the current heated discussion on benefits versus harms of antipsychotic drugs, periods of non-use of antipsychotics in schizophrenia are associated with almost three times elevated mortality risk compared to periods with antipsychotic drug use. Although similar results have been published predominantly from registries in the last decade by other groups, our study did not suffer from many of the limitations pinpointed in earlier registry studies. The findings are highly relevant and were published in national media (BT 24.10.2021).

Summing up, our research has added several pieces of evidence to guide antipsychotic drug choice in far greater detail than what has been the case, to guide implementation of pragmatic personalization of interventions. This benefits both patients and the health care system by reducing time until effective treatment is established, meaning less suffering in patients and their next of kin, less strain on the health care system, and savings on the health care budget. Our findings have also resulted in partnership in the Mohn Research Centre for Regenerative Medicine aiming to use stem cell models for further personalized medicine in psychosis treatment (Dagens Medisin 01.02.2022).

5. Sources to corroborate the impact (indicative maximum of ten references)

Stor skilnad på likestilte medisinar – NRK Vestland

Psych News Alert: Amisulpride Found More Effective Than Olanzapine or Aripiprazole

Evidence-Based Recommendations for the Pharmacological Treatment of Women with Schizophrenia Spectrum Disorders | Current Psychiatry Reports (springer.com)

ROP - Få ekstra bivirkninger ved samtidig bruk av rusmidler og antipsykotika

ROP - Rusmidler påvirker ikke effekten av antipsykotika

ROP - Et skritt på vei til mer persontilpasset behandling ved psykoselidelser

Økt risiko for å dø: – Dette bør pasientene vite før de kutter ut medisinene (bt.no)

Åpnet nytt forskningssenter for regenerativ medisin - Nyheter, Forskning, Spesialisthelsetjeneste - Dagens Medisin

Trond Mohn Stiftelse | Satser stort på avansert celleterapi (mohnfoundation.no)

Helse Bergen, Haukeland University Hospital – impact case #4

Institution: Haukeland University Hospital, Helse Bergen
Administrative unit: Department of Addiction Medicine
Title of case study: INTRO-HCV
Period when the underpinning research was undertaken: 2017-2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2016-2022
Period when the impact occurred: 2020-2022

1. Summary of the impact (indicative maximum 100 words)
This section should briefly state what specific impact is being described in the case study.

Integrated treatment of hepatitis C is a treatment model that was developed at Haukeland University Hospital and has proven to substantially increase treatment initiation and sustained virologic response to hepatitis C for people with substance use disorders including people who inject drugs. By linking treatment and care together with opioid agonist therapy while simplifying the algorithm for treatment and follow-up, Western Norway are now among the global frontrunners in elimination of hepatitis C. The model itself is built on a simple idea, but has benefitted from a close collaboration between clinicians, users, and researchers.

2. Underpinning research (indicative maximum 500 words)
This section should outline the key research insights or findings that underpinned the impact, and provide details of what research was undertaken, when, and by whom. This research may be a body of work produced over a number of years or may be the output(s) of a particular project. References to specific research outputs that embody the research described in this section, and evidence of its quality, should be provided in the next section. Details of the following should be provided in this section:

- The nature of the research insights or findings which relate to the impact claimed in the case study.
- An outline of what the underpinning research produced by the submitted unit was (this may relate to one or more research outputs, projects or programmes).
- Dates of when it was carried out.

When the project started at the end of 2016, the prevalence of chronic hepatitis C among people with currently or formerly injecting substance use was in the range of 50-60%. Globally, 3-400 000 deaths per year were related to hepatitis C with liver decompensated cirrhosis and liver cancer among the important causes of death. However, the time between transmission and the severe consequences is typically thirty years or more, with many transmitted in their early twenties being at high risk of severe consequences particularly from their fifties. Among people who have injected drugs, liver-related deaths have been found to be more common than overdoses after the age of 50. From around 2010, highly effective direct acting antiviral medications have been developed which can be given as tablets daily over a period of eighth to twelve weeks, with most receiving sustained virologic response ("cured" from hepatitis C). Even though treatment was made increasingly available from around 2014 both in Norway and in a range of other countries, two thirds of those in need of treatment had not initiated treatment by 2017. We hypothesized that the treatment delivery platform which was built on conventional principles was an important reason for a large proportion still not reached by important treatment.

The integrated treatment included a change in the organization of treatment and follow-up, with people already providing follow-up of substance use with opioid agonist therapy or from community care centers taking the leading role in the diagnostics and treatment of hepatitis C. To diagnose hepatitis C and clarify best management, this was in integrated treatment done in one single consultation with a single blood sample taken, while conventional treatment would typically require three outpatient visits to the hospital and each of these initiated by a written invitation letter by mail. When diagnosed, the integrated treatment delivery was also provided by the same teams already providing opioid agonist therapy or care from community centers, with no additional follow-up or visits required, while conventional treatment would have required usually two to three additional outpatient visits to the hospital during treatment. In addition, a blood sample was drawn three months after completion of treatment which confirmed whether treatment was successful, and this was done at the treatment and care centers where the people already received follow-up, while conventional treatment would have required an additional visit to the hospital. To simplify the procedure, a chained testing approach was used for the blood samples, where one test result decided which follow-up tests were analyzed. Even though there were many who prior to the publishing of the primary outcomes acknowledged that integrated treatment could be a simplification, there were many who questioned the safety of providing integrated treatment and care outside the hospitals' medical outpatient clinics.

Thus, with insufficient evidence on its efficacy and safety when we started in 2016/2017, we conducted a randomized controlled trial with 298 people with currently or formerly injecting substance use randomized to receive either integrated or standard treatment. For results, see section 4.

The study was led by Bergen Addiction Research with professor and senior researcher Lars Thore Fadnes as the primary investigator, together with the professors and senior researchers Kjell Arne Johannsson and Else-Marie Løberg, and senior consultant Christian Ohldieck, all employed at Department of Addiction Medicine, Haukeland University Hospital. Other people centrally involved include Christer Aas (MD, PhD), Jørn Henrik Vold (MD,PhD), Fatemeh Chalabianloo (MD, PhD), the user representatives Ole Jørgen Lygren and Ronny Bjørnestad, research nurses Jan Tore Daltveit, Maria Olsvold, Mette Nordbotn, Per Gundersen and Ewa Wilk, professor Peter Vickerman from University of Bristol, senior consultant Alexander Leiva at Haukeland University Hospital, professor Olav Dalgaard at Akershus Universitetssykehus, and professor Svetlana Skurtveit at the Norwegian Institute of Public Health, in addition to a large team of clinicians and users.

3. References to the research (indicative maximum of six references)

This section should provide references to key outputs from the research described in the previous section, and evidence about the quality of the research. All forms of output cited as underpinning research will be considered equitably, with no distinction being made between the types of output referenced. Include the following details for each cited output:

- Author(s)
- Title
- Year of publication
- Type of output and other relevant details required to identify the output (for example, DOI, journal title and issue)
- Details to enable the panel to gain access to the output, if required (for example, a DOI or URL).

All outputs cited in this section must be capable of being made available to panels. If they are not available in the public domain, the administrative unit must be able to provide them if requested by RCN or the evaluation secretariate.

2021 Fadnes LT, Aas CF, Vold JH, Leiva RA, Ohldieck C, Chalabianloo F, Skurtveit S, Lygren OJ, Dalgård O, Vickerman P, Midgard H, Løberg EM, Johansson KA; INTRO-HCV Study Group**. Integrated treatment of hepatitis C virus infection among people who inject drugs: A multicenter randomized controlled trial (INTRO-HCV).** ***PLOS Medicine****. 2021* *https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1003653*

2023 Lim AT, Aas CF, Çağlar ES, Vold **JH, Fadnes LT,** Vickerman P, Johansson KA. Cost-effectiveness of integrated treatment for hepatitis C virus (HCV) among people who inject drugs in Norway: An economic evaluation of the INTRO-HCV trial. Addiction 2023 https://onlinelibrary.wiley.com/doi/10.1111/add.16305

2023 Vold JH, Chalabianloo F, Løberg EM, Aas CF, Lim AG, Vickerman P, Johansson KA, Fadnes LT. **The efficacy of integrated hepatitis C virus treatment in relieving fatigue in people who inject drugs: A randomized controlled trial**. *Substance Abuse Treatment, Prevention, and Policy 2023* *https://substanceabusepolicy.biomedcentral.com/articles/10.1186/s13011-023-00534-1*

2022 Sælør KT, Carlsen SEL, Fadnes LT, Lorås L: **Experiences of Hope After Treatment of Hepatitis C Infection – a Qualitative Study**. *International Journal of Environmental Research and Public Health* 2022. https://www.mdpi.com/1660-4601/19/23/15732

2020 Aas CF, Vold JH, Skurtveit S, Odsbu I, Chalabianloo F, Okland JM, Leiva RAM, Vickerman P, Johansson KA, Fadnes LT**. On the path towards universal coverage of hepatitis C treatment among people receiving opioid agonist therapy (OAT) in Norway: a prospective cohort study from 2013 to 2017**. *BMJ Open. 2020* *https://bmjopen.bmj.com/content/10/8/e036355.long*

2022 Norwegian national expert committee on hepatitis C**. The Norwegian guidelines on diagnostics and treatment of hepatitis C**. 2022. *https://hepatittfag.no/pdf-hcv*.

4. Details of the impact (indicative maximum 750 words)

This section should provide a narrative, with supporting evidence, to explain:

- How the research underpinned (made a distinct and material contribution to) the impact;
- The nature and extent of the impact.

The following should be provided:

- A clear explanation of the process or means through which the research led to, underpinned or made a contribution to the impact (for example, how it was disseminated, how it came to influence users or beneficiaries, or how it came to be exploited, taken up or applied).
- Where the submitted administrative unit's research was part of a wider body of research that contributed to the impact (for example, where there has been research collaboration with other institutions), the case study should specify the particular contribution of the submitted administrative unit's research and acknowledge other key research contributions.
- Details of the beneficiaries – who or what community, constituency or organisation has benefitted, been affected or impacted on.
- Details of the nature of the impact – how they have benefitted, been affected or impacted on.
- Evidence or indicators of the extent of the impact described, as appropriate to the case being made.
- Dates of when these impacts occurred.

The results confirmed that among those randomized to integrated treatment, 98% initiated treatment for hepatitis C while the corresponding number for those who received standard

treatment was 77% (even if these also received integrated diagnostics). The difference without integrated diagnostics could be expected to be even larger. Time to treatment initiation was approximately twice as fast among those randomized to integrated treatment. Further, 93% of those who were randomized to integrated treatment and tested, had a sustained virologic response (being "cured" from hepatitis C) in contrast to 73% among those randomized to standard treatment.

The study has also been shown to be highly cost effective and in several settings probably even cost-saving. It has contributed to providing hope among the patients, enabling people to better take control in their lives including in management of substance use and risks.

By implementing integrated treatment and care of hepatitis C together with opioid agonist therapy and care while simplifying the algorithm for treatment and follow-up, Western Norway are now among the global frontrunners in elimination of hepatitis C. When the study was initiated in 2017, more than 50% were chronically infected with hepatitis C. In 2020, when the recruitment of the trial was completed, the prevalence within the group had fallen to less than 7%, more than reaching ambitious elimination goals that few settings elsewhere have been able to reach.

The study was supported by the Norwegian Research Council and the Regional Health Authority, Western Norway, with a large group of clinicians, user representatives and researchers involved.

The integrated treatment model has now become the new gold standard and is increasingly implemented in much of the world. It has substantially simplified the treatment and follow-up experience for patients while providing superior treatment outcomes.

5. Sources to corroborate the impact (indicative maximum of ten references)

https://www.helse-bergen.no/fag-og-forsking/forsking/da-hepatitt-c-ble-utryddet-pa-vestlandet#:~:text=Bergen%20og%20Stavanger%20ligger%20i,n%C3%A6rmer%20seg%20utryddelse%20av%20viruset.

Helse Bergen – Haukeland University Hospital – Impact case #1

Institution: Haukeland University Hospital
Administrative unit: Department of Microbiology
Title of case study: The impact of molecular testing on diagnostics and management of acute lower respiratory tract infections
Period when the underpinning research was undertaken: 2019-2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2019-2022
Period when the impact occurred: 2019-2022

1. Summary of the impact

Molecular testing of representative samples from patients with lower respiratory tract infections provides faster and more accurate microbial results than standard-of-care testing. Implementation of molecular testing in clinical practice can optimize patient treatment and reduce antibiotic overuse, especially in settings with high prevalence of antibiotic resistant microbes.

2. Underpinning research

Most patients with community acquired pneumonia – a leading cause of hospital admissions and death – do not receive an etiological diagnosis. Treatment is therefore based om clinical presentation and empirical guidelines. Recent developments in molecular methods can potentially increase rapidity of pathogen detection, facilitate pathogen directed treatment, reduce unnecessary antibiotic use, and improve patient outcome. Accordingly, the Department of Microbiology has streamlined an infrastructure for rapid handling of samples received from the hospital, including transportation, sample preparation, analysis for pathogens and electronic delivery of analysis reports directly to the patient information system.

There is limited scientific evidence as to the diagnostic value of rapid testing in clinical settings. To investigate the effects of rapid molecular testing of sputum from patients with lower respiratory tract infections, we therefore conducted a pragmatic, parallel-arm single-blinded, single-centre, randomised controlled superiority trial (1). The research was a collaborative effort between researchers and staff at Haukeland University Hospital (Department of Microbiology and the Emergency Care Clinic), and the University of Bergen. Funding was obtained from the Research Council of Norway (NORCAP; 288718) (principal funder), the Trond Mohn Foundation (COVID-19 CAPNOR; TMS2020TMT07 and RESPNOR; BFS2019TMT06), the University of Bergen (UoB), and Haukeland University Hospital (HUS).

Although the results of the randomised controlled trial (RCT) have not yet been published, several substudies performed between 2019 and 2022 have ascertained that routine deployment of PCR testing for pathogens provides faster and more targeted microbial treatment for patients with suspected community acquired pneumonia than time-consuming laboratory-based diagnostics (2-6). Additionally, we have recently conducted a study supporting host transcriptional signatures in peripheral blood samples as a potential tool for

guiding clinical decision-making and enhancing antibiotic stewardship in community-acquired pneumonia (7).

Research was conducted by members of the Bergen Integrated Diagnostic Stewardship cluster (BIDS), Dept. of Clinical Science, University of Bergen. Key researchers were:
Dagfinn L. Markussen, Senior consultant, Phd-candidate, HUS, UoB
Sondre Serigstad, Consultant, Phd, HUS, UoB
Christian Ritz, Professor, University of Southern Denmark, Copenhagen, Denmark
Siri T Knoop, Consultant, Phd, HUS
Marit H Ebbesen, Senior consultant, Phd, HUS
Daniel Faurholt-Jepsen, Senior consultant, Phd, Rigshospitalet, Denmark
Lars Heggelund, Professor, senior consultant, Drammen Hospital, UoB
C. H. (Henri) van Werkhoven, Associate Professor, University Medical Center Utrecht, The Netherlands
Tristan W Clark, Professor, University of Southampton, UK
Rune O Bjørneklett, Professor, senior consultant, HUS, UoB
Øyvind Kommedal, Senior consultant, Phd, HUS
Elling Ulvestad, Professor, Head of Department, UoB, HUS
Harleen M.S. Grewal, Professor, senior consultant, leader of BIDS, UoB, HUS

3. References to the research

1. Serigstad S, Ritz C, Faurholt-Jepsen D, Markussen D, Ebbesen MH, Kommedal Ø, Bjørneklett RO, Heggelund L, Clark TW, van Werkhoven CH, Knoop ST, Ulvestad E, Grewal HMS; CAPNOR study group. Impact of rapid molecular testing on diagnosis, treatment and management of community-acquired pneumonia in Norway: a pragmatic randomised controlled trial (CAPNOR). Trials 2022;23:622 Impact of rapid molecular testing on diagnosis, treatment and management of community-acquired pneumonia in Norway: a pragmatic randomised controlled trial (CAPNOR) - PubMed (nih.gov)

2. Markussen DL, Grewal HMS, Knoop ST, Serigstad S, Kommedal Ø, Ebbesen M, Ulvestad E, Bjørneklett R; CAPNOR Study Group. Comparison of rapid molecular testing methods for detecting respiratory viruses in emergency care: a prospective study. Infect Dis 2022;54:247-254. Comparison of rapid molecular testing methods for detecting respiratory viruses in emergency care: a prospective study - PubMed (nih.gov)

3. Serigstad S, Markussen D, Grewal HMS, Ebbesen M, Kommedal Ø, Heggelund L, van Werkhoven CH, Faurholt-Jepsen D, Clark TW, Ritz C, Ulvestad E, Bjørneklett R, Knoop ST; CAPNOR Study Group. Rapid syndromic PCR testing in patients with respiratory tract infections reduces time to results and improves microbial yield. Sci Rep 2022;12:326. Rapid syndromic PCR testing in patients with respiratory tract infections reduces time to results and improves microbial yield - PubMed (nih.gov)

4. Serigstad S, Markussen DL, Ritz C, Ebbesen MH, Knoop ST, Kommedal Ø, Heggelund L, Ulvestad E, Bjørneklett RO, Grewal HMS; CAPNOR study group. The changing spectrum of

microbial aetiology of respiratory tract infections in hospitalized patients before and during the COVID-19 pandemic. BMC Infect Dis 2022;22:763. The changing spectrum of microbial aetiology of respiratory tract infections in hospitalized patients before and during the COVID-19 pandemic - PubMed (nih.gov)

5. Serigstad S, Knoop ST, Markussen DL, Ulvestad E, Bjørneklett RO, Ebbesen MH, Kommedal Ø, Grewal HMS. Diagnostic utility of oropharyngeal swabs as an alternative to lower respiratory tract samples for PCR-based syndromic testing in patients with community-acquired pneumonia. J Clin Microbiol. 2023;61(9):e0050523. Diagnostic utility of oropharyngeal swabs as an alternative to lower respiratory tract samples for PCR-based syndromic testing in patients with community-acquired pneumonia - PubMed (nih.gov)

6. Markussen DL, Ebbesen M, Serigstad S, Knoop ST, Ritz C, Bjørneklett R, Kommedal Ø, Jenum S, Ulvestad E, Grewal HMS. The diagnostic utility of microscopic quality assessment of sputum samples in the era of rapid syndromic PCR testing. Microbiol Spectr 2023 :e0300223. doi: 10.1128/spectrum.03002-23. The diagnostic utility of microscopic quality assessment of sputum samples in the era of rapid syndromic PCR testing - PubMed (nih.gov)

7. Sivakumaran D, Jenum S, Vaz M, Selvam S, Ottenhoff THM, Haks MC, Malherbe ST, Doherty TM, Ritz C, Grewal HMS. Combining host-derived biomarkers with patient characteristics improves signature performance in predicting tuberculosis treatment outcomes. Commun Biol 2020;3:359. Combining host-derived biomarkers with patient characteristics improves signature performance in predicting tuberculosis treatment outcomes - PubMed (nih.gov)

4. Details of the impact

Management of severe infectious diseases necessitates rapid investigation and ascertainment of microbial pathogens and their resistance characteristics. The slowness of traditional approaches – which take at least 48 hours for identification and susceptibility testing of bacterial pathogens – drives prolongation of potentially inappropriate therapies and thereby the evolution of antimicrobial resistance.

The last couple of years has seen a gradual increase in available techniques for rapid diagnostics of pathogens and their susceptibility patterns. Such developments may fundamentally change microbiological approaches towards pathogen identification and susceptibility testing.

Application of the novel techniques is costly in terms of equipment, consumables, and infrastructure organisation. Cost-effectiveness analyses focusing on the direct benefits for patients are therefore required, for example in the form of rigorous intervention studies.

The investigations leading up to the RCT have provided information relating to performance of the novel techniques in a real-life clinical setting. Further elaboration of data from the RCT will likely provide information relating to costs in implementing molecular technologies for acute respiratory infections for the laboratory and the clinic. The RCT was, however, not designed to elaborate

whether patients receiving rapid molecular testing fared better than patients receiving traditional diagnostics.

5. Sources to corroborate the impact

D'Onofrio V, Salimans L, Bedenić B, Cartuyvels R, Barišić I, Gyssens IC. The clinical Impact of rapid molecular microbiological diagnostics for pathogen and resistance gene identification in patients with sepsis: A systematic review. Open Forum Infect Dis. 2020.
The Clinical Impact of Rapid Molecular Microbiological Diagnostics for Pathogen and Resistance Gene Identification in Patients With Sepsis: A Systematic Review - PubMed (nih.gov)

Hitchcock MM, Gomez CA, Pozdol J, Banaei N. Effective Approaches to Diagnostic Stewardship of Syndromic Molecular Panels. J Appl Lab Med 2024; 9:104-115.
Effective Approaches to Diagnostic Stewardship of Syndromic Molecular Panels - PubMed (nih.gov)

Pickens CI, Gao CA, Morales-Nebreda L, Wunderink RG. Microbiology of Severe Community-Acquired Pneumonia and the Role of Rapid Molecular Techniques. Semin Respir Crit Care Med. 2024 Microbiology of Severe Community-Acquired Pneumonia and the Role of Rapid Molecular Techniques - PubMed (nih.gov)

Helse Bergen – Haukeland University Hospital – Impact case #2

Institution: Haukeland University Hospital
Administrative unit: Dep. of Radiology (in collaboration with Dep. of Gynaecology)
Title of case study: Precision Imaging in Gynaecologic Cancer
Period when the underpinning research was undertaken: 2016-2023
Period when staff involved in the underpinning research were employed by the submitting institution: 2016-2023
Period when the impact occurred: 2016-2023

1. Summary of the impact (indicative maximum 100 words)
This section should briefly state what specific impact is being described in the case study.

Gynaecologic cancer patients diagnosed and treated at Haukeland University Hospital (HUS) are routinely offered advanced imaging by pelvic magnetic resonance imaging (MRI) and positron emission tomography-computed tomography (PET-CT) in parallel with histologic/molecular tumour profiling. A platform for artificial intelligence guided automated tumour profiling in combination with other imaging- and tissue markers has been developed. This will be utilized for further refining pretreatment staging, prognostication and monitoring of therapeutic response in gynaecologic cancers. Importantly, the implementation of imaging guided tailored treatment schemes (minimally invasive- or extended therapy) according to risk profiles, is essential for providing best standard of patient care.

2. Underpinning research (indicative maximum 500 words)

1.) The value of preoperative imaging (mostly MRI and PET-CT) for pretherapeutic staging and prognostication in endometrial cancer and cervical cancer has during 2013-23 been described in large well-annotated cohorts at HUS, and the findings have implications for imaging guidelines and the delivery of best practice in gynaecologic cancer patient care. In endometrial cancer, PET-CT has been shown to yield better accuracy than MRI for predicting lymph node metastases (Fasmer et al., Eur. Radiol. 2020); however, using selective PET in patients with high-risk MRI findings only, may represent a safe alternative to PET and MRI in all (Fasmer et al., Eur Radiol. 2023). Furthermore, preoperative pelvic MRI yields important staging information and imaging markers that may guide choice of surgical procedure (Dyvik et al., Insights Imaging 2022). In cervical cancer, interobserver reproducibility for MRI based 2018 staging parameters is good and tumour size yields strong prognostic power (Wagner-Larsen et al., Eur Radiol. 2022, Lura et al., Insights Imaging 2022). Pelvic MRI is also essential for establishing correct tumour stage pretherapeutically, guiding choice of primary treatment (primary surgery or chemoradiation with curative intent) in cervical cancer (Wagner-Larsen et al., Eur Radiol. 2022).

Key researchers involved in this initiative: Prof. Ingfrid Haldorsen (PI), senior researcher Erlend Hodneland, postdoc Kristine Fasmer, MD/PhD student Kari Wagner-Larsen, MD/PhD student Njål Lura, MD/PhD student Julie Dybvik, MD/PhD student Ankush Gulati and PhD student Jostein Sæterstøl.

2.) We have during 2018-23 developed a machine learning platform for accurate automated tumour segmentations from MRI in uterine endometrial- and cervical cancer (Hodneland et al., Scientific Reports 2021; Cancers 2022) that enables automated radiomic tumour profiling enabling better prognostication in endometrial cancer (Høivik et al., Comm. Biol.

2021; Fasmer et al., JMRI 2021) and in cervical cancer (Wagner-Larsen et al., Cancer Medicine 2023).

The artificial intelligence (AI) guided machine learning platform was awarded Innovation support of 1 MNOK from Helse-Vest Regional Health in 2024-25 (technical PI: senior researcher Erlend Hodneland) for further development and potential implementation into the standard routine clinical work-flow.

Key researchers involved in this initiative: Prof. Ingfrid Haldorsen (PI), senior researcher Erlend Hodneland, postdoc Kristine Fasmer, PhD Sathiesh Kaliyugarasan, MD/PhD student Kari Wagner-Larsen, MD/PhD student Njål Lura, MD/PhD student Julie Dybvik, MD/PhD student Ankush Gulati and PhD student Jostein Sæterstøl.

3.) The research group has during 2016-23 developed an organoid endometrial cancer mouse model (Berg et al., Commun Med 2021) where preclinical MRI- and PET-CT findings mirror imaging findings in human endometrial cancers (Espedal et al., J Transl Med 2021). This preclinical model is now utilized for further testing of novel therapies.

Key researchers involved in this initiative: Prof. Ingfrid Haldorsen (PI), Prof. Camilla Krakstad (UiB), postdoc Heidi Espedal (2018-22), postdoc Hege Berg.

-

3. References to the research (listing **six references** only out of)

1.)
- Author(s): Fasmer KE, Gulati A, Dybvik JA, Wagner-Larsen KS, Lura N, Salvesen Ø, Forsse D, Trovik J, Pijnenborg JMA, Krakstad C, Haldorsen IS
- Title: Preoperative pelvic MRI and 2-[18F]FDG PET/CT for lymph node staging and prognostication in endometrial cancer-time to revisit current imaging guidelines?
- Year of publication: 2023
- Eur Radiol. 2023, 33:221-232. **Level 2 (high-impact publication)**
- doi: 10.1007/s00330-022-08949-3.

2.)
- Author(s): Wagner-Larsen KS, Lura N, Salvesen ØO, Halle MK, Forsse D, Trovik J, Smit N, Krakstad C, Haldorsen IS
- Title: Interobserver agreement and prognostic impact for MRI--based 2018 FIGO staging parameters in uterine cervical cancer
- Year of publication: 2022
- Eur Radiol 2022, 32, 6444-6455. **Level 2 (high-impact publication)**
- doi:10.1007/s00330-022-08666-x.

3.)
- Author(s): Espedal H, Berg HF, Fonnes T, Fasmer KE, Krakstad C, Haldorsen IS
- Title: Feasibility and utility of MRI and dynamic 18F-FDG-PET in an orthotopic organoid-based patient-derived mouse model of endometrial cancer
- Year of publication: 2021
- Journal of Translational Medicine 2021, 406. **Level 2 (high-impact publication)**
- DOI: 10.1186/s12967-021-03086-9

4.)
- Author (s): Høivik EA, Hodneland E, Dybvik JA, Wagner-Larsen KS; Fasmer KE, Berg HF, Halle MK, Haldorsen IS, Krakstad C

- Title A radiogenomics application for prognostic profiling of endometrial cancer
- Year of publication: 2021
- Commun Biol. 2021
- doi: 10.1038/s42003-021-02894-5

5.)
- Author(s) : Hodneland E, Dybvik JA, Wagner-Larsen KS, Šoltészová V, Munthe-Kaas AZ, Fasmer KE, Krakstad C, Lundervold A, Lundervold AS, Salvesen Ø, Erickson BJ, Haldorsen IS
- Title Automated segmentation of endometrial cancer on MR images using deep learning
- Year of publication: 2021
- Scientific Reports, 2021
- doi: 10.1038/s41598-020-80068-9

6.)
- Author(s): Fasmer KE, Hodneland E, Dybvik JA, Wagner-Larsen K, Trovik J, Salvesen Ø, Krakstad C, Haldorsen IS
- Title: Whole-Volume Tumor MRI Radiomics for Prognostic Modeling in Endometrial Cancer
- Year of publication 2021
- J Magn Reson Imaging 2021, 53:928-937 **Level 2 (high-impact publication)**
- DOI: 10.1002/jmri.27444

4. Details of the impact (indicative maximum 750 words)

The impact of this project is manyfold:

1.) **Machine learning algorithms have been incorporated into the research PACS system at HUS** (led by Assoc. Profs. Erlend Hodneland, Hauke Bartsch, Alexander Lundervold at UiB/HVL/MMIV). This will be further developed to allow *prospective utilization of a work-flow integrated machine learning platform* (as a part of our funded NRC project) on MRI and PET data for assessing whether *this yields diagnostic-, prognostic- and therapeutic decision support in a routine clinical setting in gynaecologic cancers*. Furthermore, the imaging platform will be extended to allow sharing of imaging data and machine learning algorithms across collaborating sites which will facilitate external validation and testing in independent patient cohorts, supporting translation and potential implementation into the clinic.

2.) **We have developed a machine learning platform for radiogenomic tumour profiling** *where we extract radiomic MRI- and PET-CT profiles in combination with corresponding molecular-, transcriptomic- and genomic tumour profiles in gynaecologic cancer***.** This involves analyses of radiomic tumour features from tumour segmentations by expert radiologists and from the machine learning model in combination with results from molecular-, transcriptomic-, and genomic profiling (conducted and led by Bergen Gynaecologic Cancer Research Group).

3.) **We have established a preclinical organoid orthotopic endometrial cancer mouse model** *that is used for testing of therapeutic response during targeted therapies*. Changes in primary tumour volumes, metastatic spread, and in radiomic MRI tumour profiles during tumour growth in non-treated and treated mice are studied, with the aim to unravel early markers of therapeutic response. Importantly, the preclinical imaging findings mirror characteristic imaging findings in human endometrial cancer, and thus this imaging model

represents an excellent translational platform for the development and testing of novel therapies.

4.) **We are positioned to systematically assess diagnostic performance metrics of advanced PET-CT- and MRI markers and their clinical benefit** *for pretherapeutic staging and disease monitoring in endometrial- and cervical cancer* in large well-annotated patient cohorts (n~900 endometrial cancers; n~700 cervical cancers at HUS). The results will be discussed and presented in the context of current international treatment and staging guidelines that incorporate imaging findings into stage allocations and treatment stratifications.

Collaboration with international clinical gynaecologists/radiologists who collect imaging data on gynaecologic cancer patients will be continued, in order to ensure validation of relevant findings in external patient cohorts.

5.) **The developed research infrastructure at Mohn Medical Imaging and Visualization Centre (MMIV) will be instrumental for successful translation into better patient care.** The research facilities at MMIV provide infrastructure for running extensive machine learning studies. The high-quality offices allow hosting visiting local or international researchers/students for periods of time and accommodate up to ~40 researchers simultaneously. By being co-localized at MMIV with access to a large lunch and meeting room, all researchers are invited to regular research meetings for the different research groups and to join social lunches on a daily basis with all researchers at MMIV. The co-localization has been a great asset to our research community and has resulted in students and researchers at MMIV being overall very content.

See MMIV report 2022-23 for more information about MMIV: mmiv-annual-report-08062023-forweb.pdf

5. Sources to corroborate the impact: with references to ***public visibility/press coverage*** during 2019-23 demonstrating impact of the research.

1.) **Patients diagnosed with gynaecologic cancer are routinely offered advanced diagnostic imaging guiding treatment decisions with overall high patient satisfaction:**
Dagen etter kreftoperasjonen kunne Tordis dra hjem. Da var hun ferdigbehandlet. (bt.no)

2.) **Automated tumour segmentations in uterine cancer allow tumour profiling relevant for patient care.**
Forskning: Utvikler ny behandling for livmorkreft - VG

3.) **Imaging derived tumor markers predict survival in uterine cervical cancer**
Primary Mean Tumor ADC Values May Predict Survival | RSNA 2022

4.) **MRI refines pretherapeutic staging in uterine cervical cancer**
MRI Effective for Pre-Therapeutic Staging and Tailoring | RSNA 2020

5.) **AI guided radiogenomic tumor profiling in uterine cancer allows prediction of patients with high-risk disease**
Kunstig intelligens skal oppdaga kreft – NRK Vestland

6.) **Automated tumor segmentations is possible in gynecologic cancer**
AI-revolusjonen Snart kan Julie slippe «drittjobbene» (tv2.no)

7.) AI- guided diagnostics will transform health care

Håper dette kan hjelpe mot de dødeligste hjernegåtene (tv2.no)
Slik kan kunstig intelligens endre bildemedisinen (dagensmedisin.no)

Radiologiprofessor: - Å kombinere kunstig intelligens og genanalyse er det neste store innen kreftdiagnostisering (healthtalk.no)

Helse Bergen - Haukeland **University Hospital - Impact case** # 3

Institution: Haukeland University Hospital
Administrative unit: Division of Psychiatry
Title of case study: Personalized antipsychotic drug treatment
Period when the underpinning research was undertaken: 2012-2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2012-2022
Period when the impact occurred: 2019-2023

1. Summary of the impact (indicative maximum 100 words)

We have documented differential effectiveness between antipsychotic medications and different response patterns in patients with schizophrenia-spectrum disorder and that men and women respond differently to particular antipsychotics. We have found that childhood trauma may influence antipsychotic effectiveness but substance use does not. Use of antipsychotics compared to periods with non-use seems to strongly reduce all-cause mortality risk.

2. Underpinning research (indicative maximum 500 words)

Schizophrenia spectrum disorders are among the most severe and costly mental illnesses, with life-long episodic symptoms of psychosis (hallucinations and delusions) and functional decline in the majority of cases. Antipsychotic drugs remain the only effective pharmacological treatment, but little is still known about group level differential effectiveness between first line drugs in every-day clinical practice. Furthermore, it is largely unknown which individuals will have the optimal benefit/ harm ratio for any particular drug, as substantial, unpredictable inter-individual differences between patients exist for both wanted effects and side effects. Antipsychotic treatment of schizophrenia generally follows a trial-and-error approach with few if any qualifiers for choice of any first-line drug. The chosen antipsychotic drug should be used for 4-6 (8) weeks to evaluate its effectiveness. In the event of problematic side effects or insufficient beneficial effects, change to another antipsychotic drug is recommended followed by the same procedure of evaluation of the next drug. After two mistrials, change to clozapine, the only superior antipsychotic drug in treatment-resistant cases, is indicated. As a result of this tedious process, identifying optimal antipsychotic drug may be delayed by several months in the individual patient.

To address key shortcomings in the evidence base we designed the RCN-funded Bergen-Stavanger-Innsbruck-Trondheim Study (BeSt InTro) (Oct. 2011-Dec. 2017) to produce data with potentially major impact on clinical decision making and to compliment treatment guidelines. BeSt InTro is a pragmatic, randomized, controlled effectiveness study comparing amisulpride, aripiprazole and olanzapine, three first-line antipsychotic drugs. The study had a one-year follow-up, and was designed and conducted independently of pharmaceutical industry. A total of 144 participants were randomized, and through BeSt InTro we have found

1) clinically important differential effectiveness between the antipsychotic medications for reducing symptoms of psychosis at group level (Johnsen, 2020 (Lancet Psychiatry));
2) that men and women responded very differently to amisulpride and amulpride was less effective and had more side effects compared to in men (Hoekstra, 2021, NPJ Schizophrenia)),;
3) that concomittant substance abuse or dependence do not, contrary to common beliefs, influence effectiveness or side effects of antipsychotic drugs (Alisauskiene, 2023 (General Hospital Psychiatry);
4) that childhood trauma may influence antipsychotic effectiveness with delayed response to antipsychotic drugs (Mørkved, 2022 (Schizophrenia Research)).

Another venue of research in the group has addressed the controversial issue of how use versus non-use of antipsychotic drugs impact outcomes related to premature mortality in persons with

schizophrenia. Based on the common side effects of antipsychotic drugs related to weight gain and adverse impact on serum lipids and glucose, it has been expected that antipsychotics increase mortality risk. In a total cohort (N=696) of all patients with schizophrenia discharged after an acute hospital admission and followed for up to 10 years, we found that periods with non-use of antipsychotic drugs compared to periods with use of were associated with almost three times higher risk of deatht (Strømme, 2021 (Schizophrenia Research)), meaning use of antipsychotic drugs reduced the risk of premature death substantially. This finding has direct relevance to clinical decision making in psychosis treatment.

Erik Johnsen, Head Psychiatrist, senior researcher/ professor
Rune A. Kroken, Psychiatrist, senior researcher/ associate professor
Else-Marie Løberg, Specialist in clinical psychology, senior researcher/ professor
Vidar M. Steen, Head of department, senior researcher/ professor, consultant, MD.

3. References to the research (indicative maximum of six references)

Johnsen E, Kroken RA, Loberg EM, Rettenbacher M, Joa I, Larsen TK, et al. Amisulpride, aripiprazole, and olanzapine in patients with schizophrenia-spectrum disorders (BeSt InTro): a pragmatic, rater-blind, semi-randomised trial. The Lancet Psychiatry 2020;7(11):945-54.

Hoekstra S, Bartz-Johannessen C, Sinkeviciute I, Reitan SK, Kroken RA, Loberg EM, et al. Sex differences in antipsychotic efficacy and side effects in schizophrenia spectrum disorder: results from the BeSt InTro study. NPJ Schizophr. 2021;7(1):39.

Alisauskiene R, Johnsen E, Gjestad R, Kroken RA, Kjelby E, Sinkeviciute I, et al. Does drug use affect the efficacy of amisulpride, aripiprazole and olanzapine in patients with schizophrenia spectrum disorders? Results from a pragmatic, randomised study. Gen Hosp Psychiatry. 2023;83:185-93.

Morkved N, Johnsen E, Kroken RA, Winje D, Larsen TK, Thimm JC, et al. Impact of childhood trauma on antipsychotic effectiveness in schizophrenia spectrum disorders: A prospective, pragmatic, semi-randomized trial. Schizophr Res. 2022;246:49-59.

Stromme MF, Mellesdal LS, Bartz-Johannesen C, Kroken RA, Krogenes M, Mehlum L, et al. Mortality and non-use of antipsychotic drugs after acute admission in schizophrenia: A prospective total-cohort study. Schizophr Res. 2021;235:29-35.

4. Details of the impact (indicative maximum 750 words)

Current treatment guidelines generally recommend starting an antipsychotic drug in the presence of psychosis but offers little guidance regarding choice of particular drug except to base choices on the different side effect profiles of first-line agents. We compared three first-line antipsychotic drugs (amisulpride, aripiprazole and olanzapine) and found that amisulpride had reduced psychosis symptoms statistically significantly more than aripiprazole and olanzapine after 52 weeks of follow-up, the primary outcome. The magnitude of the difference between amisulpride and the other agents corresponds to a moderate effect size which is usually regarded as being clinically significant. The findings were disseminated in national media (NRK 19.10.2020) and in the Psychiatric News of the American Psychiatric Association (16.11.2020), quoting Professor Stephen Marder at University of California: “The advantages of amisulpride were substantial. I’m hopeful that studies like this may encourage industries to sponsor amisulpride studies in the United States”.

Furthermore, side effect differences were much smaller than what have been found in previous short-term studies. As an example, weight gain, one of the most problematic side effects of antipsychotic drugs, was of comparable magnitude for all study drugs after 52 weeks, which contrasts findings of large differences between drugs. The added value of the BeSt InTro study includes having a longer follow-up, a pragmatic design with a patient sample more representative of patients in clinical practice than most randomized controlled trials of efficacy. Taken together,

our research may substantiate a revision of current guidance that focuses primarily on drug choice being based side effect differences whereas our research identified substantial effectiveness differences and minor tolerability differences.
Next, we investigated whether gender differences existed for drug effects, as this is only rarely researched. To our surprise, we found that the superior effectiveness of amisulpride was restricted to men only. Further, women using amisulpride had substantially more hyperprolactinemia than men. This is highly relevant clinically, as recent findings indicate that prolactin-elevating antipsychotic drugs seem to be associated with increased risk of breast cancer in women. The study also contributed to the Evidence-Based Recommendations for the Pharmacological Treatment of Women With Schizophrenia Spectrum Disorder (21.10.2023). Taken together, lack of superior efficacy and possible increased cancer risk mean that amisulpride should not be a first-line agent in women.
Concomitant illicit drug abuse or dependence is frequent in people with schizophrenia, and many claims have been made on how illicit substances might counteract the beneficial effects of antipsychotic drugs or worsen side effects. Previous results from our group found no support for any of these claims as highlighted by Nasjonal kompetansetjeneste for samtidig rusmisbruk og psykisk lidelse (NKROP) (22.11.2019 and 30.09.2021), and further confirmed by results from the BeSt InTro study, meaning that similar antipsychotic drug response is to be expected in both populations with and without illicit substance abuse in addition to schizophrenia.
Childhood trauma has been established as an important risk factor for later development of schizophrenia, and some argue that its presence reduces the beneficial effects of antipsychotic drugs. We found no support for reduced effectiveness compared to those without history of trauma, but that response to treatment may be delayed in the trauma group (Nasjonal kompetansetjeneste for samtidig rusmisbruk og psykisk lidelse 07.10.2022). This is important information, as in patients with a history of adverse life events a longer expectancy may be indicated for signs of response to avoid unnecessary premature termination.
Finally, we have demonstrated that, in the current heated discussion on benefits versus harms of antipsychotic drugs, periods of non-use of antipsychotics in schizophrenia are associated with almost three times elevated mortality risk compared to periods with antipsychotic drug use. Although similar results have been published predominantly from registries in the last decade by other groups, our study did not suffer from many of the limitations pinpointed in earlier registry studies. The findings are highly relevant and were published in national media (BT 24.10.2021).

Summing up, our research has added several pieces of evidence to guide antipsychotic drug choice in far greater detail than what has been the case, to guide implementation of pragmatic personalization of interventions. This benefits both patients and the health care system by reducing time until effective treatment is established, meaning less suffering in patients and their next of kin, less strain on the health care system, and savings on the health care budget. Our findings have also resulted in partnership in the Mohn Research Centre for Regenerative Medicine aiming to use stem cell models for further personalized medicine in psychosis treatment (Dagens Medisin 01.02.2022).

5. Sources to corroborate the impact (indicative maximum of ten references)

Stor skilnad på likestilte medisinar – NRK Vestland

Psych News Alert: Amisulpride Found More Effective Than Olanzapine or Aripiprazole

Evidence-Based Recommendations for the Pharmacological Treatment of Women with Schizophrenia Spectrum Disorders | Current Psychiatry Reports (springer.com)

ROP - Få ekstra bivirkninger ved samtidig bruk av rusmidler og antipsykotika

ROP - Rusmidler påvirker ikke effekten av antipsykotika

ROP - Et skritt på vei til mer persontilpasset behandling ved psykoselidelser

Økt risiko for å dø: – Dette bør pasientene vite før de kutter ut medisinene (bt.no)

Åpnet nytt forskningssenter for regenerativ medisin - Nyheter, Forskning, Spesialisthelsetjeneste - Dagens Medisin

Trond Mohn Stiftelse | Satser stort på avansert celleterapi (mohnfoundation.no)

Helse Bergen, Haukeland University Hospital – impact case #4

Institution: Haukeland University Hospital, Helse Bergen
Administrative unit: Department of Addiction Medicine
Title of case study: INTRO-HCV
Period when the underpinning research was undertaken: 2017-2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2016-2022
Period when the impact occurred: 2020-2022

1. Summary of the impact (indicative maximum 100 words)
This section should briefly state what specific impact is being described in the case study.

Integrated treatment of hepatitis C is a treatment model that was developed at Haukeland University Hospital and has proven to substantially increase treatment initiation and sustained virologic response to hepatitis C for people with substance use disorders including people who inject drugs. By linking treatment and care together with opioid agonist therapy while simplifying the algorithm for treatment and follow-up, Western Norway are now among the global frontrunners in elimination of hepatitis C. The model itself is built on a simple idea, but has benefitted from a close collaboration between clinicians, users, and researchers.

2. Underpinning research (indicative maximum 500 words)
This section should outline the key research insights or findings that underpinned the impact, and provide details of what research was undertaken, when, and by whom. This research may be a body of work produced over a number of years or may be the output(s) of a particular project. References to specific research outputs that embody the research described in this section, and evidence of its quality, should be provided in the next section. Details of the following should be provided in this section:

- The nature of the research insights or findings which relate to the impact claimed in the case study.
- An outline of what the underpinning research produced by the submitted unit was (this may relate to one or more research outputs, projects or programmes).
- Dates of when it was carried out.

When the project started at the end of 2016, the prevalence of chronic hepatitis C among people with currently or formerly injecting substance use was in the range of 50-60%. Globally, 3-400 000 deaths per year were related to hepatitis C with liver decompensated cirrhosis and liver cancer among the important causes of death. However, the time between transmission and the severe consequences is typically thirty years or more, with many transmitted in their early twenties being at high risk of severe consequences particularly from their fifties. Among people who have injected drugs, liver-related deaths have been found to be more common than overdoses after the age of 50. From around 2010, highly effective direct acting antiviral medications have been developed which can be given as tablets daily over a period of eighth to twelve weeks, with most receiving sustained virologic response ("cured" from hepatitis C). Even though treatment was made increasingly available from around 2014 both in Norway and in a range of other countries, two thirds of those in need of treatment had not initiated treatment by 2017. We hypothesized that the treatment delivery platform which was built on conventional principles was an important reason for a large proportion still not reached by important treatment.

The integrated treatment included a change in the organization of treatment and follow-up, with people already providing follow-up of substance use with opioid agonist therapy or from community care centers taking the leading role in the diagnostics and treatment of hepatitis C. To diagnose hepatitis C and clarify best management, this was in integrated treatment done in one single consultation with a single blood sample taken, while conventional treatment would typically require three outpatient visits to the hospital and each of these initiated by a written invitation letter by mail. When diagnosed, the integrated treatment delivery was also provided by the same teams already providing opioid agonist therapy or care from community centers, with no additional follow-up or visits required, while conventional treatment would have required usually two to three additional outpatient visits to the hospital during treatment. In addition, a blood sample was drawn three months after completion of treatment which confirmed whether treatment was successful, and this was done at the treatment and care centers where the people already received follow-up, while conventional treatment would have required an additional visit to the hospital. To simplify the procedure, a chained testing approach was used for the blood samples, where one test result decided which follow-up tests were analyzed. Even though there were many who prior to the publishing of the primary outcomes acknowledged that integrated treatment could be a simplification, there were many who questioned the safety of providing integrated treatment and care outside the hospitals' medical outpatient clinics.

Thus, with insufficient evidence on its efficacy and safety when we started in 2016/2017, we conducted a randomized controlled trial with 298 people with currently or formerly injecting substance use randomized to receive either integrated or standard treatment. For results, see section 4.

The study was led by Bergen Addiction Research with professor and senior researcher Lars Thore Fadnes as the primary investigator, together with the professors and senior researchers Kjell Arne Johannsson and Else-Marie Løberg, and senior consultant Christian Ohldieck, all employed at Department of Addiction Medicine, Haukeland University Hospital. Other people centrally involved include Christer Aas (MD, PhD), Jørn Henrik Vold (MD,PhD), Fatemeh Chalabianloo (MD, PhD), the user representatives Ole Jørgen Lygren and Ronny Bjørnestad, research nurses Jan Tore Daltveit, Maria Olsvold, Mette Nordbotn, Per Gundersen and Ewa Wilk, professor Peter Vickerman from University of Bristol, senior consultant Alexander Leiva at Haukeland University Hospital, professor Olav Dalgaard at Akershus Universitetssykehus, and professor Svetlana Skurtveit at the Norwegian Institute of Public Health, in addition to a large team of clinicians and users.

3. References to the research (indicative maximum of six references)

This section should provide references to key outputs from the research described in the previous section, and evidence about the quality of the research. All forms of output cited as underpinning research will be considered equitably, with no distinction being made between the types of output referenced. Include the following details for each cited output:

- Author(s)
- Title
- Year of publication
- Type of output and other relevant details required to identify the output (for example, DOI, journal title and issue)
- Details to enable the panel to gain access to the output, if required (for example, a DOI or URL).

All outputs cited in this section must be capable of being made available to panels. If they are not available in the public domain, the administrative unit must be able to provide them if requested by RCN or the evaluation secretariate.

2021 Fadnes LT, Aas CF, Vold JH, Leiva RA, Ohldieck C, Chalabianloo F, Skurtveit S, Lygren OJ, Dalgård O, Vickerman P, Midgard H, Løberg EM, Johansson KA; INTRO-HCV Study Group**. Integrated treatment of hepatitis C virus infection among people who inject drugs: A multicenter randomized controlled trial (INTRO-HCV).** ***PLOS Medicine****. 2021* *https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1003653*

2023 Lim AT, Aas CF, Çağlar ES, Vold **JH, Fadnes LT,** Vickerman P, Johansson KA. Cost-effectiveness of integrated treatment for hepatitis C virus (HCV) among people who inject drugs in Norway: An economic evaluation of the INTRO-HCV trial. Addiction 2023 https://onlinelibrary.wiley.com/doi/10.1111/add.16305

2023 Vold JH, Chalabianloo F, Løberg EM, Aas CF, Lim AG, Vickerman P, Johansson KA, Fadnes LT. **The efficacy of integrated hepatitis C virus treatment in relieving fatigue in people who inject drugs: A randomized controlled trial**. *Substance Abuse Treatment, Prevention, and Policy 2023* *https://substanceabusepolicy.biomedcentral.com/articles/10.1186/s13011-023-00534-1*

2022 Sælør KT, Carlsen SEL, Fadnes LT, Lorås L: **Experiences of Hope After Treatment of Hepatitis C Infection – a Qualitative Study**. *International Journal of Environmental Research and Public Health* 2022. https://www.mdpi.com/1660-4601/19/23/15732

2020 Aas CF, Vold JH, Skurtveit S, Odsbu I, Chalabianloo F, Okland JM, Leiva RAM, Vickerman P, Johansson KA, Fadnes LT**. On the path towards universal coverage of hepatitis C treatment among people receiving opioid agonist therapy (OAT) in Norway: a prospective cohort study from 2013 to 2017**. *BMJ Open. 2020* *https://bmjopen.bmj.com/content/10/8/e036355.long*

2022 Norwegian national expert committee on hepatitis C**. The Norwegian guidelines on diagnostics and treatment of hepatitis C**. 2022. *https://hepatittfag.no/pdf-hcv*.

4. Details of the impact (indicative maximum 750 words)

This section should provide a narrative, with supporting evidence, to explain:

- How the research underpinned (made a distinct and material contribution to) the impact;
- The nature and extent of the impact.

The following should be provided:

- A clear explanation of the process or means through which the research led to, underpinned or made a contribution to the impact (for example, how it was disseminated, how it came to influence users or beneficiaries, or how it came to be exploited, taken up or applied).
- Where the submitted administrative unit's research was part of a wider body of research that contributed to the impact (for example, where there has been research collaboration with other institutions), the case study should specify the particular contribution of the submitted administrative unit's research and acknowledge other key research contributions.
- Details of the beneficiaries – who or what community, constituency or organisation has benefitted, been affected or impacted on.
- Details of the nature of the impact – how they have benefitted, been affected or impacted on.
- Evidence or indicators of the extent of the impact described, as appropriate to the case being made.
- Dates of when these impacts occurred.

The results confirmed that among those randomized to integrated treatment, 98% initiated treatment for hepatitis C while the corresponding number for those who received standard

treatment was 77% (even if these also received integrated diagnostics). The difference without integrated diagnostics could be expected to be even larger. Time to treatment initiation was approximately twice as fast among those randomized to integrated treatment. Further, 93% of those who were randomized to integrated treatment and tested, had a sustained virologic response (being "cured" from hepatitis C) in contrast to 73% among those randomized to standard treatment.

The study has also been shown to be highly cost effective and in several settings probably even cost-saving. It has contributed to providing hope among the patients, enabling people to better take control in their lives including in management of substance use and risks.

By implementing integrated treatment and care of hepatitis C together with opioid agonist therapy and care while simplifying the algorithm for treatment and follow-up, Western Norway are now among the global frontrunners in elimination of hepatitis C. When the study was initiated in 2017, more than 50% were chronically infected with hepatitis C. In 2020, when the recruitment of the trial was completed, the prevalence within the group had fallen to less than 7%, more than reaching ambitious elimination goals that few settings elsewhere have been able to reach.

The study was supported by the Norwegian Research Council and the Regional Health Authority, Western Norway, with a large group of clinicians, user representatives and researchers involved.

The integrated treatment model has now become the new gold standard and is increasingly implemented in much of the world. It has substantially simplified the treatment and follow-up experience for patients while providing superior treatment outcomes.

5. Sources to corroborate the impact (indicative maximum of ten references)

https://www.helse-bergen.no/fag-og-forsking/forsking/da-hepatitt-c-ble-utryddet-pa-vestlandet#:~:text=Bergen%20og%20Stavanger%20ligger%20i,n%C3%A6rmer%20seg%20utryddelse%20av%20viruset.

Institution: Haukeland University Hospital (HUH), and University of Bergen (UiB)
Administrative unit: Dep. of Neurology, and Dep of Clinical Medicine
Title of case study: High-efficacy multiple sclerosis therapy to a sustainable cost to the society
Period when the underpinning research was undertaken: 2008-2024 (2012-2022)
Period when staff involved in the underpinning research were employed by the submitting institution: 2008-2024 (2012-2022)
Period when the impact occurred: 2018-2023

1. Summary of the impact

One of the main objectives for the Bergen MS-Research Group is to provide improved and tailored treatment in multiple sclerosis (MS). Since the early 1990's, when the first approved medication for MS were launched, our group has participated in industry- or academic sponsored clinical trials in MS. The group has facilitated Norwegian participation in more than fifty clinical trials, and pioneered early implementation of new therapies, such as mitoxantrone, natalizumab, rituximab and haematopoietic stem cell transplantation (HSCT). For a decade, the group has pioneered the use of high-efficacy off-label rituximab to a low and societal sustainable cost, in parallel with performing scientific quality control of clinical practice use of the therapy. In that way, we have implemented rituximab in national treatment guidelines (https://www.helsedirektoratet.no/retningslinjer/multippel-sklerose) and made it accessible for a large number of newly diagnosed patients. Latest update (2022) indicates that 96% of newly diagnosed patients receive early high-efficacy therapy – most of them rituximab to a low cost for the society (www.norskmsregister.no).
We have also contributed to the MSIF's (https://www.msif.org/) initiative to include MS therapies, including rituximab, on the WHO's list of essential medicines – to promote world-wide access to MS-therapies.

2. Underpinning research

The Bergen MS-Research Group has since the early 1990's been the leading Norwegian MS research group, especially in clinical trials in MS. The group has participated in different trials of most of the new therapeutic developments of more than twenty different substances in about fifty different trials. It started out with modest-efficacy interferon-beta injections to the current high-efficacy B-cell depleting therapies. The group has also been central in performing academic trials in Norway and Scandinavia – searching for improved treatment strategies of available therapies. When the first reports of B-cell depletion with rituximab appeared in 2008 (https://pubmed.ncbi.nlm.nih.gov/18272891/), the group started out using this off-label therapy for single patients with breakthrough disease on standard approved medications. The surprising high efficacy from the treatment, led to gradual increase in the use, along with systematic implementation of dosing and dosing interval recomendations, in collaboration with Swedish colleagues (https://pubmed.ncbi.nlm.nih.gov/27760868/). In parallel with our increasing experience of off-label use of rituximab, we were also national coordinators for industry sponsored (Roche) development of the next generation of rituximab, the humanized form, ocrelizumab, and thus gained a systematic experience in B-cell depletion for MS. At the time when ocrelizumab (https://pubmed.ncbi.nlm.nih.gov/28002679/) was approved for MS treatment by the Food and Drug Administration (FDA), USA (2017), and by the European Medicines Agency (EMA), Europe (2018), we had already establish rituximab as an off-label routine therapy at Haukeland University Hospital.

We had also by then established a quality control system for the off-label rituximab therapy through the Norwegian MS-Registry. We were able to confirm the surprisingly high efficacy of the treatment, reported by Swedish colleagues, at least at the level that were reported from the ocrelizumab trials. Thus, based on this experience, we had established a routine treatment strategy of rituximab as a first-line therapy at an annual cost of about 7 500 NOK, and realized we would not be able to continue this practice with newly approved ocrelizumab at price of about 230 000 NOK, thus more than 30 times the price of rituximab.

Realizing this challenge, we made a strategic plan aiming at continuation for high-efficacy therapy, by off-label rituximab, at a sustainable cost for the society, which included several initiatives:

1. We submitted an initiative to perform an Norwegian Health Technology Assessment of MS-therapy, including rituximab.
2. We submitted a proposal to perform a non-inferiority, double-blinded randomized clinical trial comparing rituximab to ocrelizumab – The «OVERLORD-MS trial».
3. We submitted an initiative to update Norwegian MS-Treatment Guidelines to include rituximab as a treatment option.
4. We designed several studies for evaluation efficacy and safety of rituximab in clinical practice – thus generating real would evidence data.
5. We established international collaboration to promote rituximab at a sustainable cost for the society world-wide – through the Multiple Sclerosis International Federation

Key researchers and what positions they held at the administrative unit.
Dr Kjell-Morten Myhr (https://www.uib.no/en/persons/Kjell-Morten.Myhr), Professor in Neurology and Senior Consultant in Neurology at University of Bergen (UiB) and Haukeland University Hospital (HUH) is the chair of the Bergen MS-Research group (https://www.uib.no/en/rg/ms). **Dr Øivind Torkildsen** (https://www.uib.no/personer/%C3%98ivind.F..Grytten.Torkildsen), Professor in Neurology and Senior Consultant in Neurology at UiB and HUH is principal investigator (PI) of the «OVERLORD-MS trial**». Dr Lars Bø** (https://www.uib.no/personer/Lars.B%C3%B8) Professor in Neurology and Senior Consultant in Neurology at UiB and HUH, is the chair of the Norwegian quality and competence network for MS at HUH. **Dr Stig Wergeland** (https://www.uib.no/personer/Stig.Wergeland_1) Associate Professor in Neurology and Senior Consultant in Neurology at UiB and HUH, is the chair of the Norwegian MS-Registry at HUH. **Dr Silje Skrede** (https://www.uib.no/personer/Silje.Skrede) Professor in Clinical Pharmacology and Senior Consultant in Pharmacology at UiB and HUH, is the chair of the Pharmacology Research Group at UiB and HUH.
Drs **Gro Owren Nygaard** and **Marton König**, Clinical Neurologists and researchers at Oslo University Hospital that are key collaborators on several of the rituximab projects.

3. References to the research

1. Myhr KM, Torkildsen Ø, Lossius A, Bø L, Holmøy T. B cell depletion in the treatment of multiple sclerosis. Expert Opin Biol Ther 2019;19:261-271 (https://pubmed.ncbi.nlm.nih.gov/30632834/).
2. Hauser SL, Bar-Or A, Comi G, Giovannoni G, Hartung HP, Hemmer B, et al. ; OPERA I and OPERA II Clinical Investigators. Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis. N Engl J Med 2017;376:221-234. doi: 10.1056/NEJMoa1601277. PMID: 28002679 (https://pubmed.ncbi.nlm.nih.gov/28002679/).
3. Torgauten HM, Myhr KM, Wergeland S, Bø L, Aarseth JH, Torkildsen Ø. Safety and efficacy of rituximab as first- and second line treatment in multiple sclerosis - A cohort study. Mult Scler J Exp Transl Clin 2021;7:2055217320973049. doi: 10.1177/2055217320973049. PMID: 33796328 (https://pubmed.ncbi.nlm.nih.gov/33796328/)

4. Ocrelizumab quantitation by liquid chromatography-tandem mass spectrometry. Hallin EI, Trætteberg Serkland T, Myhr KM, Grytten Torkildsen Ø, Skrede S. J Mass Spectrom Adv Clin Lab 2022;25:53-60. doi: 10.1016/j.jmsacl.2022.07.004. PMID: 35910410 (https://pubmed.ncbi.nlm.nih.gov/35910410/)
5. König M, Torgauten HM, Tran TT, Holmøy T, Vaage JT, Lund-Johansen F, Nygaard GO. Immunogenicity and Safety of a Third SARS-CoV-2 Vaccine Dose in Patients With Multiple Sclerosis and Weak Immune Response After COVID-19 Vaccination. JAMA Neurol 2022;79:307-309. doi: 10.1001/jamaneurol.2021.5109. (https://pubmed.ncbi.nlm.nih.gov/35072702/)
6. Nygaard GO, Torgauten H, Skattebøl L, Høgestøl EA, Sowa P, Myhr KM, Torkildsen Ø, Celius EG. Risk of fingolimod rebound after switching to cladribine or rituximab in multiple sclerosis. Mult Scler Relat Disord 2022;62:103812. doi: 10.1016/j.msard.2022.103812. (https://pubmed.ncbi.nlm.nih.gov/35462167/)
7. Kvistad SAS, Burman J, Lehmann AK, Tolf A, Zjukovskaja C, Melve GK, Bø L, Torkildsen Ø. Impact of previous disease-modifying treatment on safety and efficacy in patients with MS treated with AHSCT. J Neurol Neurosurg Psychiatry 2022;93:844-848. doi: 10.1136/jnnp-2022-328797. PMID: 35508373 (https://pubmed.ncbi.nlm.nih.gov/35508373/)
8. Rød BE, Torkildsen Ø, Myhr KM, Bø L, Wergeland S. Safety of breast feeding during rituximab treatment in multiple sclerosis. J Neurol Neurosurg Psychiatry 2022;94:38-41. doi: 10.1136/jnnp-2022-329545 (https://pubmed.ncbi.nlm.nih.gov/35879056/)
9. Karlowicz JR, Klakegg M, Aarseth JH, Bø L, Myhr KM, Torgauten HM, Torkildsen Ø, Wergeland S. Predictors of hospitalization due to infection in rituximab-treated MS patients. Mult Scler Relat Disord 2023;71:104556. doi: 10.1016/j.msard.2023.104556. (https://pubmed.ncbi.nlm.nih.gov/36842313/).
10. Førde JL, Herfindal L, Myhr KM, Torkildsen Ø, Mollnes TE, Skrede S Ocrelizumab and ofatumumab, but not rituximab, trigger complement induction in vitro. Int Immunopharmacol 2023;124:111021. doi: 10.1016/j.intimp.2023.111021. (https://pubmed.ncbi.nlm.nih.gov/37816262/)
11. König M, Lorentzen ÅR, Torgauten HM, Tran TT, Schikora-Rustad S, Vaage EB, Mygland Å, Wergeland S, Aarseth J, Aaberge IAS, Torkildsen Ø, Holmøy T, Berge T, Myhr KM, Harbo HF, Andersen JT, Munthe LA, Søraas A, Celius EG, Vaage JT, Lund-Johansen F, Nygaard GO. Humoral immunity to SARS-CoV-2 mRNA vaccination in multiple sclerosis: the relevance of time since last rituximab infusion and first experience from sporadic revaccinations. J Neurol Neurosurg Psychiatry 2023;94:19-22. doi: 10.1136/jnnp-2021-327612. PMID: 34670844 (https://pubmed.ncbi.nlm.nih.gov/34670844/)

4. Details of the impact

1. **Norwegian Health Technology Assessment (HTA) of MS-therapy, including rituximab:**
The "Nye metoder" (New Methods) (https://www.nyemetoder.no/english/), the national system of managed introduction of new methods in the specialist health care services in Norway, approved our suggestion to perform an overall HTA of MS-therapy, and concluded in 2019 that rituximab had comparable efficacy and safety as other high-efficacy MS-therapies, but that more data should be available, preferable through randomized trials.

   They concluded that:
   - Rituximab is approved for treatment of relapsing remitting multiple sclerosis (RRMS) in Norway, given that the patients was informed of the off-label therapy.
   - Treatment with rituximab should be registered in the Norwegian MS registry.

2. **Suggestion of a non-inferiority, double-blinded randomized clinical trial comparing rituximab to ocrelizumab – The «OVERLORD-MS trial»:**
   By October 2019, The Regional Health Authorities of Norway (KlinBeForsk - https://kliniskforskning.rhf-forsk.org/) granted funding of 19.2 MNOK for the "Ocrelizumab VErsus Rituximab Off-Label at the Onset of Relapsing MS Disease (OVERLORD-MS) (https://classic.clinicaltrials.gov/ct2/show/NCT04578639). The clinical trial received all approvals during 2020 – and started recruitment November 2020, and was fully recruited by November 2022. This is a double blinded randomized non-inferiority study of newly diagnosed RRMS patients, with new MRI T2 lesions as endpoint. All patients are observed for 30 months and results are expected in Q2/Q3 2025

3. **Initiative to update Norwegian MS-Treatment Guidelines to include rituximab as a treatment option:**
   The Norwegian Directorate of Health accepted the suggestion of updating the MS-Guidelines, and the revised version were launched in 2022. The Norwegian MS Guidelines are among the most offensive guidelines world-wide, recommending high-efficacy therapy at diagnosis, including the option to use rituximab (https://www.helsedirektoratet.no/retningslinjer/multippel-sklerose). The latest annual report from the Norwegian MS-registry shows that 96% of newly diagnosed patients are receiving high-efficacy therapy from the time of diagnosis (https://www.kvalitetsregistre.no/sites/default/files/2023-06/%C3%85rsrapport%202022%20Norsk%20MS-register%20og%20biobank_0.pdf)

4. **Research evaluating the efficacy and safety of clinical practice using rituximab:**
   The Bergen MS-Research Group has studied various aspects of safety and efficacy of off-label rituximab therapy in RRMS. Rituximab is the most frequent used MS-therapy in MS at our Department and in Norway. We have shown that rituximab is highly effective https://pubmed.ncbi.nlm.nih.gov/33796328/), but patients receiving therapy have a small but significant increased risk of hospitalisation due infections (https://pubmed.ncbi.nlm.nih.gov/36842313/). The treatment induces long-lasting effects – and is therefore an attractive option for use prior to planned pregnancy, and we have shown that rituximab is safe during breastfeeding (https://pubmed.ncbi.nlm.nih.gov/35879056/). We have also shown that rituximab effectively reduces the risk of rebound after termination of fingolimod therapy, another MS-therapy (https://pubmed.ncbi.nlm.nih.gov/35462167/). Although rituximab reduces the humoral vaccination response (https://pubmed.ncbi.nlm.nih.gov/35072702/ and (https://pubmed.ncbi.nlm.nih.gov/34670844/) – the treatment seems safe without any increased risk for severe covid infections (***manuscript in press***)

   In addition, we are performing studies in basic pharmacology, developing methods for quantification of serum concentration of rituximab and ocrelizumab (https://pubmed.ncbi.nlm.nih.gov/35910410/), and evaluate mode of action through complement activation (https://pubmed.ncbi.nlm.nih.gov/37816262/).

5. **Establish international collaboration to promote rituximab at a sustainable cost for the society.**
   Professor Myhr, the Norwegian MS Society representative in the Scientific Advisory Bord of the Multiple Sclerosis International Federation (https://www.msif.org/), has contributed with important rituximab real world experience for the application of including MS-therapies on the WHO's Essential Medicines List – that succeeded for the first time in 2023.

In summary, the Bergen MS-Research Group's initiative for highly effective MS therapy at sustainable costs for society, will facilitate access to such therapy throughout Norway. Our initiative has contributed to the MSIF initiative to include MS therapies on the WHO's list of essential medicines. Awaiting the results of our RCT ((https://classic.clinicaltrials.gov/ct2/show/NCT04578639) – which will hopefully confirm that rituximab is not inferior compared to ocrelizumab – we will contribute with results that could have an impact across Europe and the rest of the world.

5. Sources to corroborate the impact

- **Norwegian Health Technology Assessment (HTA) of MS-therapy, including rituximab:** https://www.nyemetoder.no/4a4f08/siteassets/documents/rapporter/disease-modifying-treatments-for-relapsing-remitting-multiple-sclerosis-including-rituximab-hta-rapport-2019.pdf

- **Norwegian decision on the approval of use of rituximab for multiple sclerosis:** (https://www.nyemetoder.no/metoder/legemidler-inkludert-off-label-behandlingen-rituksimab-ved-rrms-fullstendig-metodevurdering-/

- **Norwegian Guidelines for diagnosis and treatment of multiple sclerosis:** https://www.helsedirektoratet.no/retningslinjer/multippel-sklerose

- **The Regional Health Authorities of Norway (KlinBeForsk) decision for funding the "OVERLORD-MS Trial":** https://kliniskforskning.rhf-forsk.org/149-millioner-kroner-til-klinisk-behandlingsforskning/

- **Clinicaltrials.gov registration of the "OVERLORD-MS Trial":** https://classic.clinicaltrials.gov/ct2/show/NCT04578639).

- **Annual Report of the Norwegian MS-Registry 2022:** https://www.kvalitetsregistre.no/sites/default/files/2023-06/%C3%85rsrapport%202022%20Norsk%20MS-register%20og%20biobank_0.pdf

- **Multiple Sclerosis International Federation – press release WHO Model List of Essential Medicines:** https://www.msif.org/wp-content/uploads/2023/07/MSIF_WHO-EML-decision_press-release_FINAL.pdf

- **WHO Model List of Essential Medicines - 23rd list, 2023:** https://iris.who.int/bitstream/handle/10665/371090/WHO-MHP-HPS-EML-2023.02-eng.pdf?sequence=1

Western Norway University of Applied Sciences, Faculty of Health and Soicial Sciences; TJENESTEFORSK / Comparative Services Research

Institution: HVL
Administrative unit: FHS
Title of case study: *Experiences of COVID-19 in Norwegian nursing homes*
Period when the underpinning research was undertaken: 2020-2021
Period when staff involved in the underpinning research were employed by the submitting institution: 2020-2021
Period when the impact occurred: 2021 - 2023

1. Summary of the impact

The research reported in this document had both significant research/academic impact and impact for the general society, in Norway and abroad. Besides scientific publications, results from the research have been disseminated in Norway and in other countries to practitioners in the health and care services, to decisionmakers and to the general public. Amongst other, the research resulted in a widely shared and cited report for the Norwegian Corona Commission, and results from the work was included in a Norwegian Health Directorate Report.

2. Underpinning research

The five Centres for Care Research (a Norwegian national care research structure) were appointed by the *Norwegian Corona Commission* to investigate and write a report on preparedness for and experiences of the corona pandemic at Norwegian nursing homes. This assignment was led by Centre for Care Research west, (CCRW), FHS, HVL. Researchers were recruited from the Comparative services research group (CSR / Tjenesteforsk) at the admin unit FHS. In particular, the commission asked for in-depth case studies of a smaller selection of nursing homes (NHs).

The aims of the assignment were: 1. To investigate experiences of COVID-19, including how the NHs were prepared for a pandemic, what challenges they encountered, and how they managed to deal with the pandemic. 2. To establish statistics on nursing home deaths.

Case studies were performed in five NHs in five different municipalities spread geographically, varying in size and exposure to COVID-19. Healthcare workers (leaders, nursing staff, physicians) and family/next of kin to nursing home residents were interviewed through semi-structured individual interviews and focus group interviews. Documents from the nursing homes and architectural/technical drawings have been studied, and descriptive statistics on NH mortality was developed (in cooperation with the Norwegian Institute of Public Health, FHI.

Findings:

1. Statistical findings: Data from the first year of the pandemic (March -20 to March -21): just under 50 % of all COVID-19 related deaths in Norway occurred in nursing homes. Around 3 % of residents were infected, and approximately one third of infected residents died with the disease. 4 out of 10 COVID-19 related deaths in the nursing homes occurred in the 10 institutions with the most registered deaths. To put it another way: 10 out of 800 Norwegian nursing homes accounts for around 40 % of nursing home deaths.

2. Qualitative findings: Leaders, care staff and physicians reported a decline in activities for residents, in particular in social activities. Contact with family has been a huge challenge, including in wards with no COVID-19 in affected NHs. A reorganization and redistribution of staff and other

resources took place both in NHs with and without infections, including a major investment in digital communication resources. Ethical dilemmas were experienced by all the staff categories as to measures to prevent and contain the infections.

Results:
The results from the project have been widely disseminated nationally and internationally in terms of scientific articles, conference contributions, knowledge sharing with decision-makers nationally and internationally, including a report to the Norwegian Corona Commission (Jacobsen et al., 2021) and knowledge-sharing with decision-makers in UK and Canada.

- **Names and positions of the key researchers**

Frode F. Jacobsen, Professor, project leader; Oddvar Førland, Professor, project participant. Jacobsen and Førland are core members of CSR.
Two members of CSR (with multiple membership) joined the research team: Oscar Tranvåg, Professor, HVL, and Gudmund Ågotnes, Professor, HVL. In addition, one external member of CSR was part of the research team, Associate Professor Laila Tingvold, NTNU. Finally, Irene Aasmul, Research Developer, The Dignity Centre also contributed in the project.

- Any relevant key contextual information about this area of research.

Frode F. Jacobsen, who led this investigation and the work on the report for the Norwegian government, has researched and published extensively on nursing homes in Norway and internationally since 1988. Nursing home residents proved particularly vulnerable to the COVID-19 pandemic, in Norway and beyond. NH experiences from COVID-19 is important to research in order to prepare for future pandemics and epidemics.

3. References to the research

1. **Jacobsen, Frode F**.; Arntzen, Cathrine; Devik, Siri A.; **Førland, Oddvar**; Krane, Martin S.; Madsen, Linda; Moholt, Jill-Marit; Olsen, Rose M.; **Tingvold, Laila**; **Tranvåg, Oscar**; **Ågotnes, Gudmund**; Aasmul, Irene (2021). *Erfaringer med COVID-19 i norske sykehjem. Underlagsrapport for Koronakommisjonen.* Rapport 1/2021. NTNU Gjøvik: Rapportserie for Senter for omsorgsforskning.
2. **Tingvold, Laila**; Moholt, Jill-Marit; **Førland, Oddvar; Jacobsen, Frode F.; Tranvåg, Oscar** (2023). Intended, unintended, unanticipated? Consequences of social distancing measures for nursing home residents during the COVID-19 pandemic*. Global Qualitative Nursing Research* 10:1-15, https://doi.org/10.1177/23333936231176204
3. Bjerve, Torunn; van Poel, Esther; Willems, Sara; **Jacobsen, Frode F**. (2023). Changes in work tasks and organization of general practice in Norway during the COVID-19 pandemic: results from a comparative international study. *BMC Primary Care* 24;277, https://doi.org/10.1186/s12875-023-02146-x
4. Glasdam, Stinne; Sandberg, Helena; Stjernswärd, Sigrid; **Jacobsen, Frode F.**; Grønning, Anette H.; Hybholt, Lisbeth (2022). Nurses' use of social media during the COVID-19 pandemic – A scoping review. PLOS ONE 17(2): e0263502. https://doi.org/10.1371/journal.pone.0263502
5. Glasdam, Stinne.; **Jacobsen, Frode F**.; Hybholt, Lise; Stjernswärd, Sigrid. (2022). Scandinavian Nurses' Use of Social Media during the COVID-19 Pandemic—A Berger and Luckman Inspired Analysis of a Qualitative Interview Study. *Healthcare* 10, 1254. https://doi.org/10.3390/healthcare10071254
6. Glasdam, Stinne.; **Jacobsen, Frode F**; Stjernswärd, Sigrid. (2022). Practices and Strategies of Health Professionals during the COVID-19 Pandemic—Between Limitations and Opportunities. *Healthcare* 2022, 10, 1817. https://doi.org/10.3390/healthcare10101817

4. Details of the impact

Firstly, the research was part of the basic material for the Norwegian Corona Commission for their first report (2021), an expert commission working on summing up Norwegian experiences from

the COVID-19 pandemic and advising for future actions in the event of a new pandemic. Secondly, the research has been widely distributed to decisionmakers and practitioners, besides the webpage for (https://www.regjeringen.no/no/dokumenter/nou-2021-6/id2844388/) and broadcasting of the Corona commission results, through dissemination of the nursing home specific insights and results in mass media, in meetings with decisionmakers, and, by way of participation in a Norwegian government expert committee related to infection control in nursing homes (2021-2022).

Examples of the mass media coverage are Letters to the editors by the project leader Frode F. Jacobsen in the major newspapers and magazines like Bergensavisen (BA) (3rd May 2020), Aftenposten (2nd May 2021) and Kommunal rapport (10th November 2022), and, interviews twice with the National broadcasting company (NRK) (23rd December 2021 and 7th February 2022).

Examples of communication to international decisionmakers and practitioners are meeting with the Council of Toronto meeting with the Vancouver City Council (5th June 2023), architects in Toronto, Canada, arranged by York University, Toronto (30th June 2023), two presentations at the annual conference for the European Forum for Primary Care (EFPC) (6th September 2021), and presentation at meetings between researchers, decisionmakers and practitioners at London School of Economics (online, 3rd March 2021).

Thirdly, dissemination to academics has taken place on several occasions, amongst others, at Canadian Association for Work and Labour Studies (CAWLS) conference Toronto (30th May 2023).

5. Sources to corroborate the impact (indicative maximum of ten references)

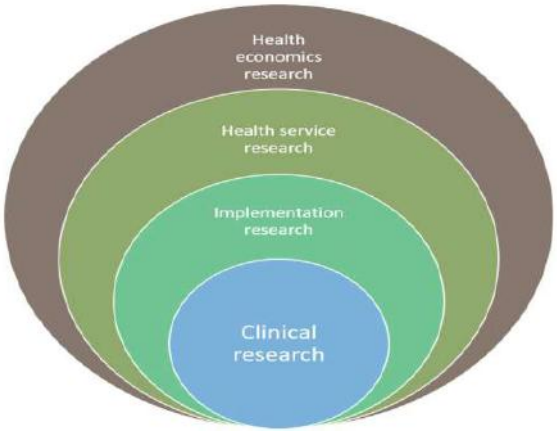
1. Frode F. Jacobsen. Nå ser vi hvor sårbare disse tjenestene er (The present pandemic situation highlights vulnerabilities in the services). Letter to the editor. *Bergensavisen* 3rd May 2020
2. Frode F. Jacobsen. "I denne koronatiden har jeg mistet min kone for tredje gang" ("In this time of Corona I have lost my wife for the third time"). Letter to the editor. *Aftenposten* 2nd May 2021
3. Frode F. Jacobsen. Hvor er sykehjemsbeboernes pårørende? (Where are the families of the nursing home residents?) Letter to the editor. *Kommunal Rapport* 10th Nov 2022.
4. Frode F. Jacobsen. Erfaringer fra prosjekt fra Koronakommisjonen (Experiences from project for the Norwegian Corona Commission). Interview *NRK Dagrevyen* 23rd December 2021.
5. Frode F. Jacobsen. Avliver myten om at eldre bare vil ha stille og naturutsikt (Scotching the myth that older adults primarily want quiet and view of nature). Interview. *NRK P2, Politisk kvarter; NRK Alltid nyheter; NRK Vestland* 7th February 2022.
6. Frode F. Jacobsen. Contribution as expert to the following chapter in a report published by the Norwegian Directorate of Health: *Bygningsmessige konsekvenser av pandemien (Consequences of the built environment for the pandemic).* Weblink, latest retrieved 22nd January 2024: https://www.helsedirektoratet.no/rapporter/omsorgstjenesten--aktivitetsutvikling-og-erfaringer-fra-pandemien/bygningsmessige-forhold--erfaringer-fra-pandemien/bygningsmessige-konsekvenser-for-pandemien
7. Frode F. Jacobsen & Gudmund Ågotnes (2021). *Ensuring residents' health and safety in nursing homes amidst COVID-19: The role of physical environment.* Conference presentation at EFPC annual conference 2021. Weblink, last retrieved 22nd January 2024: https://euprimarycare.org/efpc-2021-bergen-conference-5-7-september-2021/
8. Sara Willems, Esther van Poel, Pierre Vanden Bussche, Claire Collins, Torunn Eide, Frode F. Jacobsen, Emmily Schaubroeck, Stefanie Stark & Maria van den Muijsennb*ergh. COVID-19: Threat or opportunity for quality improvement (QI) in primary care?* Conference presentation at EFPC annual conference 2021. See weblinke, last retrieved 22nd January 2024: https://biblio.ugent.be/publication/8725787

Institution:
Administrative unit:
Title of case study: Norse Feedback – technologies for personalized mental health services
Period when the underpinning research was undertaken: 2014-2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2014 – 2022 (Christian Moltu), 2015 – 2019 (Runar Hovland), 2017 – 2022 (John Roger Andersen), 2017 – 2022 (Eli Natvik), 2018 – 2023 (Pål Andre Hegland), 2017-2022 – Kristina Osland Lavik (2016-2020)
Period when the impact occurred: 2019 →

1. **Summary of the impact** (indicative maximum 100 words)

The Norse Feedback research program spawned two medical technology spin-offs: Mental Health Informatics Holding AS and Norse Feedback AS (NF). NF developed personalized healthcare tech from institutional research, impacting Norway and beyond. Currently deployed in fifty Norwegian municipal health services, two specialist healthcare regions, and 80% of Norwegian student health services, the technology has also influenced major service organizations in the USA and the UK as part of health tech exports. In Norway, approximately 10,000 monthly patients benefit from this technology, ensuring precision and user involvement in their ongoing healthcare processes.

2. Underpinning research (indicative maximum 500 words)



The Norse Feedback research program employed a multilevel approach to health service research. This approach involves parallel knowledge creation in various areas, such as basic clinical research, clinical technology, and stakeholder needs, laying the foundation for research-based innovations. To ensure the dissemination of clinical innovations, a separate level focuses on implementation research. Additionally, individual levels within the program address health service and health economics aspects.

The following levels are key to underpinning the impact of the Norse Feedback:

Clinical research. Objective. The objective of the clinical research level has been to establish and explore clinician and patients needs, establish, explore and validate clinical constructs included in the technology, explore and validate different patient populations, and explore and validate different clinical uses, effects and utilities. Included researchers/projects:

Starting year	Researcher(s)	Project
2014	Christian Moltu, Sam Nordberg, Louis Castonguay	Clinical needs and uses of ROM/CFS
2016	Stig Magne Solstad, Christian Moltu, Louis Castonguay	Clinical application in routine care

2017	Kristina Osland, Christian Moltu, Andrew McAleavey	Clinical needs in adolescent and substance abuse sub-population
2017	Christian Moltu, John Roger Andersen, Eli Natvik, Andrew McAleavey	Clinical needs across mental and somatic healthcare settings, including primary care and obesity treatment centres
2019	Christian Moltu, Sam Nordberg, Andrew McAleavey, Marianne Helleseth	Adaptation and development after initial use

Documented outcomes: Peer-reviewed published research evidence for the needs, acceptability, feasibility and usefulness of the clinical technology.

Implementation research. Objective. To translate the clinical research level into clinical use in ordinary clinical settings, and to develop knowledge about barriers, facilitators and effective

Starting year	Researcher(s)	Project
2015	Runar Hovland, Christian Moltu	Norse Feedback and implementation science
2017	INSPIRE international implementation research arm, Christian Moltu, Susan Douglas, Kim de Jong	International Network for Psychotherapy Innovations and Research into Effectiveness (INSPIRE)
2019	Susan Douglas, Bram Bovendeerd, Maartje van Sonsbeek, Runar Hovland, Christian Moltu	A Clinical Leadership Lens on Implementing Progress Feedback in Three Countries

strategies for clinical training and uptake. Included researchers/projects:

Documented outcomes: Peer-reviewed published research evidence for implementation processes in translating developed clinical technology and knowledge to standard practice.

Health service and health economics research. Objective. To research the organizational, system level and translational effects of implementing a personalized data-driven service innovation within mental healthcare, across mental and somatic healthcare and across primary and secondary health care. Included researchers/projects:

Starting year	Researcher(s)	Project
2020	Yeu Jin Ki, Christian Moltu, Tron Moger	Economic evaluation and mental health
2017	Christian Moltu, Andrew McAleavey	Norse Feedback screener for primary care physicians
2017	John Roger Andersen, Pål Andre Hegland, Eli Natvik, Magnus Strømmen, Andrew McAleavey	Norse Feedback in an obesity setting
2018	John Roger Andersen, Kirsten Indrebø	Clinical feedback in an ostomy setting
2020	Heidi Brattland, Øyvind Kyrre Grindheim, Andrew McAleavey, Christian Moltu	FRAM: Norse Feedback and substance abuse
2021	Sam Nordberg, Hans Jacob Westbye, Andrew McAleavey, Christian Moltu	Norse Feedback for triage and ML
2020	Janne Låver, Andrew McAleavey, Christian Moltu	Beyond treating average patients
2021	Hans Jacob Westbye,	Pain after surgery and data driven monitoring

Documented outcomes: Peer-reviewed published research evidence for health service research applications, and the technology's applicability within and adaptation to secondary clinical contexts.

In addition to Western Norway University of Applied Science (HVL) as the basic institution, the following institutions have been involved in the select underpinning research listed above: Helse Førde Hospital Trust, Norway; St. Olavs University Hospital, Norway; Weill Cornell Medical School, USA; University of Bergen, Norway; University of Oslo, Norway; Norwegian University of Science and

Technology (NTNU), Norway; Penn State University, USA; Reliant Medical Group, USA; Helse Vest RHF, Norway; The Inspire Network, USA, Netherlands, Norway, UK.

3. References to the research (indicative maximum of six references)

Moltu, C., Veseth, M., Stefansen, J., Nøtnes, J. C., Skjølberg, Å., Binder, P. E., ... & Nordberg, S. S. (2018). This is what I need a clinical feedback system to do for me: A qualitative inquiry into therapists' and patients' perspectives. *Psychotherapy research*, *28*(2), 250-263.

McAleavey, A. A., Nordberg, S. S., & Moltu, C. (2021). Initial quantitative development of the Norse Feedback system: a novel clinical feedback system for routine mental healthcare. *Quality of Life Research*, *30*, 3097-3115.

Hegland, P. A., McAleavey, A., Aasprang, A., Moltu, C., Kolotkin, R. L., & Andersen, J. R. (2022). The Norse Feedback in a population of patients undergoing bariatric surgery—Psychometric properties of a digital computer-adaptive questionnaire assessing mental health. *Clinical Obesity*, *12*(1), e12491.

Douglas, S., Page, A. C., Moltu, C., Kyron, M., & Satterthwaite, T. (2023). The connections matter: Bi-directional learning in program evaluation and practice-oriented research. *Administration and Policy in Mental Health and Mental Health Services Research*, 1-18.

Solstad, S. M., Kleiven, G. S., & Moltu, C. (2021). Complexity and potentials of clinical feedback in mental health: an in-depth study of patient processes. *Quality of Life Research*, *30*, 3117-3125.

Solstad, S. M., Castonguay, L. G., & Moltu, C. (2019). Patients' experiences with routine outcome monitoring and clinical feedback systems: A systematic review and synthesis of qualitative empirical literature. *Psychotherapy Research*, *29*(2), 157-170.

Hovland, R. T., Ytrehus, S., Mellor-Clark, J., & Moltu, C. (2023). How patients and clinicians experience the utility of a personalized clinical feedback system in routine practice. *Journal of Clinical Psychology*, *79*(3), 711-728.

4. Details of the impact (indicative maximum 750 words)

How the Research Supported Norse Feedback's Impact:

Norse Feedback's impact lies in its implementation across healthcare settings, driving new processes, decisions, and treatments. As a medical tool designed for professional settings, Norse Feedback relies on empirical evidence and research.

To be mandated for use in user and organizational settings, Norse Feedback necessitates formal evidence. Thus, the research outlined above plays a pivotal role in establishing Norse Feedback as a viable technology for dissemination and implementation. Every research project within the program contributes to building the comprehensive evidence supporting the innovation's viability in the healthcare vertical.

The nature and extent of the impact:

The technology and knowledge following the Norse Feedback research program, and it's technological spin out, is far reaching. The major stakeholders experiencing and benefitting from this impact are, first and foremost, patients suffering from different health problems. Second, treatment providers benefit from the availability of new tools that make their jobs easier. Last, health care organizations are impacted positively by having evidence based technologies to support and guide their processes. Due to the vast footprint of the Norse Feedback project into Norwegian healthcare we will let select media outlets across Norway document and describe its current impact:

People suffering from substance abuse disorder receive better care and enhanced motivation:
Rusavhengige Tony (30) forteller behandleren hvordan det han har det via app: – Dette er motiverende | FriFagbevegelse

Patients are empowered toward more influence in their own treatments:
Ruspasienter får mer innflytelse på egen behandling - adressa.no

Norse Feedback supports primary care triaging for patients to get to the right treatment level:
Måler psykisk helse mellom legetimene (dagensmedisin.no)

Norse Feedback AS winning a series of health tech entrepreneurial awards:
Vant gründerpris for digitalt samtaleverktøy (dagensmedisin.no)
Årets helsegrunder (tekna.no)

Municipal health services can help more people due to Norse Feedback:
Ny helsetjeneste: - Håper å nå flere som trenger hjelp (saltenposten.no)

Health technology exports – Norse Feedback penetrates UK and US markets:
Mirah Announces Partnership with Norse Feedback to Bring Most Sophisticated Behavioral Health Measurements to the United States (prnewswire.com)
Helseteknologiselskapet sikrer distribusjonsavtale i USA (shifter.no)
Et norsk helseteknologiselskap sikrer seg den største leverandøren av måleverktøy i Storbritannia. | Norse Feedback (ntb.no)

In summary, the Norse Feedback impact case is defined by:

a) Empowering patients through active involvement in healthcare processes based on their own data
b) Disseminating precision tools and technologies across the healthcare vertical
c) Developing commercial and technological workplaces in Norway
d) Advancing international knowledge and technology exports

5. Sources to corroborate the impact (indicative maximum of ten references)

To independently corroborate the impact of Norse Feedback, the national competency center for community mental health work (NAPHA)'s coverage of the Norse Feedback impact development could serve as an independent perspective. The following three outlets from this user-based organization provides a selection of their reporting.

Første tilbakemeldingsverktøy i sitt slag utviklet i Norge - NAPHA Nasjonalt kompetansesenter for psykisk helsearbeid

Nytt tilbakemeldingsverktøy styrker behandling og bedrer relasjoner - NAPHA Nasjonalt kompetansesenter for psykisk helsearbeid

Tilbakemeldingsverktøyet Norse har lansert oppgraderingen Norse 3.1 - NAPHA Nasjonalt kompetansesenter for psykisk helsearbeid

– Enkel og rask tilgang til tjenesten er det som utgjør en forskjell - NAPHA Nasjonalt kompetansesenter for psykisk helsearbeid

[Name of the institution and name of the administrative unit] [case number]

Institution: Western Norway University of Applied Sciences (HVL)
Administrative unit:
Title of case study: The Drug-Death Related Bereavement and Recovery Project (the END-project)
Period when the underpinning research was undertaken:
Period when staff involved in the underpinning research were employed by the submitting institution: 2017-2022-
Period when the impact occurred: 1st November 2017 to 31st December 2022

1. Summary of the impact

The END-project has significantly influenced the recognition and availability of support initiatives for individuals in Norway bereaved by drug-related deaths. Awareness is raised in society and policy of drug-death bereaved persons and their situation. The projects' results have impacted key persons' willingness and engagement to prioritise this group. Changes have been made in national steering documents and local practices to ensure that this group of bereaved get the help they need. Several measures of peer support have been established, as well as a national association for bereaved after substance-related death. Educational programs, including e-learning, have been developed to strengthen the research-based foundation for professional practice.

2. Underpinning research

Drug-related death (DRD) presents a global challenge. Worldwide, millions of people die annually due to drug-related causes. In Norway, on average, 280 people die from overdoses annually, which implies that Norway has among the highest recorded rates of deaths triggered by narcotic drugs in Europe. Approximately 4000 bereaved persons are impacted by DRDs in Norway every year. Although DRDs are acknowledged by the authorities to be a serious public health issue, there has been a critical lack of knowledge concerning the living situation of DRD-bereaved persons. The END-project, launched in 2017, emerged as the largest international initiative to address this research gap. In this context, we present the most relevant research results from the project that underpins the impact.

Results show that bereaved persons after a DRD have a considerable risk of developing complicated grief reactions. 26% of the family members that participated in the END-project (parents 31.2%, siblings 21.8%, children 20.9%) experienced high levels of prolonged grief symptoms after DRDs. The strong reactions last over time (1). Results document a need for formal and informal help (acute and long-term). Although most DRD-bereaved persons reported a need for professional help after the death (*n* = 255), only about half of the participants received formal help, and less than half of these were satisfied with the help provided (2).

Mechanisms associated with stigmatisation are identified as barriers to both help-provision and help-seeking and are related to others' withdrawal and self-isolation (1,3). Peer support that is specifically for drug-death bereaved persons is desired (4). DRD-bereaved persons with substance use problems are identified as one group that needs particular awareness. They experience a lack of professional attention to their situation as a mourner; instead, the attention is predominantly directed towards their substance use problem (3).

From the helpers' perspectives, an obstacle to providing help is the lack of awareness among helpers about those bereaved by DRDs. For example, some helpers have not thought about a DRD as an unnatural death (5). Another barrier identified is the lack of concepts regarding DRD bereavement in national guidelines and a lack of local anchoring of psycho-social follow-up (6). Also, the helper calls for more knowledge on grief and substance use (5). By consistently employing the term "bereaved" rather than "next of kin" in all publications from the END-project,

an awareness has been raised about how the life situation and needs of this group differ significantly (1-6).

The research that underpins the impact derives from three work packages (WP). WP1 examined the bereaved's situation before death, strains and consequences related to the death, and help and support in the aftermath of death. WP1 built on data from a survey (*n* = 255) that examined bereaved persons' grief levels and their assessment of support and help. The survey was administered between March and December 2018 to a heterogeneous convenience sample of bereaved persons. From the survey sample, three samples of bereaved were recruited for individual interviews: parents (14), siblings (14), and close friends (18). The interviews were conducted between August 2018 and October 2020 by eight of the researchers in the END-project group.

WP2 examined helpers' perspectives and built on data from a survey (*n* = 103) and focus group interviews conducted between September 2019 and January 2020. The sample was strategically selected and consisted of six Norwegian municipalities that were part of a national network of municipalities with a high prevalence of overdose deaths. Altogether, 105 helpers participated in 24 focus group interviews. In each municipality, four focus group interviews were conducted consisting of the following helpers: a) acute helpers (e.g., first responders and emergency personnel); b) helpers from different NGOs; c) municipal helpers relevant after the acute phase; and d) local health- and welfare managers. The focus group interviews were carried out by three teams (one moderator and one co-moderator in each team) between September 2019 and January 2020. Five researchers and one practitioner from the END-project group conducted the interviews.

WP3 aimed to implement research-based knowledge from the END-project into relevant services for the DRD bereaved persons using a co-creation method named "research circle". Nine representants from different organisations participated: Ivareta, a peer support association (2), the Municipality of Oslo (2), the Municipality of Bergen (1), the Church City Mission aid (1), Fransiskushjelpen, an NGO offering grief support by professionals and volunteers (1), and HVL (2). The research circle was established in August 2021 and ended in March 2023. During 2022, most participants developed, piloted and implemented different measures for the DRD bereaved persons in their organisations.

Key researchers who have contributed to the results presented in this section are:

- Kari Dyregrov, Professor (2017-2022), Project leader from January 2017 to July 2022
- Kristine Berg Titlestad, PhD student (2018-2021), Associate professor (2021-2022), Project leader from August 2021
- Lillian Bruland Selseng, Associate professor (2017-2022), Project leader from August 2021
- Øyvind Reehorst Kalsås, PhD student (2021-2022)
- Hilde-Margit Løseth, PhD student (2020-2022)
- Monika Alvestad Reime, Associate professor (2018-2022)

3. References to the research*

1. Titlestad, K. B., & Dyregrov, K. (2022). Does 'time heal all wounds? 'The prevalence and predictors of prolonged grief Among drug-death bereaved family members: A cross-sectional study. *OMEGA-Journal of Death and Dying*, https://doi.org/10.1177/00302228221098584
2. Kalsås, Ø. R., Titlestad, K. B., Dyregrov, K., & Fadnes, L. T. (2023). Needs for help and received help for those bereaved by a drug-related death: a cross-sectional study. *Nordic Studies on Alcohol and Drugs*, *40*(5), 463-481. https://doi.org/10.1177/14550725221125378
3. Selseng, L. B., Reime, M.A., & Lindeman, S. (2023). Help and support for people experiencing both a bereavement from a drug-related death and drug use: A qualitative

study. *The European Journal of Social Work.* https://doi.org/10.1080/13691457.2023.2188146
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5. Løseth, H. M., Selseng, L. B., & Dyregrov, K. (2023). Barriers and facilitative factors in the provision of first-responder services to persons bereaved following a drug-related death: A qualitative study. *Nordic Studies on Alcohol and Drugs*, https://doi.org/10.1177/14550725231165445
6. Reime, M.A. & Dyregrov, K. (2022). Psykososial oppfølging ved narkotikarelatert død. Nasjonal styring og lokalt handlingsrom. [Psycho-social follow up for bereaved after drug-related death. National steering and local autonomy]. *Fontene Forskning 15(1),* 49-61. https://fontene-no.translate.goog/forskning/psykososial-oppfolging-ved-narkotikarelatert-dod-nasjonal-styring-og-lokalt-handlingsrom-6.584.882017.895132cf11?_x_tr_sl=no&_x_tr_tl=en&_x_tr_hl=no&_x_tr_pto=wapp

*Research outputs have undergone double blind peer review and are published in publication channels registered as level 1 or 2 in the Norwegian Register for Scientific Journals.

4. Details of the impact

An annual national conference focusing on bereavement due to DRD

When the END-project was established in 2017, no arenas for bereaved persons after DRDs existed, and neither did there exist any academic or professional arena that could contribute to shed light on this group. From 2017 to 2022 (in 2020, only digital resources were released due to the pandemic), the END-project has arranged an annual national conference about DRD bereavement (the END-conference). The conferences have gathered about 300 participants yearly and have become an important meeting place for both bereaved, professionals and researchers. The conferences have been an arena for disseminating research results and implications and a venue for bereaved and key persons to share their experiences and knowledge. Through the annual conference, the END project has contributed to raising awareness and engagement of DRD bereavement in the public discourse, empowering the bereaved and the professionals, and facilitating new networks. In November 2022, after the 5.th END-conference (A), KORUS Bergen (a regional competence centre for drugs and alcohol), the Municipality of Bergen, and the Directorate of Health took over the responsibility for arranging the conference in 2023 (B). The aim is that this conference will continue as a national arena and driving force for improving the life situation of the DRD bereaved persons.

Founding of a national association

One example of a new and formalised network is the establishment of a national association for bereaved persons after substance-related deaths: "Landsforeningen for etterlatte ved rus" ["The national association for bereaved after substance use"]. The absence of peer support for this group of bereaved individuals emerged as a recurring theme, discussed at multiple conferences. The discussions resulted in a joint initiative to work for the establishment of a national organisation. One of the bereaved conference participants, was supported economically by the END-project and surveyed the DRD bereaved persons who had participated at END-conferences to map the need for a national association. Results from the survey were presented at the 2022 END-conference and those interested in contributing to the establishment of the new organisation could register. On the 16th of November 2022, an interim board was established, and in November 2023, a new organisation became a reality (C).

Increased awareness of DRD bereavement in society and national policy

The END-project group members have actively engaged in public debates and contributed to shedding light on DRD bereaved persons and their situation by using different digital media, such as the END home page and END on Facebook, and by producing podcasts. A wide variety of recipients have been reached through local, regional, and national media (i.e., newspapers, radio, TV) and publications in more specific areas, such as workers' associations, users' associations, and

journals aimed at particular services. A search on news reports on Google in the period before the END-project was launched (2010-2016) showed no media coverage of DRD bereavement. Results from the period 2017-2022 available in Cristin show that the END-project produced 51 scientific and popular science lectures, ten media interviews, seven chronicles, and seven podcasts (D).

Through dissemination of research results and in dialogue with key actors, members of the END project group have contributed to shedding light on the importance of conceptualising bereaved persons after DRD as a distinct group with specific challenges and needs, for example, compared to next of kin. The work has impacted changes in public policy documents, guidelines, and organisational practices. For instance, in the "Drug Overdose strategy 2019-2022", a more consistent and explicit reference was made to bereaved persons after DRDs: "There is very little accumulated knowledge of the situation of bereaved after drug-related deaths, both nationally and internationally" (p. 15) and "the END-study represent a pioneering work" (p.15) (E). In 2023 "overdoses" were included as an example of sudden and unnatural deaths in the National Guidelines for psycho-social follow-up after sudden death ("Mestring, samhørighet og håp") (F) contributing to clarify DRD-bereaved' rights to psycho-social follow-up. Also, Ivareta has increased their attention to bereaved persons after DRDs and decided in 2020 to include bereaved by substance use in their under-title on their web page: "Ivareta is an association of and for bereaved and next of kin to persons having challenges with substance use or mental health".

Inclusion of grief and bereavement in educational programs

Research-based knowledge from the END-project has been implemented into several educations at HVL, and the focus on grief and bereavement has been strengthened in the curriculum of different study programs at HVL, for example within social pedagogy, social work, childcare pedagogy, and family therapy (G). An e-learning program that began to be developed in 2022 aimed at increasing students' and practitioners' competency in grief and bereavement in cases of unnatural death. Renewed educational programs will increase practitioners' knowledge of grief and bereavement in general and, in particular, the special grief and the related consequences that can follow an unnatural death. This means the research-based foundation for professional practice is strengthened, possibly impacting the quality of services provided and the practitioner's ability to identify and follow up with people at risk of complicated bereavement processes.

Impacts following from the research circle:

- Inclusion of DRD bereaved in local guidelines and practices

The work in the research circle contributed to formalising attention to and follow-up to bereaved persons after DRD in Oslo Municipality. One of the research circle participants worked in 2021-2022 with a revision of a local policy document "the Oslo standard for overdose prevention" that was launched in 2023. In the new measure "establishing crisis-preparedness in cases of overdoses" (p. 12), attention is given to the follow-up of the bereaved after a DRD, and three recommendations are given for how the districts should attend to this responsibility (H). Participants from the Municipality of Oslo also initiated a local seminar with the theme "Next of kin and bereaved in case of substance use". The seminar was held on the 12th of December 2022 and gathered 120 practitioners and managers from services to people with mental health or substance use problems (I).

- Increasing attention to bereavement in residential care

The Church City Mission aid initiated a project to improve their practices regarding the follow-up of substance-related deaths among clients or as experienced by their clients and to reduce stigma and shame in this regard. During 2022, the representative collaborated with a colleague and carried out focus group interviews where practitioners shared experiences and discussed ideas for practice improvements. Data was analysed and then presented and discussed in a joint seminar in Oslo on the 26th of September 2022 consisting of practitioners and two representatives from the END-project. Results from focus group interviews and discussions were summed up and presented in the END-conference the 16th of November 2022. Based on the results, a guide on how to use

rituals and reflections to reduce and remove shame around substance-related death was developed and implemented in 2023 (I).

- Digital grief support group for DRD bereaved persons

Also, work in the research circle led to the piloting of a digital grief support group exclusively for people bereaved after substance-related death. The grief group resulted from cooperation between Ivareta and Fransiskushjelpen, which was enabled by the research circle. Grants from the DAM Foundation supported the pilot. The grief support group, consisting of six bereaved individuals, convened five times from April to June 2022 (I).

- Targeted peer support

In Bergen, a meeting place for bereaved persons after substance-related deaths was established with KORUS Bergen and the Municipality of Bergen in charge. The first meeting was held in September 2022, followed by monthly meetings (J). The meeting place has been popular (about 10-12 bereaved persons have met each time) and contributes to meeting bereaved persons' documented needs for peer support. In the Municipality of Fredrikstad, Ivareta reached a joint agreement to offer peer support as part of the psycho-social intervention to bereaved persons after substance-related deaths. The practice was established in 2022, and a formal cooperation agreement was signed in 2023.

5. Sources to corroborate the impact

A) Etterlatte ved narkotikarelatert død 2022 - English version
B) Etterlatte ved rusrelatert død 2023 - English version
C) Landsforeningen for etterlatte ved rus - English version
D) Prosjekt #577210 - Etterlatte ved narkotikarelatert død i et recoveryperspektiv - Cristin
E) Nasjonal overdosestrategi - English version
F) Psykososiale tiltak ved kriser, ulykker og katastrofer (Mestring, samhørighet og håp) - English version
G) Relasjonelt arbeid med sorg, livskriser og traumer. Etter- og vidareutdanning - English version
H) KORUS, Oslostandard - English version
I) Forskningssirkel - English version
J) Tilbud for etterlatte etter rusrelatert dødsfall - English version

Inland Norway University of Applied Sciences, Faculty of Social and Health Sciences

Impact case #1 – Children as next of kin

Institution: Inland Norway University of Applied Sciences (INN University)
Administrative unit: Faculty of Social and Health Sciences
Title of case study: Children as next of kin (Impact case #1; Barn som pårørende)
Period when the underpinning research was undertaken: 2012- 2020
Period when staff involved in the underpinning research were employed by the submitting institution: 2012-2020
Period when the impact occurred: 2013-2023

1. Summary of the impact

The research group has actively disseminated their work through publications, presentations, and contributions to national research networks focusing on children in families with health issues. Examples include influencing parliamentary discussions on children's welfare and contributions in a handbook on supporting children with parents facing drug addiction. Wangensteen's efforts at the Tyrili Foundation include organizing seminars for parents and practitioner gatherings, with the aim of addressing challenges related to substance addiction. Söderström has worked on multidisciplinary collaboration, using research insights to enhance training and create a short film for professional reflection. The group's ongoing project explores decisions in child protection services, yielding articles and anthologies. Three research fellows of the group (Grimsgaard, Håkansson and Wangensteen) were all enrolled in the ph.d. program Children and Youth Participation and Competence development and contributed to putting the theme of vulnerable children on both the scientific and political agenda in Norway and abroad. Søderstrøm and Halsa managed to initiate a scientific collaboration with a University in Hanoi, Vietnam, from where two Vietnamese ph.d students in psychology came as guest researchers just before the pandemic hit Norway.

2. Underpinning research

Since 2006 children as next of kin has been an area of considerable political focus. From 2010 health professionals in Norway were given a duty to follow up children who are next of kin to parents suffering from mental illness, substance use disorder or somatic illness/injury. In 2011 The Research Council of Norway announced research funds to study welfare services and life conditions for children next to kin. Lillehammer University Collage (which later merged with another university college to form INN) applied to this call and received funds to the project "Children Living in Families with Parental Mental Illness and/or Substance Abuse: Participation, Competence Development and Support". Astrid Halsa and Kerstin Söderstöm were senior researchers in the project. Three research fellows were recruited and several master students (7) wrote their master thesis as part of the project. In their research they found that in particular four barriers exist associated with lack of care for children when parents are hospitalised 1) Lack of competence among healthcare professions ; 2) The patient does not want the children to be involved, i.e. receiving information and participating in conversations; 3) Work with children as next of kin is not a priority task in treatment and 4) Lack of multidisciplinary collaboration between services to adults and services to children and youth. Research in the project also document that parental substance disorder (SUD) or parental mental health problems strongly affects children. They experience fear, shame and betrayal, but they also love and feel closeness to parents. Stigma and shame are perceived as an extra burden for these children and their parents. The children are

in need but lack opportunities to create coherence and meaning through conversations with their parents, professionals or other young people in the same situation. These findings are in line with national and international research in this field.

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In our research Ulrika Håkansson studied mothers with substance disorder and caregiving for young children (up to 18 months). Parental reflective functioning (PRF) and executive functioning (EF) are both important capacities for sensitive parenting as well as often being impaired in SUD mothers. Findings in these studies indicate that development of effective interventions for mothers with SUD should have a dual focus on PRF and EF when targeting stress, dynamic intergenerational risk factors, and sensitive caregiving capacities. The considerable heterogeneity in the group of mothers stresses the importance of individually adjusted interventions in accordance with capacities and vulnerabilities to better target capacities important for sensitive caregiving. Her research was conducted in the period of 2013- 2018 and was defended as PhD. - thesis in 2018.

Cathrine Grimsgaard finished her ph.d. thesis in 2019, with the title About holding something of a child's life in one's hand. This study has a qualitative design in which the researcher has done particpant observation in groups of children with mentally ill or drug addicted parents. Her methodology in this sensitive field has led professionals to reconsider how they talk to and meet such vulnerable children. The thesis was later published as a book on Cappelen Damm Akademisk.

Turid Wangensteen finished her PhD- thesis in 2020 and her study is a qualitative study of how children and adolescents perceive their childhood with parents with substance use disorder, and what support is provided to help them create meaning related to childhood experiences. Her conclusions are in line with what is cited in the first section here.

Kerstin Söderström finished her PhD in 2013. This was a qualitive interview study of the experience of parenthood in the context of substance use disorder. She had a 50 % post doc position in the research project and worked in Innlandet Hospital Trust to develop a large competence building program in the County of Oppland 2013-2016.

Astrid Halsa has a PhD from 2008 on motherhood and childcare in the welfare state when mothers are mentally ill. In the NFR – project she studied how children and young people handled daily life when growing up with parental mental health problems or SUD.

3. References to the research

Håkansson, U (2018). Keeping Mind in Mind: Parental Reflective Functioning and Executive Functioning in Mothers with Substance Use Disorder. PhD- thesis; Inland Norway University of Applied Sciences, BUK. PhD_Håkansson_HiNN_2018 til nett.pdf (6.702Mb).

Wangensteen, T (2020). Når stigma og skam står i veien for at barn som har foreldre med rusmiddelavhengighet får beskyttelse og meningsskapende samtaler. En kvalitativ studie. PhD-thesis; Inland Norway University of Applied Sciences, BUK.

Grimsgaard, C (2019). Om å holde noe av et barns liv i sin hånd. Samtaler mellom profesjonelle og barn som har psykisk syke eller rusavhengig foreldre: et etisk og narrativt perspektiv. PhD-thesis; Inland Norway University of Applied Sciences, BUK.

Söderström, K. & Sandvig Jr. A. (2020) SIM spedbarnevern og foreldrestøtte. Simulering som undervisnings- og fagutviklingsprosjekt for studenter og praktikere [Neonatal child protection and parental support. Simulation as learning and training model for students and practicians] in Verdier i barnevern [Values in child protection], red. H. Nordby og A. Halsa, Oslo: Cappelen Damm Akademisk.

4. Details of the impact (indicative maximum 750 words)

All the researchers in the group have published both in Norwegian and English, and have participated with presentations in research conferences as well as in different professional conferences for practitioners and in education on BA- and Master- level for students in social work and psychology. Håkansson study of parental reflective functioning (PRF) and executive functioning (EF) has been disseminated at numerous national conferences in Norway, with significant participation from the field of practice. Efforts have been made to "translate" research results into clinical practice so that practitioners can use strategies in line with research.

We have all been part of the national research-network for children growing up in families with serious somatic illness, mental health problems and substance abuse. This research network has altogether published three books (anthologies) in which participants from our research group has contributed in all of them. In the first book (Barn som pårørende, 2012), Halsa & Kufås wrote an article on how health – professions experienced difficulties with their new responsibility of follow up their patients' children. In an interpellation in Parliament 2013, argumentation from this article was put forward to state that the role as "child-responsible" in hospital did not work good enough. This is an example of how small case studies may be applied and given a role in a political context.

Wangensteens' ph.d. scholarship was financed by the Tyrili Foundation, a drug treatment institution with 190 patients in eight inpatient treatment institutions. During and after her ph.d.-period Wangensteen has worked purposefully to improve the family/parental based work within The Tyrili Foundations as well as document and disseminate these experiences (Wangensteen & Dalsaune, 2021: Wangensten 2022). Over the past three years, they have organized a three-day seminar inviting all patients who are parents to discuss their relationship with their children, explore how children may experience having parents with Substance Use Disorder (SUD), and discuss ways to support the children. Each year, 30-40 parents participate in this seminar (for more details, refer to Wangensteen and Dalsaune, 2021). Furthermore, Tyrili offers "mum and dad groups" throughout the year at the local treatment institution. These groups provide guidance and support to patients regarding visitation, collaboration with the child's caregivers, and, if necessary, involvement with child protective services. Additionally, Tyrili regularly organizes gatherings for practitioners with child responsibilities. The objectives of these measures are to: a) Facilitate greater openness about how substance addiction affects the parental role. b) Highlight the life situation of children and potential experiences associated with growing up with parents struggling with substance addiction, for both parents and practitioners. c) Create a greater sense of security among practitioners to consistently integrate parenting and discussions about children into the treatment process.

Wangensteen has also written a handbook about how to support children who have parents with drug addiction. This book is written for students and practitioners that encounter this target group and instead of presenting a "given method" on how to meet parents and children in this situation, the book argues that services and help must be individually adjusted (Wangensteen & Dalsrud 2023).

Söderström and Håkansson has primarily focused on how to assist families with substance abuse problems who have young children. Håkansson has participated in a national expert group organized by Buf.dir to develop national guidelines for the follow-up of vulnerable parents of infants and young children in child welfare services. In this work, her research has contributed to the development of these national guidelines. Furthermore, for several years, she has provided systematic guidance to children and family centres across Norway, adapting the implementation of the research framework to each centre. This is utilized in practice when working with families in need of assistance from these centres.

Söderström has worked to strengthen interdisciplinary and inter-agency collaboration around these families with unborn and young children. She used insights about the target pregnant, parental and child group, for example the ambivalence, the fear for the child protection services, and the lack of coordination from the health and social services. This she did when she worked in the Inland hospital, to incorporate in the formal chain of care and a large competence building program in the relevant primary and specialist services in the county of Oppland in 2013 – 2016 (for more details on the project see Söderstöm 2015 and https://www.nord-fron.kommune). Söderström has also disseminated her research into a short film called "For Linnea" with the purposes 1) to reflect some of the experiences of the participants (hiding the problems, poor parental mentalizing, role-reversal and problematic involvement of the children, children's efforts to protect parents, and more) to enhance insights and reflections in the clinical target group, and 2) to illustrate and convey the many dilemmas and subtleties that face the professionals working with this group and type of problems, for use in professional training (Söderström 2015 B). The film was made freely accessible in 2015, and had been screened and integrated into conferences, workshops, seminars and webinars since then, latest in January 2023 for the group of health personnel that are responsible for the children-as-next-to-kin in both the somatic and mental health section of Innlandet hospital trust.

Söderström has done a lot of effort to improve the multidisciplinary collaboration between health services to adults and services towards children, in particular with the child protection services. She organised a joint simulation training for students in child protection integrated in their curriculum, and also for further education/ training for practitioners in health and social work in the County of Innlandet, involving appr. 70 practitioners and appr. 220 students over period of two years (see details in Söderström & Sandvig 2020.) Based on the research with the young and unborn children, the HINN institution were granted the role of assessing the question of the role and responsibility of the child protection services in protecting the unborn life (Netland, Stavrum & Söderström 2021). This was a report written for the Norwegian Directorate for Children, Youth, and Families following a tender announcement.

Through this research, it became evident that the child welfare services played a central role and were involved with a significant proportion of the families we examined. They were also a key collaborative partner for healthcare professionals. As a result, some of us aimed to further research the work of child welfare services and their interactions with vulnerable children and families. In collaboration with several colleagues, we applied for funding from the Norwegian Research Council's Health Welfare program in 2016 and were in 2017 granted support for the following research project: Decisions and Justification in Child Protection Services. This is still an ongoing project, and has resulted in several articeles and two scientific anthologies (Nordby & Halsa 2220 eds; Nordby, Netland & Halsa 2023 eds.) .

5. Sources to corroborate the impact

Anthologies from the national research (not INN) - network for children as next of kin:

Haugland, B., S., M., Ytterhus, B. & Dyregrov, K. (red) (2012) Barn som pårørende. Oslo. Abstract forlag.

Haugland, B.,S.,M., Bugge, K., E., Trondsen, M., V. & Gjesdal, S. (red) (2015). Familier i motbakke. På vei mot bedre støtte til barn som pårørende. Bergen. Fagbokforlaget.

Myra, S., M., Faugli, A. & Lauritzen, C. (red) 2022. Veiledning i profesjonell praksis – til fagfolk som jobber med barn, ungdom og familier. Bergen. Fagbokforlaget.

Publications and contributions from HSV/INN:

Halsa, A & Kufås, E. (2012). De nye vaktbikkjene: Barneansvarlige i helseforetak. I B.. S., M., Haugland, B., Ytterhus & K. Dyregrov (red) (2012) Barn som pårørende. Oslo. Abstract forlag

Wangensteen, T (2022). Veiledning med foreldre i rusbehandling. I S. ,M., Myra, A. Faugli & C. Lauritzen (red). Veiledning i profesjonell praksis – til fagfolk som jobber med barn, ungdom og familier. Bergen. Fagbokforlaget.

Wangensteen, T & Jansrud S., D. (2021). «Jeg vil jo så gjerne bli en god og trygg pappa». Erfaringer fra foreldreseminar med pasienter i rusbehandling. Fokus på familien (2). s- 121- 139).

Wangensteen, T. & Dalsrud, M., K. (2023). Når foreldre ruser seg. Oslo. Universitetsforlaget

Söderstöm, K. (2015). Barnet i mente: Samordnet innsats for sped- og småbarn i utviklingsrisiko (s 123- 133). I B.,S.,M., Haugland, K., E., Bugge, M., V. Trondsen & Gjesdal, S. (red) . Familier i motbakke. På vei mot bedre støtte til barn som pårørende. Bergen. Fagbokforlaget.

Söderström, K. & Sandvig Jr. A. (2020) SIM spedbarnevern og foreldrestøtte. Simulering som undervisnings- og fagutviklingsprosjekt for studenter og praktikere [Neonatal child protection and parental support. Simulation as learning and training model for students and practicians] in Verdier i barnevernet [Values in child protection], red. H. Nordby og A. Halsa, Oslo: Cappelen Damm Akademisk

Söderström, K. (2015 B) Short film "For Linnea" in collaboration with user organizations RIO, BAR and Filmmakeriet AS.

Netland, G., Stavrum. L. og Söderström, K. (April 2021). Barnevernets ansvar for det ufødte liv. Child protection services' responsibility for the unborn. Utredning på oppdrag fra Barne- ungdoms- og familiedirektoratet etter anbud.

Nordby, H. og Halsa, A. (red) (2020). Verdier i barnevern. Oslo Cappelen Damm Akademisk.

Nordby, H. Netland, G. & Halsa, A. (2023): Child Welfare and the Significance of Family. Cappelen Damm Akademisk**.**

https://www.nord-fron.kommune.no/_f/p1/i202b8fa0-62d1-49e6-9e5d-b317b1558964/fra-bekymring-til-handling.pdf

Inland Norway University of Applied Sciences, Faculty of Social and Health Sciences

Impact case #2 – Health literacy

Institution: Inland Norway University of Applied Sciences
Administrative unit: Faculty of Social and Health Sciences
Title of case study: Health literacy (impact case #2)
Period when the underpinning research was undertaken: 2013-2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2003-2022
Period when the impact occurred: 2018-2022

1. Summary of the impact

Health literacy (HL) is emphasized for developing sustainable health care and to enable people to manage their own health. HL is concerned with personal competencies necessary to access, understand, appraise, and use information and services to promote and maintain good health and well-being for themselves and those around them. HL is mediated by the organizational structures and availability of resources[I]. HL-research at HINN has impacted policy, health services, learning outcomes in higher education, and research methods and activities. Indirectly, it has also had an impact on peoples' ability to manage their own health.

[I]Health promotion glossary of terms 2021. Geneva: World Health Organization; 2021. Licence: CC BY-NC-SA 3.0IGO.

2. Underpinning research

The research related to HL at HINN has had impact both on policy and practice, and how to measure HL in populations. Firstly, the research at HINN has influenced how HL is measured. Secondly, the research findings on HL have garnered attention for how services can adapt health information and services to make them more user-friendly.

HL is an evolving concept and has been defined and measured in several ways. There has been/are a high degree of inconsistency between HL definitions and how HL instruments operationalize the concept. In addition, several instruments are somewhat lengthy and time-consuming to use. In 2018, based on modern test-theory applied on data form the Norwegian population, Finbråten et al. developed a unidimensional short version of a multidimensional 47-item instrument, and at the same time upheld the same underpinning conceptual framework [1].

HL has been a research area at HINN since 2008. Findings when it comes to HL in people with type 2 diabetes [2-4] and in the Norwegian population in general [1,4] from 2017 to 2018 have been incorporated into the national strategy for increasing HL in the population in Norway.

The results from the national part of the HLS_{19} survey* (data were collected using computer-assisted telephone interviews in April–October 2020), in which HINN was involved, found that a third of the population could be considered having low HL [5]. In addition, the challenge was found to be even larger in people with long term illness, people with low education and some immigrant groups [5,6]. The national part of the HLS_{19} study indicates an association between HL and fewer visits to the general practitioner, fewer days absent from work, and better quality of life. The international part of the survey, in which 16 European countries in addition to Norway participated, found that relatively large percentages of the European population suffer from low HL and that HL varies across countries and sub-populations. The analyses also suggested a social

gradient of HL. There was a positive association between HL and health related quality of life, and a negative association between HL and the frequency of visits to general practitioners [7].

In 2021, HINN was assigned the responsibility to conduct a feasibility study aiming to pilot a self-assessment tool for organizational HL (HL-friendliness of health care organizations; OHL) from the Norwegian Directorate of Health. The feasibility study showed that aspects of HL are mostly addressed by health professionals in direct patient contact. However, these is a lack of integration of HL in organizations' strategies, procedures and guidelines [8].

*M-POHL. "About the HLS19". Accessed 28.01.2024

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Associate professor Hanne Søberg Finbråten has been employed at HINN since 2003 and has been doing research on HL since 2008. She defended her Ph.D. thesis about HL in 2018. She is a board member of the Norwegian research network for health literacy (HELINOR) and is active in the international WHO Action Network on Measuring Population and Organizational Health Literacy (M-POHL). Within the M-POHL network she is the head of a working group on communicative HL and co-lead a working group about revising the tool for OHL. She is also a part of the national study team for the Norwegian Health Literacy Surveys 2019-21 (HLS19-NO) and 2024-2026 (HLS24-NO).

At HSV, there are two Ph.D. candidates doing research on HL, Christopher Le and Kathrine Krüger Østbøll. Both are using data from the Norwegian HLS19 survey. Le was hired in a doctoral research position in January 2021, and is exploring HL and digital HL in young people. In addition to his position at HINN, he has a part-time position at the Norwegian Directorate of Health, where he also is responsible for HL projects. Le is also a board member of HELINOR and is a policy representative in M-POHL. He is also a part of the national study team for the Norwegian Health Literacy Surveys 2019-21 (HLS19-NO) and 2024-2026 (HLS24-NO). Østbøll is doing her HL research in people with Somali background and started her doctoral research position March 2022.

The research on HL is anchored in the research group Health and Mastery in an Interdisciplinary Perspective, and HL is one of four main research themes in this group. The health promotive and interdisciplinary perspective of this group is highly relevant as this perspective is central and necessary for increasing people's HL. The Ph.D. candidates are also members of this research group. The research group has also been important for developing new projects about HL, such as HL and social media, in which combines all the main research themes in the research group.

3. References to the research

Finbråten HS, Wilde-Larsson B, Nordström G, Pettersen KS, Trollvik A, Guttersrud Ø. Establishing the HLS-Q12 Short Version of the European Health Literacy Survey Questionnaire: Latent Trait Analyses Applying Rasch Modelling and Confirmatory Factor Analysis. BMC Health Serv Res. 2018; 18: 506. https://doi.org/10.1186/s12913-018-3275-7

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6. **Le C**, **Finbråten HS**, Pettersen KS, Joranger P., Guttersrud Ø. Befolkningens helsekompetanse, del II. Helsekompetansen i fem utvalgte innvandrerpopulasjoner i Norge: Pakistan, Polen, Somalia, Tyrkia og Vietnam. The International Health Literacy Population Survey 2019-2021 (HLS19). (Rapport IS-2988). Helsedirektoratet, 2021.

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8. **Finbråten HS**, Guttersrud Ø, Spilker RS, Le C. Helsekompetansevennlige Helsetjenester: Pilotering Av Et Kartleggingsvektøy for Organisatorisk Helsekompetanse Ved Fem Helseinstitusjoner I Norge. Høgskolen i Innlandet, 2023.

4. Details of the impact

The approach for measuring HL presented by Finbråten et al in 2018 [1] gained international attention. For the international Health Literacy Survey (HLS_{19}), a European Consortium used Finbråten's approach as inspiration for developing an instrument in a similar manner [9].

The research on HL at HINN has influenced efforts and policies both nationally and internationally. Nationally, reference is made to the research on HL at HINN in the national strategy for health literacy [10] and in parliamentary white papers. Finbråten's research up to 2018 has been cited in the strategy, while results from the HLS_{19} survey are cited in parliamentary white papers, such as the parliamentary white paper about public health [11] and National Health and Hospital Plan 2020–2023 [12]. The HLS_{19} survey is also referred to in the regional development plan of South-Eastern Norway Regional Health Authority (HSØ) [13], which is their overall strategy. Researcher from HINN has also been invited by HSØ to contribute to operationalizing their goal and focus area on HL. There is also reference to the national part of the HLS_{19} survey in the newest national budget [14]. The international part of the HLS_{19} has had an impact on WHO's road map for HL [15]. In addition, HL is linked to the Sustainable Development Goals (WHO) [16] and sustainable healthcare which demonstrates that HL can also be linked to societal and economic factors and is seen as a central determinant for social inequality in health.

The HL and OHL research at HINN has contributed to an awareness of individuals' varying abilities to engage with and utilize health information and services. Researchers at HINN have been invited to present at various conferences and professional meetings (e.g in the field of rehabilitation and in hospitals). Furthermore, the research has garnered attention in the media (e.g. NRK, VG, NTB). Research on the population's HL has led services and health institutions to become more aware of how they can tailor information and services to varying HL in the population. This has resulted in collaboration with several healthcare institutions on how services can become more HL-friendly. Such attention has led to that information provided from the health services could be easier to understand at that the health services becomes easier to navigate for the users. Among other things, a researcher from HINN has been invited to talk about HL and the importance of adapting health information to the population's HL to those who are responsible for a common web solution for hospitals in Norway [17]. Moreover, researcher(s) from HINN have been invited to several municipalities (e.g. Oslo and Trondheim) to present research about HL and what services

can do to become more HL-friendly. Furthermore, there is collaboration with HINN and the regional competence service for patient and family education on research and how such education can be made more HL-friendly. By adapting services and health information to individuals' varying HL, this enables the population to be better able to follow health advice and take care of their own health. Researchers from HINN have also been invited by associations and user organizations to talk about HL.

In addition to research on HL, HL has been a teaching topic at HINN since 2010. In order for the health services to become HL-friendly, it is necessary for healthcare professionals to have sufficient knowledge and skills in health communication and HL. Hence, on basis of the research on HL, showing that a large proportion of the population has low HL, the HL-research has been formative for the curriculum in education programs for health professionals. Through RETHOS, HL has been included as a learning outcome in basic education in health and social sciences, public health nursing education, and master's in clinical general nursing. Learning outcomes on HL is included in curricula at bachelor's, master's and Ph.D. levels at HINN. In addition, Finbråten has also been invited to several universities and university colleges to teach about HL in all levels of higher education (e.g. OsloMet, NTNU). In addition to scientific papers and reports Finbråten has written chapters about HL in two textbooks. A new textbook is currently under development where both Finbråten and Le contributes to several chapters.

4. Sources to corroborate the impact

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Inland Norway University of Applied Sciences, Faculty of Social and Health Sciences

Impact case #3 – Immersive virtual nature

Institution: Inland Norway University of Applied Sciences (INN)
Administrative unit: Faculty of Social and Health Sciences (HSV)
Title of case study: Immersive virtual nature (impact case #3)
Period when the underpinning research was undertaken: 2017-2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2013-2022
Period when the impact occurred: 2020-2022

1. Summary of the impact

Immersive virtual nature offers a novel means to experience the natural world through virtual reality headsets, both as a passive experience and combined with physical activity. Its significance lies in its capacity to inspire contact with nature and promote physical activity, health, and well-being in a novel and engaging way. The technological innovations developed in this project are used across Europe to promote health and well-being, including city partners, universities, a hospital, and a nursing-home. The research outcomes indirectly shape policies via EU-funded Horizon projects and the innovations have established new standards that attracts collaborators around the world.

2. Underpinning research

The foundation of our work, which is still ongoing, was developed between 2017 and 2022, and included the world's first scientific publication on virtual green exercise using fully immersive VR technology. During this period, a series of research papers was published on the back of our developmental process, aiming to create a functional protocol for virtual green exercise, i.e., physical activity in immersive virtual nature. During this groundbreaking work, an experimental set-up was developed in collaboration with the Game School at INN and included a one-of-a-kind software tool connected to VR headsets and a treadmill or trackers that detects physical movement of the user to allow for physical activity in virtual nature environments (as examples, see youtube videos here, here and here). During this process we conducted research on the effects of different developmental techniques, how to reduce the impact of cybersickness, seasonal effects, and a variety of potential benefits to health and well-being to understand the potential and limitations of the set-up and to optimize the experience for the user. Key learnings from this research period include "do's and don'ts" of 360 degree nature video development, the importance of synchronising treadmill speed with the contents of the virtual nature environment, practical applications of cybersickness aetiology, using open street map to create modifiable virtual copies of real world cities, etc. The main outcome of this underpinning research was the worlds first (known) set-up for physical activity in immersive virtual nature, using either a treadmill or trackers, that enables positive health related outcomes without concerning side effects (e.g., cybersickness, balance issues).

The research outputs generated in this process placed us on the top of this rapidly growing field and attracted attention from international partners, which in turn put us in position to be included in a European consortium (GoGreen) that are continuously involved in EU-funded projects and has direct communication with policy makers within the EU. This funding source, combined with regional, national, and international interest has allowed us to expand our lab through

collaborations with the University of South-Eastern Norway, The University of Maynooth, and Innlandet Hospital Trust. These partners are primarily interested in further developing the impact of immersive virtual nature in context of health services, targeting different groups such as patients with depression, nursing-home residents, and people with chronic pain.

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Contributors and collaborators at HSV/INN:

Giovanna Calogiuri (Professor, HSV)
Sigbjørn Litleskare (Associate Professor, HSV)
Tadhg MacIntyre (Associate Professor, HSV)

Fred Fröhlich (Associate Professor, INN's Game School)
Ole Einar Flaten (Assistant professor, programmer, Ph.D. fellow, INN's Game School)

Harnessing the potential of immersive virtual nature, the goal is to promote health and well-being through mental rejuvenation, stress alleviation, increased physical activity, and improved sleep. The well-documented benefits of real nature, such as a weekly 120-minute nature contact, have a significant positive impact on health, akin to recommended levels of physical activity. Immersive virtual nature can extend these benefits to individuals who are unable to engage in nature-based activities, while also enabling the study of nature's effects in controlled laboratory settings.

2. References to the research

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Litleskare, S., MacIntyre, T. E., & Calogiuri, G. (2020). Enable, Reconnect and Augment: A New ERA of Virtual Nature Research and Application. Int J Environ Res Public Health, 17(5).

4. Details of the impact

Without the research described in "2. Underpinning research" the concept would not have existed, at least not to the same extent. Both in terms of knowledge needed to develop the concept and in terms software and other materials used for this concept.

Technological development

The technology developed in this project can easily be adapted for different use cases and opens new research avenues. It allows for tailored made content for different user groups and is a tool used for student projects. The concept is briefly described here, and exemplified here, here and here. This technology has attracted attention from environmental psychologists, sports scientists, health care workers, politicians, and similar, and has initiated discussions regarding the importance of nature-based activities within health care.

Education and training

Building upon our work, a practice training activity was developed as part of the BA program in nursing at the University of South-Eastern Norway (USN), which aims to train student to use immersive virtual nature as a health promoting initiative for nursing home residents. The training started in fall 2022 and is ongoing. Graduates and undergraduate students participated in internships or training periods receiving support of international mobility programs such as the Erasmus+ Student Traineeship Programme and the North-to-North programme. The software developed for GoGreenRoutes (see below) has subsequently been used by researchers and students at INN.

Health and citizens engagement

The concept was included in a H2020 Innovation Action project (GoGreenRoutes), with a transportable VR installation being displayed in various Norwegian and European cities, involving different social groups, as part of an effort to promote nature connectedness and raise awareness of the benefits of urban green. For example, the concept was placed in the citizen centre of the City of Tallin to engage citizens and to promote understanding of the benefits of including natural environments in cities and was used as an initiator for direct conversation between citizens and the municipality regarding these issues.

Applied projects

Following our initial developmental projects, several Ph.D. and research projects have been initiated to test the effectiveness of including the technology in health services targeting different target groups, such as

- A Ph.D. project investigating the effectiveness of including virtual green exercise as part of the treatment for mild to moderate depression (collaboration with Innlandet Hospital Trust, initiated in 2020),
- A Ph.D. project studying the viability and benefits of virtual green exercise for individuals at high risk for cardiovascular complications living in warm counties in Greece.
- A project applying this concept for people with fibromyalgia (collaboration with University of Staffordshire and patients' organizations, initiated in 2022)
- A Ph.D. project under development to investigate the health-promoting benefits of engaging nursing home residents with virtual green exercise technologies (collaboration with USN and nursing homes in Drammen)
- A recent start up project at the University of Maynooth.

Capacity and networking building

The research led to an ongoing and thriving collaboration between HSV and the Game school at INN. Following the success and impact of our developmental work, several international researchers and students have visited HSV to learn from our work and to expand upon our initial ideas. It has also ensured the inclusion of our team in an international consortium working towards a more nature friendly future (GoGeen).

Discourse

While the collective impact of these activities are key, our project's most profound impact likely lies in its capacity to initiate a discourse about nature's role in future societies. Along the road we have met and connected people with all sorts of backgrounds from different countries, sparking discussions in cities, universities, municipalities, hospitals, nursing-homes, schools, businesses, and in international consortiums connecting people from all these areas. Such impact is difficult to document, but it is most evident through our inclusion in the GoGreen initiative.

5. Sources to corroborate the impact

https://gogreenroutes.eu/

Kalyn Potter representing the GoGrenn initiative (Kalyn.Potter@mu.ie)

Lars Lien representing Innlandet Hospital Trust (Lars.Lien@sykehuset-innlandet.no)

Grith Overgaard representing the nursing program at USN (Grith.Overgaard@usn.no)

Suutari Taru representing the city of Lahti (Taru.Suutari@lahti.fi)

May Andresson representing the city of Tallinn (Mai.Andresson@tallinnlv.ee)

Vasiliki Stefanouli representing the University of Thessaly (vickystefa4@gmail.com)

Lena Heyn representing Centre for health and technology at USN (Lena.Heyn@usn.no)

[Lovisenberg Diaconal Hospital - ResDep] [case number 1]

Institution: Lovisenberg Diaconal Hospital (Lovisenberg)
Administrative unit: Research Department (ResDep)
Title of case study: A trend towards earlier and more standardized identification of neurodevelopmental conditions in Norway and beyond is influenced by Lovisenberg research
Period when the underpinning research was undertaken: 2012-2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2012-present
Period when the impact occurred: 2012-present

1. Summary of the impact (indicative maximum 100 words)

Research carried out by scientists at the unit has helped to improve early identification of neurodevelopmental disorders, such as autism, and to reduce unwanted variability in assessment practices and care provision. The research has identified early markers of neurodevelopmental conditions and documented variability in assessment and care attributable to sex, geographical region, and the presence of co-occurring conditions. The impact has been achieved via influence on national and international guidelines, direct input into clinical training schemes, direct communication to clinicians, patients, and families, and contributions to an improved understanding of diagnostic assessment instruments in a Norwegian context.

2. Underpinning research (indicative maximum 500 words)

Early underpinning research for this impact case investigated psychometric properties of autism screening tools that influence their utility in clinical assessment (1,2,3). First, researchers from Lovisenberg identified that the performance of measures of autism symptoms was significantly influenced by both IQ and emotional/behavioural problems, to the extent that they better discriminated autism cases from controls when these factors were taken into account (1). Second, Lovisenberg researchers demonstrated the need to incorporate information regarding parental concerns about autism when using parent-report based instruments designed to assess behavioural signs of autism (2). In the same study, it was also shown that parents contribute unique, valid information distinguishing autism cases from controls, underlining the utility of combining instruments based on parent accounts and clinician observation in evaluation of autism. Finally, these findings were further contextualised by work showing that early parental observations alone had poor sensitivity to detect cases of autism – particularly where children's cognitive skills were within a normal range (3).

As well as identifying features of assessment tools that were potentially contributing to under- and mis-identification of autism, researchers from the unit were active in establishing that regional variation in diagnostic practices was also prevalent within Norway (4). Importantly, this work by Lovisenberg researchers uncovered interplay between regional variation and other factors contributing to under-identification, such as female gender. Based on analyses of data from the nationwide Norwegian Patient Registry, researchers concluded that counties with low incidence of autism were likely missing cases of autism or diagnosing them late, and that this problem was exacerbated among girls.

In parallel to investigations focused on autism, researchers at the unit were also engaged in work aimed at understanding factors influencing assessment and care in neurodevelopmental disorders more broadly. In one salient example of this, Lovisenberg researchers collaborated in a project to

establish the link between gestational age and symptoms of attention deficit hyperactivity disorder (ADHD) in a Norwegian population-based sample, finding that preterm infants – and, especially preterm *girls* – had higher average ADHD symptom scores in early childhood, even after accounting for possible sources of familial confounding (5).

This body of research into the factors influencing timely and accurate assessment of individuals with autism and early indicators of other neurodevelopmental disorders across the impact period culminated in a leading role and co-authorship (by Havdahl) of a Lancet Commission on the future of care and clinical research in autism, initially released in 2021 (6). By this time, and on the basis of research contributions described above, Havdahl had established the Psychiatric Genetic Epidemiology (PaGE) research group at the unit, and a range of work across the group underpinned her contributions to the Lancet Commission publication. Notably, this included original empirical analyses demonstrating different rates of co-occurring emotional and behavioural problem trajectories among autistic individuals relative to the general population, and differences in the functional correlates of these trajectories depending on autism status (6).

Key researchers:

Alexandra Havdahl: Doctoral fellow (2012-2015); Research fellow (2018-2020); Research group leader of PaGE (2020-2022)

Anne-Siri Øyen: Head of Infant and preschool section, Nic Waals Institute (2012-2022); Director of clinical assessment in the Autism Birth Cohort (ABC) study (2012-2015)

3. References to the research (indicative maximum of six references)

(1) **Havdahl, K. A**., Hus Bal, V., Huerta, M., Pickles, A., Øyen, A.-S., Stoltenberg, C., Lord, C., & Bishop, S. L. (2016). Multidimensional Influences on Autism Symptom Measures: Implications for Use in Etiological Research. *Journal of the American Academy of Child & Adolescent Psychiatry*, *55*(12), 1054-1063.e3. https://doi.org/10.1016/j.jaac.2016.09.490

(2) **Havdahl, K. A**., Bishop, S. L., Surén, P., Øyen, A.-S., Lord, C., Pickles, A., von Tetzchner, S., Schjølberg, S., Gunnes, N., Hornig, M., Lipkin, W. I., Susser, E., Bresnahan, M., Magnus, P., Stenberg, N., Reichborn-Kjennerud, T., & Stoltenberg, C. (2017). The influence of parental concern on the utility of autism diagnostic instruments. *Autism Research*, *10*(10), 1672–1686. https://doi.org/10.1002/aur.1817

(3) Surén, P., **Saasen-Havdahl, A.,** Bresnahan, M., Hirtz, D., Hornig, M., Lord, C., Reichborn-Kjennerud, T., Schjølberg, S., Øyen, A.-S., Magnus, P., Susser, E., Lipkin, W. I., & Stoltenberg, C. (2019). Sensitivity and specificity of early screening for autism. *BJPsych Open*, *5*(3), e41. https://doi.org/10.1192/bjo.2019.34

(4) Surén, P., **Havdahl, A**., **Øyen, A.-S**., Schjølberg, S., Reichborn-Kjennerud, T., Magnus, P., Bakken, I. J. L., & Stoltenberg, C. (2019). Diagnostisering av autismespekterforstyrrelser hos barn i Norge. *Tidsskrift for Den Norske Legeforening*. https://doi.org/10.4045/tidsskr.18.0960

(5) Ask, H., Gustavson, K., Ystrom, E., **Havdahl, K. A.**, Tesli, M., Askeland, R. B., & Reichborn-Kjennerud, T. (2018). Association of Gestational Age at Birth With Symptoms of Attention-Deficit/Hyperactivity Disorder in Children. *JAMA Pediatrics*, *172*(8), 749–756. https://doi.org/10.1001/jamapediatrics.2018.1315

(6) Lord, C., Charman, T., **Havdahl, A.,** Carbone, P., Anagnostou, E., Boyd, B., Carr, T., Vries, P. J. de, Dissanayake, C., Divan, G., Freitag, C. M., Gotelli, M. M., Kasari, C., Knapp, M., Mundy, P., Plank, A., Scahill, L., Servili, C., Shattuck, P., … McCauley, J. B. (2022). The Lancet Commission on the future of care and clinical research in autism. *The Lancet*, *399*(10321), 271–334. https://doi.org/10.1016/S0140-6736(21)01541-5

3. Details of the impact (indicative maximum 750 words)

Improved standardisation and timeliness of diagnosis for neurodevelopmental conditions

The challenge of globally increasing prevalence of neurodevelopmental conditions, such as autism and ADHD, has been met by a trend, during recent years, towards earlier diagnosis (7,8). Earlier diagnosis of neurodevelopmental conditions is desirable for numerous reasons; not least, because it allows for supportive interventions to be put in place in time to have effect during crucial early school years. As well as timeliness, equity and accuracy are important principles in the assessment of neurodevelopmental conditions; that is, clinical tools, criteria, and practices should ideally not be applied differently among different groups, and assigned diagnoses should reflect consistent phenomena across populations and geographical regions. The impacts described in this case collectively amount to a substantive contribution, by Lovisenberg researchers, to the process of improvement of diagnostic practices and care pathways across these different criteria during the reporting period, in Norway and beyond.

Lovisenberg research influences clinical guidelines, training, and public understanding

The incorporation and influence of Lovisenberg research (1-4) in clinical guidelines (9) and government-commissioned reports (10) is evidence of one route via which it has been involved in shaping practices of assessment of and care for individuals with neurodevelopmental conditions in Norway during the reporting period. Clinical guidelines in Norway set the standards for care and clinical practice that are followed nationwide. We also have evidence of our research being used internationally in the development of clinical guidelines (e.g., 11), illustrating the fact that impacts from work of this nature extend beyond national borders.

A second route by which the research described in the previous section has been translated into practical impacts on clinical assessment and care in Norway and abroad is via training. Lovisenberg researchers, using insights from research carried out at the unit, have been involved in developing and delivering training programmes for clinicians using standardised assessment tools for neurodevelopmental conditions in Norway and the U.S. (12). In addition to direct training, by contributing to clinician-focused publications designed to "contribute to informed choices and proper use of tests and mapping tools in the field of practice" (13), impacts of relevant work were propagated more widely and for a more sustained period domestically.

A final route by which the underpinning research was translated into impact during the reporting period was via direct communication with a diverse range of stakeholders, in the forms of talks and lectures to clinicians, other specialists, patients, and family members. Examples of these during the reporting period included an invited lecture on autism at 2018 annual meeting of

Norwegian neuropsychologists' association (14) and an invited presentation on identification and assessment of autism in girls and women at Felleskonferansen 2022 (2000 participants) (15).

Recent work cements Lovisenberg contributions for the benefit of patients and families

The Lancet Commission report on the future of care and clinical research in autism (6) is worthy of specific mention, in respect of its current and future potential impact. Lancet Commission reports are commonly influential in the development of clinical guidelines around the world, and feature in World Health Organization reports designed to influence policy and draw focus to unmet health needs on a global scale. It is anticipated that the impact of Lovisenberg research in this report, which was published towards the end of the eligible period, will be extensive in the coming years.

The primary beneficiaries of the earlier and more standardized identification of neurodevelopmental conditions are those individuals receiving diagnoses and their family members. For example, earlier receipt of a diagnosis, or receipt of a diagnosis by an individual in a group where diagnoses were previously missed, may provide the gateway to special educational support and allow neurodivergent children to thrive in school environments. Secondary beneficiaries are clinicians, whose task in providing these diagnoses is made easier by having received empirically-informed training and by having access resources that allow them to use diagnostic tools more effectively and consistently.

5. Sources to corroborate the impact (indicative maximum of ten references)

(7) *Meta-analytic evidence demonstrating global time trend of earlier diagnosis of autism in the impact period:* van 't Hof, M., Tisseur, C., van Berckelear-Onnes, I., van Nieuwenhuyzen, A., Daniels, A. M., Deen, M., Hoek, H. W., & Ester, W. A. (2021). Age at autism spectrum disorder diagnosis: A systematic review and meta-analysis from 2012 to 2019. *Autism, 25*(4), 862–873. https://doi.org/10.1177/1362361320971107

(8) *Psykiske plager og lidelser hos barn og unge. I: Folkehelserapporten - Helsetilstanden i Norge [nettdokument].* Bang L, Surén P, Støle HS, Odsbu I, Handal M, Furu K, Hartz I et al. Oslo: Folkehelseinstituttet [updated 14.09.2023; read 12.12.2023]. Accessible from: https://www.fhi.no/he/folkehelserapporten/psykisk-helse/psykisk-helse-hos-barn-og-unge/?term=#gjennomgripende-utviklingsforstyrrelser-autismespekterforstyrrelser

(9) *Research contribution to patient pathway for assessment of ADHD and other neurodevelopmental conditions* https://www.helsedirektoratet.no/nasjonale-forlop/psykiske-lidelser-barn-og-unge/kartlegging-og-utredning-psykiske-lidelser-pakkeforlop-barn-og-unge/adhd-og-andre-nevroutviklingsforstyrrelser

(10) *Research used in government-commissioned Norwegian Public Statement (NOU) on Services for people with autism spectrum disorders and for people with Tourette syndrome – handed to Ministry of Health and Welfare on 6 February 2020* https://www.regjeringen.no/no/dokumenter/nou-2020-1/id2689221/

(11) *Research used internationally in development of best practice guidelines for screening, evaluation, and treatment of autism (Michigan state, U.S.A.)* https://www.michigan.gov/-/media/Project/Websites/autism/Reference-Guides/Medicaid_ASD_Best_Practice_Guidelines_October_2019.pdf?rev=080b79a38db64f16a2d23ac00822beef

(12) *Input to clinical training programmes at UCSF and WCMC https://autism.ucsf.edu/ados-2-adi-r-certified-trainers*

(13) *Research incorporated in 'Measurement properties of the Norwegian version of ADOS-2'* on PsykTestBarn, a clinician-focused publication outlet designed to "Contribute to informed choices and proper use of tests and mapping tools in the field of practice" https://psyktestbarn.r-bup.no/no/artikler/ados-2-autism-diagnostic-observation-schedule-second-edition#

(14) *Delivered invited lecture on autism at 2018 annual meeting of Norwegian neuropsychologists association* https://www.psykologforeningen.no/norsk-nevropsykologisk-forening/aktuelt/2018/nnf-aarsmoetekonferanse-15.-17.-november-2018

(15) *Delivered invited presentation on identification and assessment of autism in girls and women at Felleskonferansen 2022* (2200 registered participants, including health care personnel in specialised and primary care, autistic people and their families, policy makers and general audience) https://sites.google.com/view/felleskonferansen-2022

[Lovisenberg Diaconal Hospital - ResDep] [Case 2]

Institution: Lovisenberg Diaconal Hospital (Lovisenberg)
Administrative unit: Research Department (ResDep)
Title of case study: Advancement in Understanding and Enhancing Treatment for Advanced Shoulder Conditions by Lovisenberg Research: Easing Pain and Restoring Functionality
Period when the underpinning research was undertaken: 2012-2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2012 - present
Period when the impact occurred: 2012 - present

1. Summary of the impact (indicative maximum 100 words)

Our research has refined the treatment of superior labral (SLAP II) tears in the shoulder. SLAP II tear is a complete detachment of the superior labrum and the long head biceps tendon, and typically causes pain, range-of-motion problems and clicking, popping or grinding in the shoulder, especially while lifting the arm over the head. In the late 1990's, surgical labral repair was the most common treatment for these lesions and was being performed in large and growing numbers all over the world, leading to increasing concerns about complications such as pain and stiffness. Surprisingly, no randomized controlled studies had been performed to evaluate whether surgical treatment was superior to physiotherapy.

To address this lack of empirical evidence, a randomized double-blind, placebo-controlled study was designed with ground-breaking methodology, including sham surgery control group. Strikingly, the results showed no significant difference between surgical labral repair, tenodesis of the long biceps tendon and sham surgery. These findings have received global attention after being published in esteemed journals and presented at international conferences. The profound impact of our study is anticipated to bring forth a significant reduction in unnecessary and ineffective surgeries for patients suffering from SLAP II tears.

2. Underpinning research (indicative maximum 500 words)

Starting in the late 1990's, there was an increase in the number of patients treated with surgical labral repair for a SLAP II lesion. The increased incidence and high complication rates of labral repair were documented in a study by Weber et al. in *Am J Sports Med* 2012. Moreover, a shift from labral repair to biceps tenodesis for SLAP lesions was also documented in a study by Patterson et l in *Am J Sports Med* in 2014. As there was a discussion about the clinical relevance of these lesions, we decided that if we were going to perform surgical labral repair, we should include the patients in a study and follow them prospectively. The first study prospectively followed 107 patients after labral repair and assessed postoperative function, pain, and patient satisfaction by patient age. Four experienced shoulder surgeons performed the operations and an independent examiner performed the postoperative patient evaluations. Our observational findings indicated that surgical labral repair yielded good results with regard to function and pain regardless of age, but a worrying 13% of the patients experienced postoperative stiffness. We published the results of this study in 2012.[1]

Despite the good clinical results for labral repair overall, the complications and the fact that there were no studies with a high level of evidence showing the necessity of these operations indicated that a randomized, controlled study was needed. We therefore developed and published a study protocol,[2] obtained ethical approval, and registered the trial in

ClinicalTrials.gov NCT00586742. The aim of this three-arm, participant- and observer-blinded, randomized placebo-controlled trial (RCT) was to compare the short-term (6 months) and long-term (2-year) efficacy of labral repair, biceps tenodesis, and placebo/sham surgery (diagnostic arthroscopy) for alleviating pain and improving function for SLAP II tears.

Patient inclusion started in January 2008 and ended in January 2014. A total of 118 patients with an isolated SLAP II lesion were enrolled. Our findings indicated that labral repair, biceps tenodesis and sham surgery all led to significant improvement in both objective and subjective measures among these patients. There were no significant differences among the patients in the three study arms. The clinical impact of these findings is that patients with these lesions should be informed that non-operative treatment has a good probability of success, and further studies are needed to establish what treatment is best for the patients. The study was published in *Br J Sports Med* in 2016.[3] An analysis of sick leave and return to work after surgical repair of SLAP II lesions was also published in 2020.[4]

During the years of studying patients with a SLAP II tear prior to the sham surgery RCT, a subgroup of patients emerged. Some patients develop a paralabral cyst that compresses the suprascapular nerve and leads to pain and weakness in the affected muscles. When we first encountered this entity, the literature was scarce and decompressing the cyst seemed risky given its close proximity to the nerve. We therefore chose to do an isolated labral repair, a more conservative surgical approach, and followed the patient. Magnetic resonance imaging control at 3 months showed total cyst resolution. To investigate this phenomenon further, we designed a prospective study of patients receiving this treatment. The purpose was to assess whether labral repair alone would lead to cyst resolution and pain relief. A total of 42 patients were followed by an independent examiner with clinical assessment and scoring and all had MRI control. At last follow-up, 88% of the cysts were resolved and the patient satisfaction was high. These findings were published in *J Bone Joint Surg Am* in 2008[5] and in *J Shoulder Elbow Surg* in 2018.[6]

Key researchers:

- Cecilie Piene Schrøder (MD, Orthopaedic Surgeon)
- Øystein Skare (MT, PhD, Manual Therapist)
- Kirsten Lundgreen (MD, Orthopaedic Surgeon)

3. References to the research (maximum of six; Lovisenberg researchers are **bolded**)

1. **Schrøder CP, Skare Ø**, Gjengedal E, *et al*. Long-term results after SLAP repair: a 5-year follow-up study of 107 patients with comparison of patients aged over and under 40 years. *Arthroscopy* 2012;28:1601-7. DOI: 10.1016/j.arthro.2012.02.025
   (findings from observational study preceding the sham surgery RCT)

2. **Schrøder CP, Skare Ø**, Reikerås O, Mowinkwl P, Brox JI. Sham surgery versus labral repair or biceps tenodesis for type II SLAP lesions of the shoulder: a three-armed randomized clinical trial. *Br J Sports Med.* 2017;51:1759-66. DOI: 10.1136/bjsports-2016-097098
   (published protocol for the sham surgery RCT)

3. **Skare Ø, Schrøder CP**, Reikerås O, Mowinckel P, Brox JI. Efficacy of labral repair, biceps tenodesis, and diagnostic arthroscopy for SLAP lesions of the shoulder: a randomised controlled trial. *BMC Musculoskelet Disord*. 2010;11:228. DOI:10.1186/1471-2474-11-228
   (main publication of findings from the sham surgery RCT)

4. Brox JI, **Skare Ø**, Mowinckel P, Brox JS, Reikerås O, **Schrøder CP**. Sick leave and return to work after surgery for type II SLAP lesions of the shoulder: a secondary analysis of a randomised sham-controlled study. *BMJ Open*. 2020;10(4):e035259. DOI:10.1136/bmjopen-2019-035259
(publication of secondary outcomes for the sham surgery RCT)

5. **Schrøder CP, Skare Ø**, Stiris M, Gjengedal E, Uppheim G, Brox JI. Treatment of labral tears with associated spinoglenoid cysts without cyst decompression. *J Bone Joint Surg Am*. 2008;90:523-30. DOI: 10.2106/JBJS.F.01534.
(observational findings about a patient subgroup preceding the sham surgery RCT)

6. **Schrøder CP, Lundgreen K**, Kvakestad R. Paralabral cyts of the shoulder treated with isolated labral repair: effect on pain and radiologic findings. *J Shoulder Elbow Surg.* 2018;27:1283-9. DOI: 10.1016/j.jse.2017.12.022
(observational findings about a patient subgroup preceding the sham surgery RCT)

4. Details of the impact (indicative maximum 750 words)

Our studies have had several significant impacts:

1. **Impact on clinical practice**: Our 2017 finding that operative treatment for Type II SLAP tears is no more effective than sham surgery is likely to result in the reduction of unnecessary and ineffective surgeries and consequent reductions in health care costs. However, changing the indications for and performance of operative treatment in orthopaedic surgery is a long process that is rightfully dependent on a body of evidence rather than individual studies. Nonetheless, there is growing evidence that our findings are leading to reductions in unnecessary SLAP repairs and treatment of paralabral cysts with isolated labral repair, as advocated by our studies.

   Upon publication of our RCT findings, several editorials were written in top orthopedic journals highlighting their impact.[7,8] Additionally, a prominent orthopaedic surgeon and journal editor in the United States described this study as “possibly the most important paper on SLAP lesions I have ever read since Dr. Snyder's original description” (personal communication).

   Changes in clinical practice are often instigated by discussions that take place at professional scientific meetings and the findings of our four studies have received considerable international attention at such meetings. This attention has led to several invitations to present the results at well-recognized professional scientific meetings of shoulder surgeons:

   - The French Shoulder Association invited us to present at both the 2018 Nice Shoulder Course and the 2019 Val D` Isere Advanced Shoulder Arthroscopy Course.[9]
   - The British Elbow & Shoulder Society invited us to present at their 2018 Shoulder to Shoulder Meeting.
   - The German Association for Shoulder and Elbow Surgery invited us to present the studies at the 2022 Berlin International Shoulder Course
   - Recently, we received a second invitation to present our long-term results from the randomized controlled trial at the next Nice Shoulder Course.

   Changes to clinical practice are also implemented through standards of practice and clinical guidelines. Although new findings can take time to be incorporated into such standards and

guidelines, hospitals in Norway are already recommending non-surgical approaches as first-line treatment for SLAP II lesions and cite our findings in support of these approaches.[10]

2. **Impact on users/patients:** One way that our findings have had impact on users/patients is through articles in the popular press. One article published in Aftenposten, Norway's largest newspaper, highlighted our findings including an interview with the study's lead research and a discussion of the possible impact of the findings.[11] In addition, we have published an opinion article[12] in an open access journal to make our findings more broadly available to users/patients, medical professional, and researchers around the world. As local evidence of the impact on users, patients have been coming to our hospital already aware of our research findings that surgery is not always the answer. This has helped them be more receptive to non-operative physiotherapy interventions as a first-line treatment approach and has contributed to more informed participation in shared decision-making.

3. **Impact on evidence-based medicine**: Our research also represents a considerable step forward in strengthening evidence-based medicine. Surgical interventions have often lacked high-quality evidence of their efficacy, often due to the challenges of designing a suitable control group. A recent systematic review[13] of methodological limitations of placebo-controlled trials of surgical interventions identified Schrøder et al.'s sham surgery study as one of only a few studies that addressed such limitations. As one of the first sham surgery studies in orthopaedics, we demonstrated that such rigorous studies can be conducted and in a way that adheres to the highest ethical standards. As a result, our substantial contributions to evidence-based medicine have been recognized through several prestigious awards.[14-15] Thus, our research has helped establish higher methodological and empirical standards for evidence-based medicine, not only in orthopaedics but for all surgical treatments.

   The Norwegian Minster of Health has acknowledged the need for more evidence-based medicine such as ours by publicly asking hospitals in Norway to stop performing surgeries that have no effect and highlighting our sham surgery study of SLAP II repairs.[16]

5. Sources to corroborate the impact (indicative maximum of ten references)

7. *Editorial about sham study:*
McCormack RG, Hutchinson MR. Rocking the shoulder surgeon's world. *Br J Sports Med* 2017; 51:1727. DOI: 10.1136/bjsports-2017-097726 [Lovisenberg_ResDep_Case 2 McCormack attachment.pdf]

8. *Editorial about sham study:*
Cools AM, Borms D. Lessons to be learned from the study "Sham surgery versus labral repair or biceps tenodesis for type II SLAP lesions of the shoulder: a three-armed randomized clinical trial". *Br J Sports Med* 2017;51(24):1780. DOI: 10.1136/bjsports-2016-097098 https://bjsm.bmj.com/content/51/24/1759.long

9. *One of many invited presentations:*
https://www.valdisereshoulder.com/images/Val_dIsere_2019.pdf

10. *Oslo University Hospital clinical guidelines recommending non-operative approaches as first-line treatment for SLAP II lesions and citing Schrøder's dissertation*:
https://metodebok.no/index.php?action=topic&item=CDgV62C7

11. *Article in Norway's largest newspaper about our sham surgery study:*
https://www.aftenposten.no/amagasinet/i/QVOWq/marianne-eide-ble-lagt-i-narkose-men-kirurgene-opererte-henne-aldri-likevel-ble-hun-frisk

12. *Opinion article in open-access journal*:
Schrøder CP. SLAP lesions, An Opinion Piece. *Open Orthop J*. 2018;12:342-345. DOI:10.2174/1874325001812010342

13. *Systematic review highlighting our study:*
Cousins S, Blencowe NS, Tsang C, et al. Reporting of key methodological issues in placebo-controlled trials of surgery needs improvement: a systematic review. *J Clin Epidemiol*. 2020;119:109-116. doi:10.1016/j.jclinepi.2019.11.016

https://www.jclinepi.com/article/S0895-4356(19)30744-9/fulltext

14. *The Norwegian Medical Association awarded Dr. Schrøder the Marie Spångberg Prize in 2018, which recognizes the most valuable original scientific article written by a Norwegian female doctor in a Norwegian or international journal each year*.
https://tidsskriftet.no/2018/06/aktuelt-i-foreningen/prisdryss-til-leger

15. *The Norwegian Arthroscopy Association awarded Dr. Schrøder the Nimi Prize at their 2017 Sports Medicine Autumn Congress, recognizing her sham surgery study as the best article published in an international journal.*
https://www.facebook.com/465851473533771/photos/a.491190347666550/1490672354385006/?type=3

16. *The Norwegian Minster of Health asks hospitals in Norway to stop performing surgeries that have no effect highlighting Schrøder et al.'s 2017 sham surgery study*:
https://www.aftenposten.no/norge/i/VRnjk1/helseministeren-ber-sykehusene-slutte-med-operasjoner-som-ikke-har-effekt

Rocking the shoulder surgeon's world

Robert G McCormack,[1] Mark Robert Hutchinson[2]

Dr Schrøder and colleagues[1] are to be congratulated on performing a high-quality study to address this controversial topic. Randomised surgical trials are difficult to perform, particularly with such a convincing 'control' group.

As they point out, the enthusiasm for SLAP repairs has waned over recent years, but it remains a commonly performed operation, which makes this study very relevant.

From a design and performance perspective, the study has many strengths. It was a double-blinded, randomised design with an adequate sample size to detect a clinically relevant difference. The CONSORT flow chart appropriately tracks the screening process and only 14 out of 445 screened patients declined to participate. This rules out significant selection bias. All patients failed a non-operative programme (that included formal therapy) and an experienced subspecialist shoulder surgeon performed all surgeries. This reduces the risk of a performance bias.

Post-operative rehabilitation was standardised for all patients and the follow-up was exceptional with less than 2% lost to FU at the primary end point (6 months) and less than 4% lost to FU at 2 years.

The outcome measures the authors used were specific for this joint and validated for this particular patient population. The results were almost identical for each group, at all time points, and consistent when analysed using both 'intention to treat' and 'per protocol'.

As with any study there are limitations. The conclusions apply only to type 2 SLAP lesions—the most common indication for SLAP surgery. The average age is 40 years, which is relatively old for a sport injury population. This means the results can be applied to middle-aged patients (where the diagnosis is common) but may not apply to athletes and specifically throwers. Indeed, only 7/118 patients were athletes (6%), and the authors acknowledge that while they saw no difference by age the numbers were too small to perform subgroup analysis.

The other significant issue relates to the number of crossovers and secondary surgeries. While it is impressive that no patients breached the protocol before the 6-month assessment, there were more secondary surgeries in the sham group (14) versus. repair (4) or tenodesis (6). Of course this is not be surprising as a patient that is not completely satisfied after 'sham' surgery is more likely to proceed to what they think might be 'definitive' treatment than one that has already had an intervention.

This is supported by the fact that the 14 crossovers from the sham group had similar outcomes to the 14 worst patients from the two other study groups.

The fact that this study challenges commonly held beliefs will inevitably mean many will criticise it. However, from an 'evidence-based medicine' perspective, it is head and shoulders above other published work on the topic. The other well-known surgical trial to include a 'sham surgery' arm was the trial by Moseley *et al*[2] regarding arthroscopy for degenerative joint disease of the knee. The results of that study did not sit well with surgeons who routinely performed the procedure, but the findings were subsequently corroborated by high-quality studies in a variety of different jurisdictions.

Time will tell if the same process will occur here, but the burden of responsibility is now with proponents of SLAP surgery to perform good quality trials to determine possible subgroups where surgery is justified. As John Maynard Keynes once stated: The difficulty lies not so much in developing new ideas as in escaping from old ones.

[1]Department of Orthopaedics, University of British Columbia, New Westminster, Canada
[2]Department of Orthopaedics, University of Illinois at Chicago, Chicago, Illinois, USA

Correspondence to Dr Robert G McCormack, Department of Orthopaedics, University of BritishColumbia, New Westminster, Canada; drbobmccormack@me.com

Competing interests None declared.

Provenance and peer review Commissioned; externally peer reviewed.

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Br J Sports Med 2017;**51**:1727.
doi:10.1136/bjsports-2017-097726

REFERENCES

1 Schrøder CP, Skare Ø, Reikerås O, *et al*. Sham surgery versus labral repair or biceps tenodesis for type II SLAP lesions of the shoulder: a three-armed randomised clinical trial. *Br J Sports Med* 2017;51:1758–65.
2 Moseley JB, O'Malley K, Petersen NJ, *et al*. A controlled trial of arthroscopic surgery for osteoarthritis of the knee. *N Engl J Med* 2002;347:81–8.

[Lovisenberg Diaconal Hospital - ResDep] [Case 3]

Institution: Lovisenberg Diaconal Hospital (Lovisenberg)
Administrative unit: Research Department (ResDep)
Title of case study: BMJ Rapid Recommendations
Period when the underpinning research was undertaken: 2016-2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2017-2022
Period when the impact occurred: 2016-2022

1. Summary of the impact (indicative maximum 100 words)

BMJ Rapid Recommendations, a collaboration between MAGIC and the medical journal BMJ, reimagines clinical practice guideline creation for enhanced policy and practice impact. This project yields four significant outcomes:

Firstly, it directly influences global clinical practice through through the 22 guidelines recommending new and effective treatments or against the use of wasteful or harmful treatments. Secondly, it showcases the efficient creation and open access of trustworthy guidelines globally via www.magicapp.org. Thirdly, it introduces the concept of "living guidelines," exemplified by WHO's COVID-19 therapeutics guidance. Lastly, it advances methods, processes, and platforms for the creation of trustworthy guidelines and systematic reviews.

2. Underpinning research (indicative maximum 500 words)

For MAGIC, the BMJ Rapid Recommendations have become a highly productive laboratory for research and innovation to fix problems with clinical practice guidelines, as an integral part of an enhanced evidence ecosystem. This represents the key research insight, but several more specific findings speak to the global impact of this project on policy and practice. This is further outlined below, through the story of this project that started in 2016 and is still ongoing in 2023, with 8 ongoing guideline initiatives, now including AI and precision medicine.

BMJ Rapid Recommendations (https://www.bmj.com/rapid-recommendations) was initiated by MAGIC in 2016 as a reaction to how most organisations worldwide struggle to react to practice changing evidence with trustworthy and accessible guideline recommendations to inform health care professionals and their patients. The hypothesis was that a network of unconflicted clinicians, researchers, methods experts and patient partners would collaborate at the global level to rapidly produce trustworthy guideline recommendations to inform policy and practice. The guideline panels would follow best current standards and methods for trustworthy guidelines (GRADE), further enhanced by innovative processes and platforms as co-created by MAGIC and BMJ in what has become a very successful ongoing partnership. Since trustworthy guidelines need to be informed by high quality systematic reviews specifically answering the clinical questions from the guideline panel, we also identified the need to produce linked systematic reviews on effectiveness, supported by systematic reviews on prognosis and values and preferences as needed.

As the responsible organisation, MAGIC has created and published 22 guidelines in the BMJ Rapid Recommendations program, each with one or more linked high quality systematic reviews. Each of these packages of guidelines and systematic reviews have typically included more than 30 authors, demonstrating the global network of clinicians, researchers, methods experts and patient-partners that collaborate to innovate the field of clinical practice guidelines.

In 2020, MAGIC offered to support the WHO with their COVID-19 guidelines, proposing to move to living evidence (i.e., dynamically updated recommendations) within the context of the BMJ Rapid Recommendations. These living WHO guidelines have been updated 14 times and are still being dynamically updated based on new and practice-changing evidence. The guidelines exemplify a breakthrough for the concept of living evidence, as highlighted in a Nature paper. The guidelines are informed by a living network meta-analysis of all COVID-19 therapeutics performed by colleagues at McMaster University in Canada. During the pandemic, MAGIC supported national living guidelines in Australia, Germany and the UK using our MAGICapp platform. All this development has been contingent on our work in BMJ Rapid Recommendations where we have been able to continuously perform research and innovation coupled to scientific publication in a wide- reaching journal such as BMJ.

In 2022, MAGIC became partner in 4 EU Horizon projects and 1 Norwegian Research Council (NRC) funded project (ReMeDy) where our contribution is to transform new research evidence to practice through trustworthy clinical practice guidelines, disseminated in user-friendly formats. Three of these projects include BMJ Rapid Recommendations and cover new topics such as AI in gastroenterology (polyp detection during colonoscopies) and personalised medicine (therapeutic drug monitoring with infliximab for immune-mediated inflammatory diseases). The BMJ Rapid Recommendations have now become synonymous with high quality, high impact guidelines focussed on practice changing topic areas.

Key researchers:

- Per Olav Vandvik, Founder, CEO and Research Director MAGIC
- Linn Brandt, Founder and CTO MAGIC
- Anja Fog Heen, MD, PhD (dissertation 29 January 2024), Assistant Head of Department of Medicine, Lovisenberg Diaconal Hospital (from March 2024)
- Per Olav Løvsletten, PhD Student (defence in 2024)

3. References to the research:

1) Agarwal A, Hunt B J, Stegemann M, Rochwerg B, Lamontagne F, Siemieniuk RA, et al. (**Vandvik PO** last author). A living WHO guideline on drugs for covid-19. *BMJ* 2020;370:m3379. doi: 10.1136/bmj.m3379

2) **Vandvik PO**, Lähdeoja T, Ardern C, Buchbinder R, Moro J, Brox JI, et al. Subacromial decompression surgery for adults with shoulder pain: a clinical practice guideline. *BMJ* 2019;364:l294. doi: 10.1136/bmj.l294

3) Li S, **Vandvik PO**, **Lytvyn L, Guyatt GH**, Palmer SC, Rodriguez-Gutierrez R, et al. SGLT-2 inhibitors or GLP-1 receptor agonists for adults with type 2 diabetes: a clinical practice guideline. *BMJ* 2021;373:n1091. doi: 10.1136/bmj.n1091

4) **Vandvik PO**, Otto CM, Siemieniuk RA, Bagur R, **Guyatt GH, Lytvyn L**, et al. Transcatheter or surgical aortic valve replacement for patients with severe, symptomatic, aortic stenosis at low to intermediate surgical risk: a clinical practice guideline. *BMJ* 2016;354:i5085. doi: 10.1136/bmj.i5085

5) Foroutan F, **Guyatt GH,** Brien K, Bain E, Stein M, Bhagra S, et al. (**Vandvik PO** last author). Prognosis after surgical replacement with a bioprosthetic aortic valve in patients with severe symptomatic aortic stenosis: systematic review of observational studies. *BMJ* 2016;354:i5065. doi: 10.1136/bmj.i5065

6) **Heen AF**, **Lytvyn L,** Shapiro M, **Guyatt GH,** Siemieniuk RAC, Zhang Y, Manja V, **Vandvik PO**, Agoritsas T. Patient values and preferences on valve replacement for aortic stenosis: a systematic review. *Heart* 2021;107(16):1289-1295. doi: 10.1136/heartjnl-2020-318334.

4. Details of the impact

The research contributed to the above-described impact by broadly:

1. **Improving scientific methods, processes and platforms** for trustworthy – and eventually living – clinical practice guidelines and high-quality systematic reviews across a broad area of disciplines and topics, all with evidence with a likelihood to change practice.
2. **Disseminating the guidelines** both in a top 5 medical journal and through the advanced MAGICapp platform that further facilitates re-use, adaptation, translation and implementation in clinical practice. The journal publications include user-friendly and innovative Infographics and MAGICapp includes consultation decision aids, to facilitate shared decision-making in clinical practice.
3. **Disseminating systematic reviews** – including highly advanced network meta-analysis for highly relevant topics that may change clinical practice.
4. **For practice-changing research evidence that would improve patient care**, these guidelines have provided globally accessible, trustworthy and timely recommendations that can inform health care professionals, including user-friendly Infographics and tools for shared decision-making directly linked to conditional/ weak recommendations. Topics include COVID-19 therapeutics (reference 1), new diabetes drugs (reference 3), TAVI (a new device to replace open heart surgery for severe aortic stenosis, reference 4-6),), HIV treatment for pregnant women and lipid lowering therapies as a few examples.
5. **For the breakthrough of living guidelines**, the WHO COVID-19 therapeutics represent the most rigorous effort so far in demonstrating how systematic reviews with network meta-analysis and guideline recommendations can be efficiently and dynamically updated at the global level, informing clinical practice worldwide in real-time. The impact of this project also relates to the need for the MAGICapp; an authoring and publication platform that can fully serve the needs for organisations (e.g., features to updated content and for versioning) aiming to move to living guidelines.
6. **Recommendations against ineffective or harmful treatments**: Many of our BMJ Rapid Recommendations provide strong recommendations against the use of certain treatments, which has an important impact by reducing waste and harmful treatments, for example, recommendations against the use of surgical treatments (e.g., subacromial decompression surgery, reference 2), drug treatments and oxygen, across primary and specialist health care. These guidelines should have a direct impact by reducing overdiagnosis and overtreatment across primary health care and specialist health care and are also adapted by countries around the world leading to further impact locally.
7. **For screening**, we provide trustworthy guideline recommendations against the use of PSA for prostate cancer screening (also related to overdiagnosis and waste) and risk-stratified recommendations for colorectal cancer, including tools for shared decision-making.
8. **For the concept of patient partnership**, we have demonstrated how people with lived experience of a variety of diseases and conditions can fully participate in guideline development and updating. As one patient partner (Maureen Smith, later to become chair of Cochrane's Consumer Executive) put it after contributing to one of our guidelines in 2018: *"The aha moment for me was when I simply stated the realities of consultations and short appointment times with orthopaedic surgeons, based on my lived experience. I remember saying: "Have you attended an appointment with an orthopaedic surgeon? If they spend time explaining a device to me that has very little effectiveness on my recovery rather than interventions such as the importance of physiotherapy, that's not very helpful to me."*

And then (I believe it was you): "Get that down so we can put it in the report". At that point I realized that I did have a contribution to make .... and the impact of that led me to many other projects and championing patient, caregiver, and public involvement in evidence synthesis". In this guideline, the burden of treatment reported by patients directly impacted on what became a strong recommendation against the use of a device for healing bone fractures.

9. **For the concept of prognosis**, we have repeatedly demonstrated the importance of doing systematic reviews to inform clinical practice guidelines. This relates to the often-ignored but yet critical role of baseline risk estimates to inform the absolute estimates of effect across benefits and harms of treatment alternatives. Here, we have also advanced new research methods, as exemplified in reference 5 (e.g., making inferrals from Kaplan-Meyer curves) and in our systematic review on minimally important differences that informed the guidelines in knee arthroscopy.
10. **For the concept of values and preferences**, our systematic reviews of such studies serve as a constant reminder of how little we know about what most patients would want of treatment if they were well informed about the benefits and harms. We have therefore developed new research approaches to gather evidence on values and preferences to inform guideline recommendations development. This includes surveys of guideline panel members in the absence of access to representative samples of patients.

5. Sources to corroborate the impact (maximum of ten references)

Published clinical guideline content is normally measured based on the access metrics and citation metrics. These Rapid Rec guidelines perform significantly better than other guideline content in the BMJ, demonstrating that this innovative approach increases the impact the guidelines have. Below we provide some data on the top five most accessed Rapid Recs. We do not have data to substantiate the fact that these are accessed more often than normal guidelines as that is considered commercially confidential information by the BMJ, but they have confirmed that Rapid Recs perform better than normal guidelines.

Page Title	Unique Page Views	Sessions	Total citations
A living WHO guideline on drugs for Covid-19 – BMJ (2020)	368,052	315,412	477
Gastrointestinal bleeding prophylaxis for critically ill patients: a clinical practice guideline – BMJ (2020)	127,230	109,542	44
Thyroid hormones treatment for subclinical hypothyroidism: a clinical practice guideline – BMJ (2019)	82,050	68,623	110
Antibiotics after incision and drainage for uncomplicated skin abscesses: a clinical practice guideline – BMJ (2018)	76,296	74,804	24
Oxygen therapy for acutely ill medical patients - a clinical practice guideline – BMJ (2018)	75,017	59,886	125

A newer measure that goes beyond traditional citation and access data is the Altmetric score. Our leading Rapid Rec has an Altmetric score of over 8500 in its 14th iteration, which places it in the top 5% of all research outputs scored by Altmetric. The full breakdown of this score shows how widely accessed this content is by clinicians, scientists and members of the public and how distributed this impact is across the globe: https://bmj.altmetric.com/details/89469739

Impact case guidelines

Each case study should include sufficiently clear and detailed information to enable the evaluation committee to make judgements based on the information it contains, without making inferences, gathering additional material, following up references or relying on members' prior knowledge. References to other sources of information will be used for verification purposes only, not as a means for the evaluation committee to gather further information to inform judgements.

In this evaluation, impact is defined as an effect on, change or benefit to the economy, society, culture, public policy or services, health, the environment or quality of life, beyond academia.

Timeframes

- The impact must have occurred between 2012 and 2022
- Some of the underpinning research should have been published in 2012 or later
- The administrative units are encouraged to prioritise recent cases

Page limit

Each completed case study template will be limited to **five pages** in length. Within the annotated template below, indicative guidance is provided about the expected maximum length limit of each section, but institutions will have flexibility to exceed these so long as the case study as a whole remains no longer than **five pages** (font Calibri, font size 11). Please write the text into the framed template under the sections 1–5 below. The guiding text that stands there now, can be deleted.

Maximum number of cases permitted per administrative unit

For up to 10 researchers: one case; for 10 to 30 researchers: two cases; for 30-50 researchers: three cases; for 50-100 researchers: four cases, and up to five cases for units exceeding 100 researchers.

Naming and numbering of cases

Please use the standardised short name for the administrative unit, and the case number for the unit (1,2,3, etc) in the headline of the case. Each case should be stored as a separate PDF-document with the file name: [Name of the institution and name of the administrative unit] [case number]

Publication of cases

RCN plans to publish all impact cases in a separate evaluation report. By submitting the case the head of the administrative units consents to the publication of the case. Please indicate below if a case may not be made public for reasons of confidentiality.

If relevant, describe any reason to keep this case confidential:

There is no reason to keep these cases (case 1 and 2) confidential.

Martina Hansens Hospital (MHH) – Martina Hansens Hospital Clinic (MHH-C)

Case number 1.

Institution: Martina Hansens Hospital (MHH)
Administrative unit: Martina Hansens Hospital Clinic (MHH-C)
Title of case study: Exercise therapy or arthroscopic partial meniscectomy for degenerative meniscal tear in middle aged patients: randomised controlled trial with two-year follow-up
Period when the underpinning research was undertaken: 2009-2016
Period when staff involved in the underpinning research were employed by the submitting institution: 2002-2024
Period when the impact occurred: 2016-today

1. Summary of the impact

This randomized controlled trial contributed largely to a worldwide paradigm shift in treatment practice of degenerative meniscal tears of the knee.

This study, the first to compare surgical treatment to exercise therapy, showed no benefit of surgery. This implied alteration of treatment guidelines from recommendation of surgery, as the primary treatment, to physiotherapist-assisted exercise therapy.

Previously, meniscal surgery was among the most frequently performed procedures. Hence, beside implications for the individual patient (avoids surgery and sick leave), the altered practise has had impact on hospital priorities (frees up capacity) and on socioeconomical conditions (fewer sick leaves and health finance redirection).

2. Underpinning research

The study design:
This randomised controlled trial was a multi-centre project with international collaborations. The trial compared two different treatment interventions of degenerative meniscal tears, a common condition which is often the first sign of osteoarthritis of the knee, one of the most frequent rheumatologic diseases.

140 middle-aged patients with degenerative meniscal tears were during October 2009-September 2012 recruited from two Norwegian orthopaedic hospitals, Ullevål University Hospital (54 patients) and Martina Hansens Hospital (MHH-C) (86 patients). The patients were randomized (1:1) to treatment with either surgery or exercise therapy. The surgery was performed as an arthroscopic procedure ("keyhole" surgery) with excision of meniscal tissue and the exerciser therapy program included physiotherapist-assisted strengthening exercises twice or three times a week over a period of 12 weeks. The follow-ups at 3, 6, 12 and finally 24 months included patient reported outcomes measures (PROMs) and physical performance and muscle strength tests. The surgical patients went through arthroscopy at the hospital they

were recruited from. And the exercise patients were treated at one of two external physiotherapy institutes, Gnist and NIMI in collaboration with Ullevål University Hospital. The follow-ups were performed at NIMI.

Who performed the project:
The key researcher at MHH-C organised and led the logistics needed for collaborations with the other institutes, performed recruitment of 86 patients, did all but one of the surgeries of the MHH-C patients, performed the statistics assisted by a statistician and wrote the manuscript in collaboration with her supervisors. MHH-C contributed with access to polyclinic areas, operating theaters and equipment, and covered expenses for radiological examinations and external physiotherapy.

The results:
The main outcome was KOOS-4 (Knee injury and Osteoarthritis Outcome Score), a PROM reporting the patients´ self-esteemed knee function. We found no difference between the intervention groups 2 years following treatment. Other outcome measures confirmed the main outcome.

Conclusion:
Because non-invasive treatment is preferred to surgery due to risk for complications, costs and need for sick leaves, the conclusion then was to recommend exercise therapy as the primary treatment for middle-aged patients with degenerative meniscal tears.

Key researcher: Nina Jullum Kise had a position as orthopaedic surgeon at MHH-C during the whole period this research was ongoing.

This research was part of her PhD-project, and main supervisor was May Arna Risberg, PhD, Norwegian Reasearch Centre for Active Rehabilitation and Oslo university Hospital and co-supervisors were Ewa M. Roos. PhD, University of Southern Denmark and Lars Engebretsen, PhD, University of Oslo.

3. References to the research

Authors: Nina Jullum Kise, MD, May Arna Risberg, Prof., PhD, Silje Stensrud, PhD, Jonas Ranstam, PhD, Lars Engebretsen, prof., PhD, MD, Ewa M Roos, Prof., PhD

Title: Exercise therapy versus arthroscopic partial meniscectomy for degenerative meniscal tear in middle aged patients: randomised controlled trial with two year follow-up

Year of publication: 2016

Link to the article:
https://www.bmj.com/content/bmj/354/bmj.i3740.full.pdf

Reference:
Kise NJ, Risberg MA, Stensrud S, Ranstam J, Engebretsen L, Roos EM. Exercise therapy versus arthroscopic partial meniscectomy for degenerative meniscal tear in middle aged patients: randomised controlled trial with two-year follow-up. BMJ. 2016 Jul 20;354:i3740. doi: 10.1136/bmj.i3740.

4. Details of the impact

Underpinning the impact:
In the years prior to publication of this trial´s results, a few other randomised controlled trials had shown equal results in groups of patients treated with surgical meniscal excision in addition to exercise therapy, or surgery compared to "sham" surgery (where no tissue was removed).
As a result, during the early 2010s, there was a trend towards a change of treatment practice towards less surgery. However, no previous study had compared surgery alone to exercise therapy alone. Therefore, this study, revealing no difference between the treatment groups, was an important and necessary contribution that confirmed previous studies.

The results were published in British Medical Journal in July 2016 and had an immediately major response both among medical professionals and among non-academical environments worldwide. During the first 24 hours after publication the paper had more than 1000 Altimetric scores and currently, the paper has been cited in 208 scientific publications.

Quickly after publication, medical journalists picked up the news, and newspaper articles and radio-interviews of the researchers, contributed to public information and education. The results were discussed in formal and informal canals, like social media like Facebook and Twitter, and later in medical congresses and orthopedic courses.

The results of this study led to rewriting of clinical guidelines and change of practice, and to a changed attitude among patients towards more positive view of conservative treatments. During the first few years following publication, the number of meniscal surgeries due to degenerative meniscal tears dropped significantly. From 2016-2021, the number of arthroscopic (keyhole surgery) of the knee was reduced by nearly 50% in Norway (unpublished data, personal communication from one of the authors of an upcoming study).

Hence, this project has had impact both on patients´welfare with avoiding surgery and risk for complications and fewer sick leaves, on the hospitals capasity for treating other conditions, on health budgets and finally, the project has had influence on socioeconomical conditions.

5. Sources to corroborate the impact

Lundberg M, Søndergaard J, Viberg B, Lohmander LS, Thorlund JB. Declining trends in arthroscopic meniscus surgery and other arthroscopic knee procedures in Denmark: a nationwide register-based study. Acta Orthop. 2022 Sep 28;93:783-793. doi: 10.2340/17453674.2022.4803. PMID: 36173141; PMCID: PMC9521053.

Abram SGF, Judge A, Beard DJ, Wilson HA, Price AJ. Temporal trends and regional variation in the rate of arthroscopic knee surgery in England: analysis of over 1.7 million procedures between 1997 and 2017. Has practice changed in response to new evidence? Br J Sports Med. 2019 Dec;53(24):1533-1538. doi: 10.1136/bjsports-2018-099414. Epub 2018 Oct 2. PMID: 30279217.

Holtedahl R, Brox JI, Aune AK, Nguyen D, Risberg MA, Tjomsland O. Changes in the rate of publicly financed knee arthroscopies: an analysis of data from the Norwegian patient registry from 2012 to 2016. BMJ Open. 2018 Jun 15;8(6):e021199. doi: 10.1136/bmjopen-2017-021199. PMID: 29909370; PMCID: PMC6009626.

Rongen JJ, van Tienen TG, Buma P, Hannink G. Meniscus surgery is still widely performed in the treatment of degenerative meniscus tears in The Netherlands. Knee Surg Sports Traumatol

Arthrosc. 2018 Apr;26(4):1123-1129. doi: 10.1007/s00167-017-4473-2. Epub 2017 Mar 3. PMID: 28258326; PMCID: PMC5876260.

Martina Hansens Hospital (MHH) – Martina Hansens Hospital Clinic (MHH-C)

Case number 2.

Institution: Martina Hansens Hospital (MHH)
Administrative unit: Martina Hansens Hospital Clinic (MHH-C)
Title of case study: Extended Ultrasound Examination of Large Vessels in Patients with Giant Cell Arteritis.
Period when the underpinning research was undertaken: 2020 - -
Period when staff involved in the underpinning research were employed by the submitting institution: 2020 - -
Period when the impact occurred: 2020-today

2. Summary of the impact

Ultrasound of temporal arteries and large vessels is an emerging diagnostic tool for GCA. The use of ultrasound can significantly reduce the visual loss rates and may prevent vascular complications. The method has high sensitivity and specificity in the diagnostics of GCA, and the recommended first-line evaluation by The European Alliance of Associations for Rheumatology (EULAR) and British Society for Rheumatology (BSR). However, the recommended examination technique only assesses the temporal and axillary arteries. In this project, we used an extended ultrasound examination technique. The project has shown that extended ultrasound examination identified more patients with large vessel involvement than the limited ultrasound method.

2. Underpinning research

The study design:
Patients with new-onset GCA were included at the time of diagnosis. One hundred and thirty-three patients were included in this cohort study. All patients were examined using limited ultrasound (ultrasound of the axillary artery as visualized in the axilla) and an extended A2-ultrasound method (which also includes the carotid, vertebral, subclavian and proximal axillary arteries), in addition to temporal artery ultrasound.

Who performed the project: The key researcher at MHH-C organised the study together with her supervisors. MHH-C contributed with access to polyclinic areas and equipment.

The results: Ninety-three of the 133 GCA patients (69.9%) had LV involvement when examined by extended A2-ultrasound, compared with only 56 patients (42.1%) by limited ultrasound ($P < 0.001$). Twelve patients (9.0%) had vasculitis of the vertebral arteries as the only LVs involved. Five patients (3.8%) would have been missed as having GCA if only limited ultrasound was performed. Forty patients (30.0%) had isolated cranial GCA, 21 patients (15.8%) had isolated large vessel GCA and 72 patients (54.1%) had mixed-GCA.

Conclusion: Extended A2-ultrasound examination identified more patients with LV involvement than the limited ultrasound method.

Key researcher: Anne Christine Bull Haaversen had a position as a consultant rheumatologist. This research was part of her PhD-project.

Main supervisor: A P Diamantopoulos, PhD, had a position as a consultant rheumatologist.

Co-supervisors: Tanaz Kermani is an associate professor at the University of California in Los Angeles. Øyvind Molberg is a professor at the University of Oslo.

3. References to the research

Anne Christine Bull Haaversen, Lene Kristin Brekke, Tanaz A Kermani, Øyvind Molberg, Andreas P Diamantopoulos, Extended ultrasound examination identifies more large vessel involvement in patients with giant cell arteritis, *Rheumatology*, Volume 62, Issue 5, May 2023, Pages 1887–1894, https://doi.org/10.1093/rheumatology/keac478

Peter M Andel, Stavros Chrysidis, Julia Geiger, Anne C Bull Haaversen, Glenn Haugeberg, Geirmund Myklebust, Berit D Nielsen, Andreas P Diamantopoulos, Diagnosing giant cell arteritis: a comprehensive practical guide for the practicing rheumatologist, *Rheumatology*, Volume 60, Issue 11, November 2021, Pages 4958–4971, https://doi.org/10.1093/rheumatology/keab547

Haaversen AB, Brekke LK, Bakland G, Rødevand E, Myklebust G, Diamantopoulos AP. Norwegian society of rheumatology recommendations on diagnosis and treatment of patients with giant cell arteritis. Front Med (Lausanne). 2023 Jan 6;9:1082604. doi: 10.3389/fmed.2022.1082604. Frontiers | Norwegian society of rheumatology recommendations on diagnosis and treatment of patients with giant cell arteritis (frontiersin.org)

4. Details of the impact

Giant Cell Arteritis (GCA) is the most common form of vasculitis. It is a systemic vasculitis affecting individuals older than 50 years. The incidence of GCA in Norway is one of the highest worldwide affecting 29-32 patients/100 000 persons/year in the adult population. Emerging evidence based on the extended use of modern imaging modalities shows that GCA may involve the cranial vessels and the aortic tree.

The long-term complications associated with the disease are severe; Up to 37% of GCA patients will suffer from visual disturbances, 24% will become blind , and 7% will suffer from stroke. The primary treatment of GCA consists of high doses of corticosteroids. It is expected that 86% of GCA patients will suffer from corticosteroid side effects.
Large vessel involvement is a marker of frequent relapses and refractory disease. Numerous studies have shown that patients with large vessel involvement require higher cumulative doses of corticosteroids and immunosuppressive agents. In addition, large vessel involvement is associated with an increased relative risk of developing aneurysms in the thoracic aorta. Consequently, it is essential to identify large vessel involvement in patients with GCA.

Ultrasound is extensively used today in all rheumatologic departments for diagnosis and follow-up of patients with inflammatory arthritis. This project has demonstrated the usefulness of ultrasound in large vessel vasculitis improving the quality of healthcare provided locally in regional hospitals and thereby reducing the use of resources.

The project has shown that extended ultrasound examination identified more patients with large vessel involvement than the limited ultrasound method.

5. Sources to corroborate the impact

Dejaco C, Ramiro S, Bond M*, et al*

EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice: 2023 update
Annals of the Rheumatic Diseases Published Online First: 07 August 2023. doi: 10.1136/ard-2023-224543 EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice: 2023 update | Annals of the Rheumatic Diseases (bmj.com)

Bosch P, Bond M, Dejaco C, Ponte C, Mackie SL, Falzon L, Schmidt WA, Ramiro S. Imaging in diagnosis, monitoring and outcome prediction of large vessel vasculitis: a systematic literature review and meta-analysis informing the 2023 update of the EULAR recommendations. RMD Open. 2023 Aug;9(3):e003379. doi: 10.1136/rmdopen-2023-003379. PMID: 37620113; PMCID: PMC10450079. Imaging in diagnosis, monitoring and outcome prediction of large vessel vasculitis: a systematic literature review and meta-analysis informing the 2023 update of the EULAR recommendations | RMD Open (bmj.com)

Andel PM, Diamantopoulos AP, Myklebust G, Haugeberg G. Vasculitis distribution and clinical characteristics in giant cell arteritis: a retrospective study using the new 2022 ACR/EULAR classification criteria. Front Med (Lausanne). 2023 Nov 13;10:1286601. doi: 10.3389/fmed.2023.1286601. PMID: 38020143; PMCID: PMC10681091. Frontiers | Vasculitis distribution and clinical characteristics in giant cell arteritis: a retrospective study using the new 2022 ACR/EULAR classification criteria (frontiersin.org)

Impact case 1

Institution: Modum Bad
Administrative unit: Research Institute
Title of case study: Mental health and adherence during the COVID-19 pandemic (MAP-19)
Period when the underpinning research was undertaken: 2020-ongoing
Period when staff involved in the underpinning research were employed by the submitting institution: one since 1985 – ongoing, one since 2017 – ongoing and one since 2019 - ongoing
Period when the impact occurred: 2020-

Summary of the impact

The Norwegian COVID-19, Mental Health and Adherence Project (MAP-19) is a large-scale longitudinal study led by researchers from the University of Oslo and Modum Bad Psychiatric Hospital. It examines the impact of non-pharmacological interventions on mental health during the pandemic. With over 10,000 participants and 50 measurement time-points over three years, the project aims to inform policymakers, healthcare professionals, and the public about the psychological implications of COVID-19 measures. Results will help develop interventions, understand factors influencing adherence to viral mitigation behaviors, and identify vulnerable subgroups. It has garnered international recognition and plays a central role in understanding the mental health consequences of the pandemic.

1. Underpinning research

Key researchers in the project were Professor Sverre Urnes Johnson, Professor Asle Hoffart and Ph.D. candidate Omid Ebrahimi.
Together with several collaborators they have published more than 30 scientific articles describing the mental health during the pandemic. Furthermore, the project has contributed the COVIDMENT consortium. The COVIDMENT consortium is a collaborative research initiative formed to address the mental health implications of the COVID-19 pandemic. Comprised of esteemed researchers, clinicians, and experts in the field of mental health, the consortium aims to investigate the psychological impact of the pandemic on individuals across different populations. Through their multidisciplinary approach, the consortium strives to identify risk factors, develop interventions, and promote resilience in the face of the mental health challenges arising from the pandemic. Their collective efforts encompass comprehensive data collection, analysis, and dissemination of findings to inform evidence-based mental health support during and beyond the pandemic.

- **References to the research**

The project has led to more than 25 articles.
Selection of three articles.

- Ebrahimi, Omid Vakili; Hoffart, Asle; Bauer, Daniel J. & Johnson, Sverre Urnes (2022). A Critical Period for Pandemic Adaptation: The Evolution of Depressive Symptomatology in a Representative Sample of Adults Across a 17-Month Period During COVID-19. *Journal of Psychopathology and Clinical Science*. ISSN 2769-7541. doi: 10.1037/abn0000786.
- Magnúsdóttir, Ingibjörg; Lovik, Anikó; Unnarsdóttir, Anna Bára; McCartney, Daniel L.; Ask, Helga & Kõiv, Kadri [Vis alle 23 forfattere av denne artikkelen] (2022). Acute COVID-19 severity and mental health morbidity trajectories in patient populations of six nations: an observational study. *The Lancet Public Health*. ISSN 2468-2667. 7(5), s. 406–416. doi: 10.1016/S2468-2667(22)00042-1.

- Sinkerud Johnson, Miriam; Skjerdingstad, Nora; Ebrahimi, Omid Vakili; Hoffart, Asle & Johnson, Sverre Urnes (2021). Parenting in a Pandemic: Parental Stress, Anxiety and Depression Among Parents During the Government-Initiated Physical Distancing Measures Following the First Wave of COVID-19. *Stress and Health*. ISSN 1532-3005. s. 1–16. doi: 10.1002/smi.3120.

2. Details of the impact (indicative maximum 750 words)

The key impact of the Norwegian COVID-19, Mental Health and Adherence Project (MAP-19) is the comprehensive examination of the relationship between non-pharmacological interventions (NPIs) implemented to combat the SARS-CoV-2 virus and mental health symptoms in the general adult population. Led by researchers from the University of Oslo and Modum Bad Psychiatric Hospital, the project aims to inform policymakers, the general public, scientists, and healthcare practitioners about the psychological implications associated with government-initiated measures during the pandemic. By studying adherence to viral mitigation behaviors, the research also aims to understand the associations between demographic variables, psychological symptoms, and adherence rates, which can contribute to the development of effective strategies to combat the COVID-19 virus.

The MAP-19 project has gained significant attention and recognition in the international pandemic literature and across national news platforms.

The project is a large-scale longitudinal study spanning over three years, with data collection starting in March 2020, shortly after NPIs were implemented in Norway. With a sample size of 10,061 participants, the study collects repeated-measures data at 50 measurement time-points over the three-year period, covering all major infection waves of the pandemic. The research also includes intensive longitudinal measurements conducted daily over 40 days.

To ensure reliable results, the study employs a systematic and pre-defined rationale for the timing of assessments. Data collection occurs approximately two weeks after modifications to pandemic mitigation protocols, allowing for the examination of robust associations between mental health and these protocols. The study design includes a stopping rule to immediately end data collection if new information from the government necessitates changes to pandemic protocols during data collection.

The project seeks to provide a foundation for policymakers and healthcare professionals to implement interventions that protect the public against psychological stressors related to the pandemic. The MAP-19 project has significant implications for understanding the impact of NPIs on mental health, guiding policymakers in implementing effective interventions, and identifying vulnerable subgroups within the population. The findings and recommendations from this project can contribute to global efforts in combating the COVID-19 pandemic and mitigating its psychological consequences.

3. Sources to corroborate the impact

Asle.hoffart@modum-bad.no
o.v.ebrahimi@psykologi.uio.no
karianne.vrabel@modum-bad.no

Key articles that have cited the different papers:

Wallis, H., Holzen, V., Sieverding, T., Matthies, E., & Schmidt, K. (2023). How do appraisal as threat or challenge, efficacy, and environmental quality affect wellbeing in the COVID-19 pandemic? *Frontiers in Psychiatry, 13,* Article 1009977. https://doi.org/10.3389/fpsyt.2022.1009977

Shahar, S., Lynch, S., Dornbush, R., Klepacz, L., Smiley, A., & Ferrando, S. J. (2023). Frequency and Characteristics of Depression and Its Association with Diminished Quality of Life in a Cohort of Individuals with Post-Acute Sequelae of COVID-19. *Neuropsychiatric disease and treatment*, *19*, 2069–2079. https://doi.org/10.2147/NDT.S427957

Jarvers, I., Ecker, A., Schleicher, D., Brunner, R., & Kandsperger, S. (2023). Impact of preschool attendance, parental stress, and parental mental health on internalizing and externalizing problems during COVID-19 lockdown measures in preschool children. *PloS one*, *18*(2), e0281627. https://doi.org/10.1371/journal.pone.0281627

Impact case 1

Institution: Modum Bad
Administrative unit: Research Institute
Title of case study: Randomzied Controlled Trial at the department of Anxiety Disorders
Period when the underpinning research was undertaken: 2013-2017
Period when staff involved in the underpinning research were employed by the submitting institution: one since 1985 and ongoing, one since 2013 and ongoing
Period when the impact occurred: 2017-2022

Summary of the impact

The Johnson et al study published in 2017 in the Journal of Anxiety Disorders made a notable impact on the field. Their research focused on a novel therapeutic approach for anxiety disorders, metacognitive therapy, providing valuable insights into its effectiveness. The study's rigorous methodology and comprehensive analysis attracted attention within the scientific community. It influenced clinical practices, prompting further research and exploration in this area. It garnered citations and contributed to the development of evidence-based practices. Overall, the paper played a significant role in advancing the understanding and treatment of anxiety disorders. Additionally, the RCT was combined with a process-outcome study on a within-person level using repeated measures.

1. Underpinning research

The article is cited 83 times since 2017, which indicate its impact.

Johnson, S. U., Hoffart, A., Nordahl, H. M., & Wampold, B. E. (2017). Metacognitive therapy versus disorder-specific CBT for comorbid anxiety disorders: A randomized controlled trial. *Journal of anxiety disorders*, *50*, 103–112. https://doi.org/10.1016/j.janxdis.2017.06.004

2. References to the research

Johnson was the Ph.D. candidate in the project and the main supervisor was Professor Asle Hoffart. Professor Hans Nordahl and Professor Bruce Wampold was co-supervisors.

Performing clinical research in psychiatric departments requires a careful consideration of various factors to ensure the highest quality of data and participant safety. It was established clear guidelines for participant recruitment and it was ensured that well-trained research personnel effectively communicated with patients and assess their suitability for participation. Furthermore, data collection tools and protocols were carefully designed and validated to capture meaningful and reliable information.

Clinical research conducted in normal clinical practice is highly valuable for several reasons. Firstly, it allows for the evaluation of interventions, treatments, or strategies in real-world settings, providing practical and applicable results. By conducting research in the context of routine clinical practice with research intake criteria similar to the clinical intake criteria, researchers can assess the effectiveness and feasibility of new approaches in a diverse patient population, reflecting the complexities and challenges encountered in everyday healthcare delivery. This can lead to improved patient outcomes and the implementation of evidence-based practices.

Additionally, conducting research in clinical practice settings can help bridge the gap between research and clinical practice. It allows for the continuous evaluation of existing protocols and practices, identifying areas for improvement and facilitating knowledge translation. By involving healthcare providers, researchers can gather crucial feedback and insights from those directly involved in patient care, fostering collaboration and ensuring that research findings are relevant and applicable in practice.

Moreover, clinical research conducted in normal clinical practice provides an opportunity to conduct studies on diverse populations. This can lead to more robust and generalizable results, contributing to the advancement of medical knowledge and the development of evidence-based guidelines and protocols.

Overall, clinical research in normal clinical practice enhances the integration of research and clinical care, improving patient outcomes and optimizing healthcare delivery.

3. Details of the impact (indicative maximum 750 words)

The impact of the Johnson et al study published in the Journal of Anxiety Disorders in 2017 was significant and noteworthy. This study shed light on the efficacy of a new treatment approach for individuals suffering from anxiety disorders.

The researchers conducted a randomized controlled trial to evaluate the effectiveness of a novel therapeutic intervention. They compared this intervention to the standard treatment methods currently used for anxiety disorders.

The findings of the study revealed that the new treatment approach led to a significant reduction in anxiety symptoms compared to the standard treatment (cognitive-behavioral therapy). This indicates that the new intervention holds promise for improving the outcomes of individuals with anxiety disorders.

Moreover, this study provided valuable insights into the underlying mechanisms of anxiety disorders and their treatment. It contributed to the existing body of knowledge in the field and opened up new avenues for further research and development of therapeutic strategies.

The publication of this study in a reputable journal like the Journal of Anxiety Disorders also increased its visibility and credibility among researchers, clinicians, and other stakeholders in the field of mental health. It served as a reference point for future studies, clinical practice, and policy-making related to anxiety disorders.

Overall, the Johnson et al study made a considerable impact on the understanding and treatment of anxiety disorders. Its findings have the potential to improve the lives of individuals who suffer from these conditions and shape future research and clinical practices in the field.

Based on these findings, a new treatment section focusing on anxiety disorders will be established at the department. This section is scheduled to launch in 2024. Since the publication of these findings in 2017, Johnson has received messages from numerous clinicians expressing interest in visiting the clinic and learning about Metacognitive therapy and the utilization of transdiagnostic treatments.

The significance of process outcome studies becomes apparent when delving into the significance of within-person processes in therapy. For a considerable period of time, a pivotal question in psychotherapy research has been the identification of the mechanisms at play during specific time points. To effectively address these inquiries, an RCT design is considered optimal, as it enables a concentrated focus on the treatment itself. In the Johnson study, repeated measures of process and outcome were conducted throughout the treatment duration, thereby facilitating the exploration of change mechanisms. This approach led to specific articles which gave valuable insights into the intricate dynamics of therapeutic progress and its underlying factors

4. Sources to corroborate the impact

Asle.hoffart@modum-bad.no
Heidi.berg.houmb@modum-bad.no.
Karianne.vrabel@modum-bad.no

Key articles that have cited the RCT-study:

Capobianco, L., Reeves, D., Morrison, A. P., & Wells, A. (2018). Group Metacognitive Therapy vs. Mindfulness Meditation Therapy in a Transdiagnostic Patient Sample: A Randomised Feasibility Trial. *Psychiatry Research, 259*, 554-561. doi: https://doi.org/10.1016/j.psychres.2017.11.045

Normann, N., & Morina, N. (2018). The Efficacy of Metacognitive Therapy: A Systematic Review and Meta-Analysis. *Frontiers in Psychology, 9*, 2211-2211. doi: https://doi.org/10.3389/fpsyg.2018.02211

Johnson, S. U., Hoffart, A., Nordahl, H. M., Ulvenes, P. G., Vrabel, K., & Wampold, B. E. (2018). Metacognition and cognition in inpatient MCT and CBT for comorbid anxiety disorders: A study of within-person effects. *J Couns Psychol, 65*(1), 86-97. doi: https://doi.org/10.1037/cou0000226

Wells, A. (2019). Breaking the Cybernetic Code: Understanding and Treating the Human Metacognitive Control System to Enhance Mental Health. *Frontiers in Psychology, 10*. doi: https://doi.org/10.3389/fpsyg.2019.02621

Impact case guidelines

Each case study should include sufficiently clear and detailed information to enable the evaluation committee to make judgements based on the information it contains, without making inferences, gathering additional material, following up references or relying on members' prior knowledge. References to other sources of information will be used for verification purposes only, not as a means for the evaluation committee to gather further information to inform judgements.

In this evaluation, impact is defined as an effect on, change or benefit to the economy, society, culture, public policy or services, health, the environment or quality of life, beyond academia.

Timeframes

- The impact must have occurred between 2012 and 2022
- Some of the underpinning research should have been published in 2012 or later
- The administrative units are encouraged to prioritise recent cases

Page limit

Each completed case study template will be limited to **five pages** in length. Within the annotated template below, indicative guidance is provided about the expected maximum length limit of each section, but institutions will have flexibility to exceed these so long as the case study as a whole remains no longer than **five pages** (font Calibri, font size 11). Please write the text into the framed template under the sections 1–5 below. The guiding text that stands there now, can be deleted.

Maximum number of cases permitted per administrative unit

For up to 10 researchers: one case; for 10 to 30 researchers: two cases; for 30-50 researchers: three cases; for 50-100 researchers: four cases, and up to five cases for units exceeding 100 researchers.

Naming and numbering of cases

Please use the standardised short name for the administrative unit, and the case number for the unit (1,2,3, etc) in the headline of the case. Each case should be stored as a separate PDF-document with the file name: [Name of the institution and name of the administrative unit] [case number]

Publication of cases

RCN plans to publish all impact cases in a separate evaluation report. By submitting the case the head of the administrative units consents to the publication of the case. Please indicate below if a case may not be made public for reasons of confidentiality.

If relevant, describe any reason to keep this case confidential:

Please write the text here

[Molde University College, Faculty of Health Sciences and Social Care]

[case number 1]

Institution: Molde University College
Administrative unit: Faculty of Health Sciences and Social Care
Title of case study: Maximal strength training: from basic discoveries to clinical practice
Period when the underpinning research was undertaken: 2019-2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2019-2022
Period when the impact occurred: 2019-2022

1. Summary of the impact (indicative maximum 100 words)

This case study describes the translation of basic physiological discoveries to implementation in clinical care for numerous patient groups. It shows the importance of maximal strength training for the older, healthy population to maintain and improve neuromuscular characteristics, and how the same principles can be applied to enhance muscular strength and quality of life in patients in a real-life clinical setting.

2. Underpinning research (indicative maximum 500 words)

The research undertaken between 2019-2022 by the research group in Physiology aims to meet the expected increase in health-related challenges associated with the growing proportion of elderly in our society, with the clear goal of providing novel and noteworthy discoveries in the application of exercise as medicine. Physiology remains the essential link between genes and clinical care. In this impact case, we aimed to understand the neuromuscular system in the older population, and how it adapts to activity and inactivity. By examining physiological responses in the outer extremes of the population, from patients to highly trained master athletes, we are looking to pinpoint the nature of aging per se contrasted to the nature of disease and inactivity and discover effective training strategies that can be implemented and used by different populations.

Our research has shown that highly strength trained older adults maintain a functional status and muscular strength characteristics that can far exceed even healthy young adults. In contrast, untrained older adults are characterised by lowered functional status, strength, and rapid force characteristics. The latter is also accompanied by a reduced efferent neural drive to the maximally contracting skeletal muscle, which appears to be maintained to a higher degree in strength trained.

We have also showed that to induce efferent neural drive enhancements in older adults, external high resistance is imperative. Thus, strength training with high resistance must be applied to this population to enhance neuromuscular performance. This is of critical importance to maintain independence for longer, improve mobility and prevent falls. We have therefore adopted a strength training model using near-maximal loads of ~90 of maximal strength, termed maximal strength training (MST). This is an intensity that can only be performed few times (3-5) before there is a need for a rest period. Importantly, we also use maximal intended velocity in the concentric phase to maximize neural drive to the muscle. This training method appears to rely primarily on neural adaptations, in the form of increased efferent neural drive from the central nervous system to the peripheral muscles contracting.

The findings in the basic discoveries can be translated to patient groups, as exemplified by three patient groups here. For instance, women undergoing breast cancer treatment have performed MST during treatment, showing a staggering improvement in neuromuscular performance, maintenance of muscle mass and improved walking economy. Similarly, patients with Parkinson's Disease (PD) have used the same model and shown large improvements in strength characteristics

as well as efferent neural drive. Considering that PD is a neurodegenerative disease, these results are quite remarkable. Finally, the same training principles were applied to hip fracture patients right after surgery, which resulted in better recovery than conventional therapy following surgery. Thus, it appears that many, even frail, patient groups can utilize the same training principles and attain similar adaptations as healthy older adults.

- Names of the key researchers:
- Eivind Wang, PhD, Professor
- Ole Kristian Berg, PhD, Associate Professor
- Mathias Brobakken, PhD, Associate Professor (employed in 2021)
- Tiril Tøien, PhD candidate

3. References to the research (indicative maximum of six references)

Tøien T, Unhjem R, **Berg OK**, Aagaard P, **Wang E**. Strength versus endurance trained master athletes: Contrasting neurophysiological adaptations. Exp Gerontol. 2023 Jan;171:112038. doi: 10.1016/j.exger.2022.112038. Epub 2022 Nov 25. PMID: 36442699.

Unhjem R, **Tøien T**, Kvellestad ACG, Øren TS, **Wang E**. External Resistance Is Imperative for Training-Induced Efferent Neural Drive Enhancement in Older Adults. J Gerontol A Biol Sci Med Sci. 2021 Jan 18;76(2):224-232. doi: 10.1093/gerona/glaa160. PMID: 32614394.

Berg OK, Kwon OS, Hureau TJ, Clifton HL, Thurston TS, Le Fur Y, Jeong EK, Trinity JD, Richardson RS, **Wang E**, Layec G. Skeletal Muscle Mitochondrial Adaptations to Maximal Strength Training in Older Adults. J Gerontol A Biol Sci Med Sci. 2020 Nov 13;75(12):2269-2277. doi: 10.1093/gerona/glaa082. PMID: 32253421; PMCID: PMC7896183.

Helgerud J, Thomsen SN, Hoff J, Strandbråten A, Leivseth G, Unhjem R, **Wang E**. Maximal strength training in patients with Parkinson's disease: impact on efferent neural drive, force-generating capacity, and functional performance. J Appl Physiol (1985). 2020 Oct 1;129(4):683-690. doi: 10.1152/japplphysiol.00208.2020. Epub 2020 Aug 13. PMID: 32790593.

Cešeiko R, Thomsen SN, Tomsone S, Eglītis J, Vētra A, Srebnijs A, Timofejevs M, Purmalis E, **Wang E**. Heavy Resistance Training in Breast Cancer Patients Undergoing Adjuvant Therapy. Med Sci Sports Exerc. 2020 Jun;52(6):1239-1247. doi: 10.1249/MSS.0000000000002260. PMID: 31876673.

Berg OK, Stutzer JM, Hoff J, **Wang E**. Early Maximal Strength Training Improves Leg Strength and Postural Stability in Elderly Following Hip Fracture Surgery. Geriatr Orthop Surg Rehabil. 2021 Apr 30;12:21514593211015103. doi: 10.1177/21514593211015103. PMID: 34017617; PMCID: PMC8114282.

4. Details of the impact (indicative maximum 750 words)

The research outlined above has been the basis for implementation into clinical practice with our partners in the Training Clinic (Treningsklinikken.no) in Trondheim, Norway. Here, patients with numerous diseases train using the same principles as outlined above. These are patients with rheumatic and inflammatory diseases, cardiovascular diseases, lung diseases such as chronic obstructive pulmonary disease (COPD), post COVID-19 disease, obesity, cancer, multiple sclerosis, and Parkinson’s disease. Moreover, the same training has been implemented at the Training Clinic for patients with severe mental disorders at St. Olavs Hospital in Trondheim (see publication below).

Severe mental disorders, i.e. schizophrenia, bipolar disorders, and severe depression, often involve comorbidities leading to accelerated ageing and a significantly shortened life expectancy. Thus, physical exercise can aid patients regain their physical health, and potentially alleviate some psychological symptoms (particularly depressive symptoms).

Moreover, effective strength training people with inflammatory rheumatic diseases can improve function, quality of life, and reduce symptom burden (e.g., pain and fatigue). It is also documented that this patient group has an increased risk of developing other chronic diseases, including cardiovascular diseases. Therefore, the Training clinic offers a rehabilitation program centred around physical training as both a therapeutic and preventive measure. One paper has been published to exemplify these results from rheumatic disease patients (see below).

Between 2019 and 2022 the Training clinic (Treningsklinikken.no) treated around 400 patients. The treatment is offered three times per week for eight weeks of two times per week for 12 weeks, and consists of effective training, education, nutrition, and is closely followed by exercise physiologists, physiotherapists, doctors, nurses and nutritionists, and is supervised by professors in medicine.

One patient with rheumatic disease has described the experience with the training in this way: "I walk faster, am stronger in my legs, and have less pain. I notice that I am happier. I still have some ups and downs, but the very difficult times are further apart. After all, we are just as trainable as healthy individuals, but we need to train correctly." She is focused on getting more people into exercise, especially young individuals with rheumatic conditions. Receiving the news of a chronic illness is heavy, but with training, you can live much better with the disease.

The Training Clinic is funded by the regional health trust. Thus, a thorough research based approach is necessary to ensure that the patients receive the best treatment possible to make good use of the public funds allocated to patient rehabilitation. The body of evidence submitted here was part of that knowledge base, which we continue to develop alongside our colleagues in Trondheim (the Training Clinic, MyWorkout, and St. Olavs Hospital Training Clinic).

5. Sources to corroborate the impact (indicative maximum of ten references)

Haglo H, **Berg OK**, Hoff J, Helgerud J, **Wang E**. Maximal strength training in patients with inflammatory rheumatic disease: implications for physical function and quality of life. Eur J Appl Physiol. 2022 Jul;122(7):1671-1681. doi: 10.1007/s00421-022-04948-w. Epub 2022 Apr 19. PMID: 35438424; PMCID: PMC9197881.

Nygård M, **Brobakken MF**, Taylor JL, Reitan SK, Güzey IC, Morken G, Lydersen S, Vedul-Kjelsås E, **Wang E**, Heggelund J. Strength training restores force-generating capacity in patients with schizophrenia. Scand J Med Sci Sports. 2021 Mar;31(3):665-678. doi: 10.1111/sms.13863. Epub 2020 Nov 16. PMID: 33113211.

[Molde University College, Faculty of Health Sciences and Social Care]

[case number 2]

Institution: Molde University College
Administrative unit: Faculty of Health Sciences and Social Care
Title of case study: SAFE Pilot study
Period when the underpinning research was undertaken: 2012-2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2012-2022
Period when the impact occurred: 2012-2022

2. Summary of the impact (indicative maximum 100 words)
This section should briefly state what specific impact is being described in the case study.

3. Underpinning research (indicative maximum 500 words)

The underpinning research relates to the study of mental health problems, violence and aggression and substance abuse. Assessing violence risk amongst forensic patients is a vital legal and clinical task. The research evidence is very strong for high recidivism rates of violence after discharge from forensic facilities. A main goal in secure forensic mental health services is to reduce violence within facilities and violent recidivism by patients after discharge. Thus, the main aims with the research were to find predictors of violence following discharge from forensic mental health.

The first listed references pertain to risk assessment and management of patients discharged from high and medium security psychiatric facilities; and criterion-triggered preventive interventions when indicators of increased risk emerge in the individual patient. This project was termed the Safe Pilot study. The risk assessment of patients in the Safe Pilot study was especially centered around Personality disorder; Lack of insight; Active symptoms of serious mental disorder; Exposure to risk situations; Lack of support in the network; Stress.

Control group patients committed almost nine times more violent episodes and had a much higher rate of severe violence. Thus, being in the Safe pilot group appeared to be protective against violence.

Moreover, we aimed to test the predictive validity of three psychotic symptom scales for violence, to analyze main and interaction effects between psychotic symptoms and previous criminal conviction. As psychotic symptoms are dynamic, fluctuating, and amenable to treatment, we wanted to explore whether psychotic symptoms had an impact on risk of violence in patients with criminal convictions and to explore how the two risk factors interacted. For psychotic persons with a history of criminal conviction, our results indicate that the interaction between repeated dynamic measurements with scales for auditory hallucinations and persecutory delusions may be scrutinized further to explore if they enhance predictive validity in assessment of risk of violence.

Similarly, we examined the role of three potentially important but understudied dynamic protective factors: hope, insight, and resilience, along with a history of criminality, in terms of their impact on violence. Importantly, there were significant interactions between resilience and past criminal convictions, with higher levels of resilience leading to lower violence, most amongst those with criminal convictions, and between resilience and hopelessness related emotional distress, in

that higher resilience at high levels of patient acknowledged emotional distress due to hopelessness led to lower violence.

This section should outline the key research insights or findings that underpinned the impact, and provide details of what research was undertaken, when, and by whom. This research may be a body of work produced over a number of years or may be the output(s) of a particular project. References to specific research outputs that embody the research described in this section, and evidence of its quality, should be provided in the next section. Details of the following should be provided in this section:

- The nature of the research insights or findings which relate to the impact claimed in the case study.
- An outline of what the underpinning research produced by the submitted unit was (this may relate to one or more research outputs, projects or programmes).
- Dates of when it was carried out.

- Stål Kapstø Bjørkly, PhD, Professor in Clinical Psychiatry
- Solveig Bø Vatnar, PhD, Professor (joined the administrative unit in 2018)

4. References to the research (indicative maximum of six references)

Bjørkly S, Wærstad JM, Selmer LE, Wærp J, Bjørnstad M, Leinslie JV, Eidhammer G, Douglas KS. Violence after discharge from forensic units in the safe pilot study: a prospective study with matched pair design. Psychol Res Behav Manag. 2019 Aug 28;12:755-766. doi: 10.2147/PRBM.S214270. PMID: 31695530; PMCID: PMC6717845.

Bjørkly S, Laake P, Roaldset JO, Douglas KS. The Safe pilot study: A prospective naturalistic study with repeated measures design to test the psychosis - violence link in and after discharge from forensic facilities. Psychiatry Res. 2021 Apr;298:113793. doi: 10.1016/j.psychres.2021.113793. Epub 2021 Feb 9. PMID: 33582528.

Bjørkly S, Laake P, Douglas KS. The safe pilot study: A prospective naturalistic study with repeated measures design to test protective factors against violence in and after discharge from forensic facilities. Psychiatry Res. 2023 Feb;320:115017. doi: 10.1016/j.psychres.2022.115017. Epub 2022 Dec 19. PMID: 36610319.

4. Details of the impact (indicative maximum 750 words)

- importance to recognise pattern of forensic mental health patients
- Both positive and negative patterns
- Prevention
- Treatment
- Protect society
- Protect potential partners (intimate partner violence)
- Protect the patient and health care workers
- Been implemented?
- How, where, when?

This section should provide a narrative, with supporting evidence, to explain:

- How the research underpinned (made a distinct and material contribution to) the impact;
- The nature and extent of the impact.

The following should be provided:
- A clear explanation of the process or means through which the research led to, underpinned or made a contribution to the impact (for example, how it was disseminated, how it came to influence users or beneficiaries, or how it came to be exploited, taken up or applied).
- Where the submitted administrative unit's research was part of a wider body of research that contributed to the impact (for example, where there has been research collaboration with other institutions), the case study should specify the particular contribution of the submitted administrative unit's research and acknowledge other key research contributions.
- Details of the beneficiaries – who or what community, constituency or organisation has benefitted, been affected or impacted on.
- Details of the nature of the impact – how they have benefitted, been affected or impacted on.
- Evidence or indicators of the extent of the impact described, as appropriate to the case being made.
- Dates of when these impacts occurred.

5. Sources to corroborate the impact (indicative maximum of ten references)

Vatnar SK, Bjørkly S. Lethal intimate partner violence: an interactional perspective on women's perceptions of lethal incidents. Violence Vict. 2013;28(5):772-89. doi: 10.1891/0886-6708.vv-d-12-00062. PMID: 24364122.

Eidhammer G, Fluttert FA, **Bjørkly S**. User involvement in structured violence risk management within forensic mental health facilities -- a systematic literature review. J Clin Nurs. 2014 Oct;23(19-20):2716-24. doi: 10.1111/jocn.12571. Epub 2014 Feb 23. PMID: 25280135.

Fosse R, Eidhammer G, Selmer LE, Knutzen M, **Bjørkly S**. Strong Associations Between Childhood Victimization and Community Violence in Male Forensic Mental Health Patients. Front Psychiatry. 2021 Feb 1;11:628734. doi: 10.3389/fpsyt.2020.628734. PMID: 33633598; PMCID: PMC7901946.

Vatnar SKB, Leer-Salvesen K, **Bjørkly S**. Mandatory Reporting of Intimate Partner Violence: A Mixed Methods Systematic Review. Trauma Violence Abuse. 2021 Oct;22(4):635-655. doi: 10.1177/1524838019869102. Epub 2019 Aug 25. PMID: 31446848.

Eriksen BMS, Færden A, Lockertsen Ø, **Bjørkly S**, Roaldset JO. Predictive validity and gender differences in a biopsychosocial model of violence risk assessment in acute psychiatry. Psychiatry Res. 2018 Jun;264:270-280. doi: 10.1016/j.psychres.2018.04.021. Epub 2018 Apr 9. PMID: 29655971.

Ørke EC, Bjørkly S, Dufort M, **Vatnar SKB**. Attachment Characteristics Among Women Victimized in No, One, and Multiple IPV Relationships: A Case-Control Study. Violence Against Women. 2021 Dec;27(15-16):2945-2970. doi: 10.1177/1077801220981157. Epub 2021 Feb 11. PMID: 33573515; PMCID: PMC8521374.

Roaldset JO, Hartvig P, **Bjørkly S**. Psychometric properties and predictive validity of a police version of a violence risk screen - A pilot study. Int J Law Psychiatry. 2017 Sep-Oct;54:133-139. doi: 10.1016/j.ijlp.2017.06.007. Epub 2017 Jun 28. PMID: 28668227.

Langeveld J, **Bjørkly S**, Auestad B, Barder H, Evensen J, Ten Velden Hegelstad W, Joa I, Johannessen JO, Larsen TK, Melle I, Opjordsmoen S, Røssberg JI, Rund BR, Simonsen E, Vaglum P, McGlashan T, Friis S. Treatment and violent behavior in persons with first episode psychosis during a 10-year

prospective follow-up study. Schizophr Res. 2014 Jul;156(2-3):272-6. doi: 10.1016/j.schres.2014.04.010. Epub 2014 May 15. PMID: 24837683.

Roaldset JO, Hartvig P, Morten Linaker O, **Bjørkly S**. A multifaceted model for risk assessment of violent behaviour in acutely admitted psychiatric patients. Psychiatry Res. 2012 Dec 30;200(2-3):773-8. doi: 10.1016/j.psychres.2012.04.038. Epub 2012 May 18. PMID: 22609226.

Fluttert FA, Van Meijel B, **Bjørkly S**, Van Leeuwen M, Grypdonck M. The investigation of early warning signs of aggression in forensic patients by means of the 'Forensic Early Signs of Aggression Inventory'. J Clin Nurs. 2013 Jun;22(11-12):1550-8. doi: 10.1111/j.1365-2702.2012.04318.x. Epub 2012 Oct 9. PMID: 23043702.

[Molde University College, Faculty of Health Sciences and Social Care]

[case number 3]

Institution: Molde University College
Administrative unit: Faculty of Health Sciences and Social Care
Title of case study: Children with disabilities & UN rights conventions
Period when the underpinning research was undertaken: 2012 and still ongoing
Period when staff involved in the underpinning research were employed by the submitting institution: Before 2012 and still ongoing
Period when the impact occurred: 2022

5. Summary of the impact (indicative maximum 100 words)

The awareness and knowledge of the rights of children and persons with disabilities described in the UN Convention on the Rights of the Child (CRC) and the UN Convention on the Rights of Persons with Disabilities (CRPD) have increased among children with/without disabilities and schoolteachers in Tanzania and Norway. The knowledge about disabilities has increased in the population in Tanzania. The proportion of children with disabilities in Tanzania who have their right to education fulfilled has increased. The use of corporal punishment in schools in Tanzania has been reduced. The collaboration between academia and practicing schools for children with and without disabilities in Arusha and Dar es Salaam has increased.

2. Underpinning research (indicative maximum 500 words)

The enhanced knowledge derived from recent research on collaboration, co-creation, innovation, and interventions for children and youth with special needs forms the basis for the development of the collaboration methods in this ongoing and still new case. An important goal has been to achieve a well-functioning and productive collaboration between partners in Norway and Tanzania, including both staff and students, practitioners, as well as children and youth with psychosocial difficulties and/or various disabilities. Knowledge about facilitating and inhibiting factors for successful collaboration across professions, agencies, and levels has been and continues to be crucial in this cross-cultural collaboration. The various research studies referred to here were carried out from 2012 to 2021, some of which were conducted as part of the Horizon 2020 project, Co-Lab, which focused on collaboration between mental health and criminal justice systems.

To develop this co-producing and multifaceted collaboration, knowledge about the inclusion of vulnerable children and youth has also been of great importance. In particular, knowledge about adolescents' subjective views on participation in interprofessional teams since 2016, as well as about children's mental health and global issues since 2020, has been important.

Knowledge about communication in collaborative relationships, joint learning, joint working, innovation, and leadership has been and continues to be of essential importance. Research results from this field that have been fundamental to this case have been conducted in the period 2012-2021.

Prof. Atle Ødegård and Assoc. Prof. Siv E.N. Sæbjørnsen have been and continue to be key researchers in the research group. Ødegård is a specialist psychologist who was promoted from associate professor to professor in 2013. Sæbjørnsen is a social educator [vernepleier] with a master's degree in social work and a PhD in interprofessional collaboration since 2017. Sæbjørnsen's position from 2012-2017 was a PhD candidate and associate professor from 2017. They are both key researchers in this case. Their research on collaboration and aspects of

collaboration aimed at services or interventions for people in vulnerable situations is fundamentally important for this case.

3. References to the research (indicative maximum of six references)

1. Sæbjørnsen, S. E. N., Hean, S., & Ødegård, A. (2021). Facilitating Understanding of Ex-Prison Service Users' Needs: The Utility of Q Method as a Means of Representing Service User Voices in Service Development. In *Improving Interagency Collaboration, Innovation and Learning in Criminal Justice Systems: Supporting Offender Rehabilitation* (pp. 341-374). Cham: Springer International Publishing.
2. Sæbjørnsen, S. E. N., Hean, S., Røvik, K., Larsen, B. K., & Ødegård, A. (2021). Do We Need the Users' Voice? An Empirical Research Example Comparing Views of Service Providers and Ex-Prisoners: Implications for Practice. In *Improving Interagency Collaboration, Innovation and Learning in Criminal Justice Systems: Supporting Offender Rehabilitation* (pp. 375-399). Cham: Springer International Publishing.
3. Willumsen, E., Sæbjørnsen, S. & Ødegård, A. (2020). *Mental health and children: Global issues and local contexts in interprofessional work: A case illustration.* I Parker, J. and Crabtree S. A. Human Growth and Development Children and Young People Vol I. Human Growth and Development in Children and Young People Theoretical and Practice Perspectives. Bristol: University Press
4. Ødegård, A.og Bjørkly, S. (2020). Communication in co-creation processes. [Kommunikasjon i samskapingsprosesser.] In, Elisabeth Willumsen og Atle Ødegård (Eds.). Co-creation [Samskaping.] Oslo: Universitetsforlaget.
5. Ødegård, A., Sæbjørnsen, S. E. N., Lindqvist, S., Vasset, F., Iversen, H. P., Willumsen, E., Sirnes, T. og Almås. S. H. (2020). Interprofessional collaborative learning in the professional educations – a contribution to innovation? [Tverrprofesjonell samarbeidslæring i profesjonsutdanningene – et bidrag til innovasjon?] In Elisabeth Willumsen og Atle Ødegård (Eds.). Co-creation [Samskaping]. Oslo: Universitetsforlaget.
6. Sæbjørnsen, Siv Elin Nord; Ødegård, Atle. (2016). Adolescents' subjective views about interprofessional team participation. A Q methodological study. Journal of Comparative Social Work 2016. Volum 11.(2) s. 1-26.

4. Details of the impact

CHILDREN WITH DISABILITIES & UN RIGHTS CONVENTIONS

The NOREC project "Children with disabilities & UN rights conventions" (hereafter referred to as the NOREC project) was initiated in 2019 with the aim of improving the quality of life for children with disabilities in Norway and Tanzania by implementing the UN rights conventions CRC (1989) and CRPD (2008). In both countries, many children with disabilities do not have their rights fulfilled, but the situation is more severe in Tanzania. In Tanzania, many children with disabilities do not survive to adulthood, many are kept hidden and isolated from the outside world, and there is a strong superstition associated with disabilities in general. Therefore, the activities of the NOREC project in Tanzania have largely focused on the basic needs of the children, such as safety and protection from violence, as well as raising awareness and educating about children with disabilities, including their needs and rights. In these activities, we collaborate with stakeholders such as the Ministry of Education Science and Technology (URT, 2021), Unicef (2021), and others. Corporal punishment is still practiced in the majority of schools in the country, but an increasing number of schools are now distancing themselves from such practices and are trying, for example, to replace punishment with encouragement and rewards for good behavior and work.

The research mentioned in the previous section has primarily contributed to the improvement of knowledge about collaboration and communication across different boundaries. This knowledge is also crucial in the ongoing development of effective and productive collaboration between organizations and individuals from different cultures, disciplines, educational levels, and the inclusion of end-users in the NOREC project. So far, the NOREC project has achieved positive

results since 2019 and has had an impact on a societal level since 2022. There is still a long way to go to achieve the goal of implementing the CRC and CRPD, but there are plans for several more project rounds in the coming years.

COLLABORATION IN PARTNERSHIP

The NOREC project was initially based on a partnership between the bachelor program in social education [vernepleie] at Molde University College and Patandi Teacher's College of Special Needs Education. The project also involved schools that had students with disabilities as practice partners, such as Patandi Primary School and several primary, secondary, and high schools in Molde and the surrounding area. In this mutual exchange project, the partner institutions had mutual responsibility as hosts and senders of exchange participants, i.e., students, staff, and representatives from practice partners. A project team was established at both partner institutions, which had primary responsibility for program design, implementation, and guidance for exchange participants, as well as recruitment and training of participants going on exchange, and follow-up of participants and their further program after the exchange. The programs and associated activities aimed to contribute to increased quality of life for children with disabilities in both Norway and Tanzania, by disseminating knowledge and creating awareness about the rights and needs of children and individuals with disabilities to children and adults in all social strata. The project teams frequently collaborated among themselves, led by the project coordinator at the coordinating partner.

The project teams and project participants collaborated with staff at the practice institutions to plan and implement steps in the practical implementation of rights. An example of successful practical implementation of rights from Tanzania was the work to end corporal punishment and other humiliating methods of punishment. As a result of this work such methods are no longer used at this and several other schools, but teachers also report a new trust among students, reduced absenteeism, increased engagement in classes, and improved academic results among students.

From 2023, the partnership was expanded with two more partners, namely Western Norway University of Applied Science (Norway) and Open University of Tanzania. Molde University College is still the coordinating partner, and Siv Sæbjørnsen is the project coordinator. The collaboration model with project teams, participants and practitioners remains the same as described above, but now there are four project teams, even more practice partners, and a total of 40 participants in the annual exchange.

Based on research on collaboration across professions, disciplines, levels, and cultures, this NOREC project has focused on developing a strong partnership to promote sustainable development. Important principles in the development of the partnership include equality despite differences in contributions and benefits, mutual responsibility and commitment, recognition and development of trustworthy relationships among partnership key persons, intercultural understanding, transparency in all processes and relationships, and a clear anti-corruption policy.

METHODS AND TECHNIQUES IN ACTIVITIES AND COLLABORATION

In this ongoing NOREC project, a variety of methods and techniques are used to disseminate knowledge about disabilities, needs, and rights, as well as to create awareness and contribute to a change in mindset in the population. The target groups range from academia, practitioners (school staff and students), health, social, and education authorities at the national, regional, and district levels, politicians, as well as children and extended families throughout the country. This effort is being made in both countries, but particularly in Tanzania where knowledge about disabilities is less widespread and the practice field has implemented the CRC and CRPD to a lesser extent than in Norway.

An important part of the project activities aimed at knowledge dissemination and awareness raising are the conferences "Children with disabilities and quality of life - challenges and possibilities" in Arusha, Tanzania. In 2022 and 2023, these were held as three-day conferences, with the first day dedicated to an international research conference, while the next two days were used for keynote speeches, seminars/workshops, and plenary presentations and debates. The conference participants included representatives from academia (staff and students), practitioners, national, regional, and district authorities, politicians, and stakeholders. The participants worked together in mixed groups to develop concrete solutions to specific problems in the implementation of rights for children with disabilities. Research that had been presented and discussed on the first day of the conference was used as a resource in the group work, which was evident in the groups' presentations and discussions in plenary. The cultural elements during the conference included, among other things, children with disabilities singing and dancing. This also sends a strong message that "disability is not inability," that children with disabilities have the right to life and should not be hidden away, and that children have the right to participate in forums that concern them.

Parts of the research presented at the conference were preliminary results from the now open access published book "Change Agents - An interprofessional book about children with disabilities" consisting of peer-reviewed articles. The book is a result of the collaboration in this project, where the editors were Siv Sæbjørnsen, Mariana Makuu, and Atle Ødegård.

Another method that was used was a workshop series at the practice schools, together with project participants and school staff. The collaboration process involved sharing experiences and perspectives based on their own viewpoint and culture, together defining the problem or potential for improvement for the implementation of rights (CRC and CRPD) at the school, and then agreeing on goals and a plan to improve the chosen problem area. Several collaboration meetings were held during the implementation plan to monitor progress and find solutions to any challenges along the way. Several school staff members who had participated in the workshop series engaged in further awareness raising activities, such as starting and conducting workshops using the same model at other schools.

Participants from Tanzania who are on exchange in Norway are actively disseminating knowledge to children and adults, practice fields, and academia in various ways. In Norway, Tanzanian participants are also developing their own follow-up plan for further work on implementing rights in their own workplace and local community in Tanzania. The student participants come from all over the country, and they are largely successful in their work, partly because the NOREC project is well-known and supported by authorities at various levels, and because a cooperation agreement has been signed between the partners and the Ministry of Education, Science, and Technology. Representatives from the project team and project management have visited several former student participants after their accomplishment of the study programme and having returned to their workstation. These visits also involve visits to and discussions with regional and district authorities, which are activities that also contribute to the goal of spreading knowledge and creating awareness about the conditions for children with disabilities in the country. During the visits, results from the previous exchange participants' work have been documented and observed, and they constitute the data basis for ongoing research. Several research studies are in progress, some of which have been submitted to publishers.

As a result of the project collaboration, a course in health and environmental work for people with disabilities has now been developed. The course incorporates elements from Norwegian disability nursing education but is particularly tailored to Tanzanian conditions. The goal is for the course to be integrated into the bachelor's program in social work at the Open University of Tanzania, while

also being made available to employees at partner institutions and former project participants. The accreditation process for the new bachelor's program is expected to be completed by November 2024. The development of this course is also the subject of research and is planned to be published towards the end of the year.

A range of additional activities and ongoing research that have an impact at the societal level could have been mentioned here. Several studies are expected to be published during this year and the next.

UNICEF. (2021). *Situation analysis of children and young people with disabilities in mainland Tanzania and Zanzibar.* https://www.unicef.org/tanzania/reports/children-and-young-people-disabilities-tanzania

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5. Sources to corroborate the impact (indicative maximum of ten references)

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Iversen, H. P., Werner, G. F., & Sæbjørnsen, S. E. N. (2023). Disability as a socially-relational process–and so what?. In *Change Agents: An interprofessional book about children with disabilities in Tanzania and Norway* (pp. 109-130). https://doi.org/10.18261/9788215057903-23-06

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Hean, S. (2023). Interprofessional collaboration and research networking in Global North–Global South partnerships. In *Change Agents: An interprofessional book about children with disabilities in Tanzania and Norway* (pp. 159-178). https://doi.org/10.18261/9788215057903-23-09

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Brask, O. D., Østby, M., & Ødegård, A. (2023). The professional helper–a presentation of a reflection model developed in Norway. In *Change Agents: An interprofessional book about children with disabilities in Tanzania and Norway* (pp. 195-216). https://doi.org/10.18261/9788215057903-23-11

Sæbjørnsen, S. E., Makuu, M. J., & Ødegård, A. (Eds.). (2023). Change Agents: An interprofessional book about children with disabilities in Tanzania and Norway. https://www.idunn.no/doi/book/10.18261/9788215057903-23

[Molde University College, Faculty of Health Sciences and Social Care]

[case number 4]

Institution: Molde University College
Administrative unit: Department of Health and Social Sciences
Title of case study: ADHD in a life course perspective – associations with chronic pain and DHD
Period when the underpinning research was undertaken: 2020 ->
Period when staff involved in the underpinning research were employed by the submitting institution: 2019
Period when the impact occurred: 2020

Summary of the impact (indicative maximum 100 words).

Epidemiological studies demonstrate that ADHD is highly heritable and significantly associated with somatic complaints such as chronic pain. The risk of developing pain is affected by health-, biological-, and genetic factors with a complex relationship between chronic pain and genes. Genes act at many levels to shape the experience of chronic pain, influencing emotional, behavioural, and biological processes. This project involves parents of children with ADHD, and is clinical and epidemiological, involving Child and Adolescent Psychiatry (St. Olavs Hospital), and the general population (HUNT – HUNT-All-In pain), and collaborates with Aarhus University.

2. Underpinning research (indicative maximum 500 words)

1. 2020: *Ingunn Mundal et al. Faculty of Health Sciences and Social Care, Molde University College, Norway and RKBU/NTNU, Trondheim, Norway*

We aimed to assess whether a peer co-led educational parenting program would be effective in reducing disruptive behavior and ADHD symptoms in school-aged children. The active involvement of parents in educational interventions, incorporating their knowledge to help other parents may therefore be beneficial. We aimed to evaluate the acceptability and feasibility of the intervention to evaluate if a full-scale RCT was likely to be feasible. As well as if the parents were eligible to be recruited, randomized, and complete questionnaires including Multicultural Quality of Life Index (MQLI), Beliefs about Medicine Questionnaire (BMQ), Medication Adherence Rate Scale (MARS) and Parent-Patient Activation Measure (P-PAM). However, due to the pandemic, the involved clinics were not to recruit parents to the RCT. The RCT protocol is updated and aims to carry out a full-scale RCT.

2. 2021: *Ingunn Mundal et al. Faculty of Health Sciences and Social Care, Molde University College, Norway and RKBU/NTNU, Trondheim, Norway*

Parents of children with ADHD: Considering parents' experience of living with children with ADHD, we examined parents' quality of life and parental engagement. Assessing the aspects of quality of life in clinical practice is considered an important aspect of care and may help health personnel focus on the utmost importance of the family environment. We validated the MQLI for a Norwegian population together with the initial originator of the questionnaire, finding it to be robust and recommended for use to measure parental quality of life.

3. 2022-2023: *Ingunn Mundal et al. Faculty of Health Sciences and Social Care, Molde University College, Norway and RKBU/NTNU, Trondheim, Norway*

We also measured parent activation to understand what factors influence parent activation and how to target these factors to develop and deliver more helpful interventions. It is of critical importance that parents feel confident and self-efficacious to actively manage their child's health on behalf of their child.

Pain studies – affiliated with HUNT All-In Pain consortium:
4. 2021: *Cindy Boer et al., Department of Internal Medicine, Erasmus MC, Medical Center, 3015CN Rotterdam, the Netherlands*
We identified 57 previously unknown osteoarthritis genetic risk variants, finding risk depending on joint sites, the association with osteoarthritis genetic components, and pain-related phenotypes.
5. 2021: *Shafiqur Rahman et al., Department of Twin Research and Genetic Epidemiology, School of Life Course Sciences, King's College London, London, UK.*
We conducted a genome-wide association study (GWAS) to gain insight into the genetic background of chronic widespread pain (CWP) and found a novel association of RNF123 locus and a suggestive association of ATP2C1 with CWP which are consistent with the calcium regulation in CWP.
6. 2022: *Samar Khoury et al.* Alan Edwards Centre for Research on Pain, McGill University, Montreal, QC H3A 0G1, Canada
Chronic overlapping pain conditions (COPC) are proposed to have common genetic, neurological, and psychological vulnerabilities. We aimed to understand the genetic basis of chronic pain manifestation at one body site versus multiple body sites and identified a distinct genetic basis for COPC pointing to netrin-drive axogenesis, and a genetic and structural basis of CNS input.

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3. References to the research (indicative maximum of six references)

1. Mundal, I., Gråwe, R. W., Hafstad, H., Cuevas, C. L., & Lara-Cabrera, M. L. (2020). Effects of a peer co-facilitated educational programme for parents of children with ADHD: a feasibility randomised controlled trial protocol. *BMJ Open*, *10*(12), e039852.

2. Mundal, I., Laake, P., Mezzich, J., Bjørkly, S. K., & Lara-Cabrera, M. L. (2021). Assessment of the Quality of Life in Parents of Children With ADHD: Validation of the Multicultural Quality of Life Index in Norwegian Pediatric Mental Health Settings. *Front Psychol*, *12*, 638006. https://doi.org/10.3389/fpsyg.2021.638006
3. Mundal, I., Laake, P., Bjørkly, S. K., & Lara-Cabrera, M. L. (2023). Factor structure and internal consistency of the parent patient activation measure (P-PAM) in parents of children with ADHD in norwegian paediatric mental health. *BMC Psychiatry*, *23*(1), 60. https://doi.org/10.1186/s12888-023-04550-0

Pain studies – affiliated with HUNT All-In Pain consortium (Mundal is affiliated)
4. Boer, C. G., Hatzikotoulas, K., Southam, L., Stefánsdóttir, L., Zhang, Y., Coutinho de Almeida, R., Wu, T. T., Zheng, J., Hartley, A., Teder-Laving, M., Skogholt, A. H., Terao, C., Zengini, E., Alexiadis, G., Barysenka, A., Bjornsdottir, G., Gabrielsen, M. E., Gilly, A., Ingvarsson, T., . . . Zeggini, E. (2021). Deciphering osteoarthritis genetics across 826,690 individuals from 9 populations. *Cell*, *184*(18), 4784-4818.e4717. https://doi.org/10.1016/j.cell.2021.07.038

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6. Rahman, M. S., Winsvold, B. S., Chavez Chavez, S. O., Børte, S., Tsepilov, Y. A., Sharapov, S. Z., Aulchenko, Y. S., Hagen, K., Fors, E. A., Hveem, K., Zwart, J. A., van Meurs, J. B., Freidin, M. B., & Williams, F. M. (2021). Genome-wide association study identifies RNF123 locus as associated with chronic widespread musculoskeletal pain. *Ann Rheum Dis*, *80*(9), 1227-1235. https://doi.org/10.1136/annrheumdis-2020-219624

4. Details of the impact (indicative maximum 750 words)

This research includes several aspects that have made a cumulative impact on the development of the research. We started with the parents of children with ADHD, and cooperation with the child and adolescent outpatient clinics in Kristiansund, Trondheim, Levanger, and Namsos, and the psychoeducational parental programs to evaluate potential questionnaires for an upcoming RCT. The project and the single studies regarding parents of children with ADHD were developed and carried out in collaboration with user representatives and ADHD-Norway. The validation studies are not yet finished – two studies are under preparation. The validation studies were founded by Extrastiftelsen (DAM). The link to the project 'ADHD in a life course perspective' came into existence through an announcement and further agreement with HUNT and HUNT All-In Neuropsychiatry as well as the Child and Adolescent Outpatient Psychiatric Clinic (CAP) in Mid-Norway. This project is funded by "Regionalt Fagmiljø for autism, ADHD, Tourettes syndrome and narkolepsi".

In addition to accepted publication until 2022, an article comparing chronic pain prevalence in adolescents and young adults with ADHD (in CAP) with adolescents and young adults in the general population, is published. We found that chronic pain was highly prevalent in adolescents and young adults with ADHD, and that multisite pain was exceedingly prevalent in young females with ADHD. This study is conducted in collaboration with professor and psychiatrist Per Hove Thomsen at Aarhus University. This collaboration will be continued, exploring predictors for chronic pain.

Furthermore, we have ethical approvement of conducting genetic analyses using HUNT and UK Biobank. These analyses will examine the genetic relationship between ADHD and chronic musculoskeletal pain including chronic widespread pain in HUNT and UK – Biobank. Genetic studies of quantitative ADHD symptom scores in children support the hypothesis that ADHD is the extreme of a quantitative trait. Combining genetic data from population-based and case-cohort may help understand the relationship between ADHD and chronic pain conditions. This study will be initialized in autumn 2024 in cooperation with Professor Per Hove Thomsen and HUNT All-In Neuropsychiatry.

5. Sources to corroborate the impact (indicative maximum of ten references)

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Lundqvist, S., Knez, R., Nagy, K., Nasic, S., Kerekes, N., & Kantzer, A. K. (2023). Prevalence of chronic pain in children and adolescents with psychiatric conditions. *Paediatr Neonatal Pain*, *5*(2), 50-56. https://doi.org/10.1002/pne2.12100

Mundal, I., Schei, J., Lydersen, S., Thomsen, P. H., Nøvik, T. S., & Kvitland, L. R. (2023). Prevalence of chronic and multisite pain in adolescents and young adults with ADHD: a comparative study between clinical and general population samples (the HUNT study). *Eur Child Adolesc Psychiatry*. https://doi.org/10.1007/s00787-023-02249-x

Department of Sports Medicine [1]

Institution: Norwegian School of Sport Sciences
Administrative unit: Department of Sports Medicine
Title of case study: SKADEFRI: Keeping athletes fit to play – preventing health problems in youth sports
Period when the underpinning research was undertaken: 2000-2024
Period when staff involved in the underpinning research were employed by the submitting institution: 2000-2024
Period when the impact occurred: 2008-2024

1. Summary of the impact (indicative maximum 100 words)

SKADEFRI is a free, evidence-based resource based on two decades of research from the Oslo Sports Trauma Research Center and international partners, providing guidance to coaches, parents and athletes on sports injury prevention with programs and exercises for 59 different sports and 11 body-parts. With the website www.skadefri.no (English: www.fittoplay) and smartphone app SKADEFRI (international version: Get Set, available in 11 major languages) as the foundation, the program includes: 1. Ambassador grassroot level sport club courses, 2. National coach certification programs across sports, 3. Sport academy educational programs for youth elite athletes, 4. supported by a social media strategy.

2. Underpinning research

The Oslo Sports Trauma Research Center (OSTRC) was established at the Department of Sports Medicine in May 2000 based on external grants. The main objective is to protect the health of athletes through a long-term research program on the prevention of injuries and other health problems in sport (including studies on epidemiology, risk factors, injury mechanisms, and interventions). The program focuses mainly on three sports (football, team handball, and alpine skiing/snowboarding), as these account for more than 50% of all sports-related injuries treated in Norwegian emergency rooms, and addresses the most common (e.g. ankle, hamstrings) and the most serious (e.g. ACL, concussions) injuries seen in these and other sports. Youth and children are the primary target groups.

The center was the first research group in the world to develop specific injury prevention programs and conduct appropriately designed randomized clinical trials to test their efficacy. The first large-scale study, on 1837 youth handball players, was published in BMJ in 2005 (Olsen et al.), documenting a 47% reduction in injury risk. The second large RCT, on a football-specific program tested on 1892 youth players, showed a 45% reduction in the risk of more severe injuries, published by BMJ in 2008 (Soligard et al.). At the same time the group also addressed interventions addressing other risk factors for injury, where RCTs are less amenable. One example is a case-control study on helmet use for alpine skiers and snowboarders published in JAMA in 2006 (Sulheim et al.), showing that helmets reduce the risk of head injuries by 60%.

Since these landmark studies, the center has published close to 1000 papers involving >50 PhD-students related to injury and illness prevention in sports, addressing their causes (injury mechanisms, pathophysiology, external and internal risk factors) as the basis for interventions targeting specific health problems, sometimes also targeting specific sports. A more recent focus has been overuse problems, injuries without a specific inciting event, but developing gradually over time. Examples of successful interventions are one RCT addressing shoulder problems in

handball players (Andersson et al. 2017) and one on groin problems in football players (Harøy 2019), both showing substantial reductions in injury risk. Overall, evidence from our studies and those from other groups show that injury rates generally are reduced by about 50% when specific, targeted intervention programs are implemented, across different sports (e.g. football, handball, volleyball) and injury types (e.g. to the knee, ankle, groin, hamstrings, shoulder).

Key research staff:
- Prof. Thor Einar Andersen MD PhD
- Prof. Roald Bahr MD PhD
- Ass. prof. Hilde Moseby Berge MD PhD
- Ass. prof. Ben Clarsen PT PhD
- Prof. Lars Engebretsen MD PhD
- Prof. Morten Wang Fagerland PhD
- Ass. prof. Hege Grindem PT PhD
- Prof. Tron Krosshaug PhD
- Prof Gilbert Moatshe MD PhD
- Ass. prof. Christine Holm Moseid MD PhD
- Prof. Grethe Myklebust PT PhD
- Ass. prof. Merete Møller PT PhD
- Ass. prof. Kathrin Steffen (-2023) PhD

As well as multiple PhD-students (51 completed) and Postdocs

Current SKADEFRI implementation team:
- Ass. prof. Christine Holm Moseid
- Erling Hisdal
- Emilie Bratt Jakhelln
- Ingrid Eir Thorp Eythorsdottir

3. References to the research

Exercises to prevent lower limb injuries in youth sports: cluster randomised controlled trial. Olsen OE, Myklebust G, Engebretsen L, Holme I, Bahr R. BMJ. 2005;330(7489):449. doi: 10.1136/bmj.38330.632801.8F.

Helmet use and risk of head injuries in alpine skiers and snowboarders. Sulheim S, Holme I, Ekeland A, Bahr R. JAMA. 2006;295:919-24. doi: 10.1001/jama.295.8.919.

Comprehensive warm-up programme to prevent injuries in young female footballers: cluster randomised controlled trial. Soligard T, Myklebust G, Steffen K, Holme I, Silvers H, Bizzini M, Junge A, Dvorak J, Bahr R, Andersen TE. BMJ. 2008;337:a2469. doi: 10.1136/bmj.a2469.

ACL injury incidence in female handball 10 years after the Norwegian ACL prevention study: important lessons learned. Myklebust G, Skjølberg A, Bahr R. Br J Sports Med. 2013;47:476-9. doi: 10.1136/bjsports-2012-091862.

Preventing overuse shoulder injuries among throwing athletes: a cluster-randomised controlled trial in 660 elite handball players. Andersson SH, Bahr R, Clarsen B, Myklebust G. Br J Sports Med. 2017;51:1073-1080. doi: 10.1136/bjsports-2016-096226.

The prevalence and severity of health problems in youth elite sports: A 6-month prospective cohort study of 320 athletes. Moseid CH, Myklebust G, Fagerland MW, Clarsen B, Bahr R. Scand J Med Sci Sports. 2018;28:1412-1423. doi: 10.1111/sms.13047.

The Adductor Strengthening Programme prevents groin problems among male football players: a cluster-randomised controlled trial. Harøy J, Clarsen B, Wiger EG, Øyen MG, Serner A, Thorborg K, Hölmich P, Andersen TE, Bahr R. Br J Sports Med. 2019;53:150-157. doi: 10.1136/bjsports-2017-098937.

4. Details of the impact

As shown above, RCTs across several sports have documented that injury prevention programs reduce the risk of sport injuries by about 50%. However, the next step, wide-scale implementation of such programs in youth sport had never been attempted. As a first step at closing the gap between injury prevention research and real-life implementation, OSTRC therefore developed and launched the first version of the website www.skadefri.no in 2008. The strategy was to depart from the then traditional model of conference dissemination, hoping to reach the end user, the coaches and athletes, through the complex governing bodies where sports are organized and played. Instead, the website was designed with coaches, parents and youth athletes in mind, with ready-made, well-documented programs and other resources for football, handball and alpine skiing – ready for use.

Building on this initial platform, SKADEFRI (eng. “free from injury”) has since been expanded and revised using state-of-the-art web design and now covers all sports disciplines organized within the Norwegian Confederation of Sports and Olympic and Paralympic Committee, a total of 59 sports with specific exercise-based injury prevention programs, as well as a host of other resources. SKADEFRI also includes dedicated programs for 11 body regions such as the knee and ankle, covering all the most common injury types seen in sports. The SKADEFRI website communicates information on injury prevention through live video, text animations, pictures, posters and training programs, and is implemented by school authorities nationwide in the physical education curriculum for high schools. Early research showed that nationwide implementation based on the website program and coach seminars reduced the number of acute severe knee injuries, anterior cruciate ligament injuries, in Norwegian handball by half, and that this was sustained for at least 5 years (Myklebust et al, 2013). The website content is also translated into English (www.fittoplay.no) and is recognized world-wide as a prime resource on injury prevention for youth and adolescents playing sports.

This recognition lead to the next milestone, the development of the smartphone application “GETSET train smarter” in 2014, on invitation and initially funded by the International Olympic Committee for the inaugural Nanjing Youth Olympic Games in 2014. The app includes detailed exercise programs for injury prevention for all Olympic and Paralympic sports (the same as the SKADEFRI website). The app (in Norway known as the SKADEFRI app) has also been redesigned recently based on user feedback and is translated to 11 major languages. The target groups and their needs are addressed through an interactive design developed in a close cooperation with communication experts, various stakeholders and end users.

With the website and smartphone app content as the foundation and main tools, the program includes four pillars: 1. Ambassador grassroot level sport club courses, 2. National coach certification programs across sports, 3. Sport academy educational programs for youth elite athletes, 4. supported by a social media strategy.

The first pillar is grassroot level sport club courses, developed to reach coaches, athletes, parents and sport club staff at a local level. Courses are held by a nationwide cadre of 288 SKADEFRI-educated sports physiotherapists –our ambassadors. From evaluations we know that the courses lead to increased knowledge, immediate implementation (98%), retained at least for 3 months (86%).

Second, in partnership with the Norwegian Confederation of Sports and Olympic and Paralympic Committee we have developed level 1 and level 2 courses integrated in their national coach certification program. The level 1 courses are e-learning modules, aimed particularly towards parents and other volunteers coaching young athletes. The level 2 courses are more advanced and sport specific.

As the third pillar we have developed NÆRMERE BEST (Eng. Prep to be Pro), an educational program targeting youth elite athletes enrolled in Sport Academies from age 13 through 18. These schools provide an opportunity for approximately 3000 Norwegian youth and adolescents to combine a college-entry high school education with sports development programs designed to reach the international elite level, but resulting in a large burden of health problems due to high training and competition loads (Moseid et al, 2018). The program is a toolbox for their teachers and coaches consisting of 10 different modules, all athlete- and coach oriented. The modules address physical and psychological challenges typically faced by developing young elite athletes, seeking to increase the young athlete's overall robustness and resilience. One key component is the SKADEFRI preventive exercise programs.

The fourth pillar is a social media program, designed to underpin all activities and market the tools through Instagram and Facebook, with coaches and athletes as the two main target audiences.

Finally, there are multiple international invitations and initiatives to implement the different SKADEFRI components by stakeholders world-wide. Examples include the continuing close collaboration with the International Olympic Committee, and a current EU-funded project, SONAR, in partnership between seven European countries (Spain, Norway, the Netherlands, Croatia, Bulgaria, Germany and France), developing an E-learning program for youth coaches, modelled from SKADEFRI.

5. Sources to corroborate the impact

Dr. Richard Budgett, director, Medical Department, International Olympic Committee
Dr. Jiri Dvorak, former director, Medical Department, FIFA
Dr. Andy Massey, current director, Medical Department, FIFA
Dagfrid Forberg, leder breddeidrett, organisasjon og utvikling, Norges idrettsforbund og olympiske og paralympiske komité
Tore Øvrebø, toppidrettsjef, Olympiatoppen
Elen Thoresen, seniorrådgiver, Kulturdepartementet

Norwegian School of Sport Sciences Department of Sports Medicine (IIM) [2]

Institution: Norwegian School of Sport Sciences
Administrative unit: Department of Sports Medicine (IIM)
Title of case study: The Norwegian National Physical Activity Surveillance Study (NNPAS)
Period when the underpinning research was undertaken: 2012-2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2012-2022
Period when the impact occurred: 2012-2022

1. Summary of the impact (indicative maximum 100 words)

NNPAS is a national surveillance system of device- measured sedentary time, physical activity (PA) in the Norwegian population. Since 2005 we have informed public health authorities with unique knowledge on the level of and temporal changes in physical activity and sedentary behaviour. Such data is crucial to evaluate the effect of, and plan for new, PA promoting strategies and data have formed the basis of several national action plans for PA and is used as an national indicator of the PA target for NCD`s in WHO`s strategy. Including data from NNPAS we are currently leading the Adult Accelerometer Consortium (ACC) which research output has strongly influenced the new PA recommendations from WHO 2020.

2. Underpinning research (indicative maximum 500 words)

In Norway, a national surveillance system for device measured – NNPAS, was initiated in 2005 as a direct consequence of the National Action Plan for Physical Activity (2005-2009) - "Sammen for fysisk aktivitet" – where one of the actions was to establish a system for monitoring PA in the Norwegian population. Six surveillance studies with device-based PA measures have been conducted (2005, 2008, 2011, 2014, 2018 and 2022) providing a unique opportunity to examine the current status and temporal trends of physical activity and sedentary time. The data generated, provide indispensable knowledge to inform targeted actions and interventions, and to guide global an national policy action towards ensuring that the population is achieving sufficient levels of PA. These data have formed the basis of several national action plans (i.e. Sammen om aktive liv 2020-2029) and provides public health authorities such as The Norwegian Directorate of Health and Norwegian Institute of Public Health with official statistics on levels of physical activity and sedentary time. Moreover, data are used as an national indicator of the PA target for NCD`s in WHO`s strategy towards 2030. In 2017 researchers from the unit established an international Adult Accelerometer consortium (ACC) including data from NNPAS - aiming to examine the dose-response relationship between accelerometer-measured PA, sedentary time, and mortality among adults. This consortium is led by Prof Ulf Ekelund (IIM) and the scientific output from this consortium has strongly influenced the new and revised PA recommendations from WHO in 2020 and more recent PA recommendations in Norway 2022.

Key personell:

- Ulf Ekelund, Professor, IIM
- Sigmund Alfred Anderssen, Professor and head of department IIM
- Jostein Steene-Johannessen, Professor, IIM
- Elin Kolle, Associate professor, IIM
- Bjørge Herman Hansen, professor II, IIM
- Jakob Tarp, Post-doc (2016-2019), IIM
- Knut Eirik Dalene, PhD student and Post Doc (2014-2021)

3. References to the research (indicative maximum of six references)

Steene-Johannessen, Jostein; Anderssen, Sigmund Alfred; Kolle, Elin; Hansen, Bjørge Hermann; Bratteteig, Mari; Dalhaug, Emilie Frederikke Mass; Andersen, Lars Bo; Nystad, Wenche; Ekelund, Ulf & Dalene, Knut Eirik. Temporal trends in physical activity levels across more than a decade – a national physical activity surveillance system among Norwegian children and adolescents (2021) ISSN 1479-5868. 18. doi: 10.1186/s12966-021-01120-z

Hansen BH, Kolle E, Steene-Johannessen J, Dalene KE, Ekelund U, Anderssen SA. Monitoring population levels of physical activity and sedentary time in Norway across the lifespan. (2019) Scand J Med Sci Sports. 2019 Jan;29(1):105-112. doi: 10.1111/sms.13314. Epub 2018 Oct 11.

Ekelund, Ulf; Tarp, Jakob; Steene-Johannessen, Jostein; Hansen, Bjørge Hermann; Jefferis, Barbara; Fagerland, Morten; Whincup, Peter; Diaz, Keith M.; Hooker, Steven P.; Chernofsky, Ariel; Larson, Martin G.; Spartano, Nicole; Vasan, Ramachandran S.; Dohrn, Ing-Mari; Hagströmer, Maria; Edwardson, Charlotte; Yates, Thomas; Shiroma, Eric; Anderssen, Sigmund Alfred & Lee, I-Min. Dose-response associations between accelerometry measured physical activity and sedentary time and all cause mortality: systematic review and harmonised meta-analysis (2019).The BMJ. ISSN 1756-1833. 366. doi: 10.1136/bmj.l4570.

Ministry of Health and Care Services, Together for Active Lives. Action Plan for Physical Activity 2020-2029 Departementenes handlingsplan (regjeringen.no)

Norwegian Institute of Public Health. Indicators for non-communicable diseases connected to the national and global strategy for non-communicable diseases. Prevalence of insufficiently physically active adolescents, defined as less than 60 minutes of moderate to vigorous intensity activity daily and Age-standardised prevalence of physically active persons aged 18+ years (defined as less than 150 minutes of moderate-intensity activity per week, or equivalent).

WHO guidelines on physical activity and sedentary behaviour. Geneva: World Health Organization; 2020. ISBN 978-92-4-001512-8 (electronic version)

4. Details of the impact (indicative maximum 750 words)

The activity level of the Norwegian population has since 2005 been monitored through regular national surveys (NNPAS). The NNPAS surveys have been conducted by the Norwegian School of Sport Sciences in collaboration with the Norwegian Directorate of Health (2005-2014) and the Norwegian Public Health Institute (2017-). The surveys have assessed physical activity using accelerometers. The use of device-based PA measures overcome well known flaws in the interpretation of prevalence estimates from self-report, such as recall- and social desirability biases. NNPAS is providing a unique opportunity to examine temporal PA trends and thus provide indispensable knowledge in order to carry out targeted actions and interventions, and to guide global and national planning of policy action towards ensuring that the population is achieving sufficient levels of PA. In particular, the scientific output (see part 3) from NNPASS on status and trends form the knowledgebase of the current Norwegian action plan for physical activity (2020-2029). The action plan is the government's action plan and the primary target group is state sectors with responsibility and tools to develop an activity-friendly society. Key actors in achieving the goals are municipalities and county municipalities, as well as civil society, voluntary and private sector. In such, output from the NNPAS studies not only inform national but also regional planning

of policy action towards ensuring that the population is achieving sufficient levels of PA. One of the main targets in the action plan is to increase the proportion of the adult population meeting health recommendations for physical activity by 15 percentage points by 2030. This target corresponds to the World Health Organization (WHO) and the UN's Sustainable Development Goals. In 2016, WHO Europe launched a European action plan for increased physical activity, followed by a ten-year global action plan for increased physical activity in 2018. The main target is a decrease in the prevalence of physical inactivity by 15 percentage points by 2030 (from a baseline in 2015). This should contribute to reducing premature mortality from NCDs by 33 percent between 2015-2030. The NNPAS studies is used as the main data source for this target in Norway.

Data from NNPAS also include a longitudinal part allowing to investigate the associations between physical activity and sedentary time with all-cause and cause-specific disease mortality. In 2017 researchers from the unit established an international Adult Accelerometer consortium including data from NNPAS and other recent cohort studies using device-based methods (i.e., accelerometry) - aiming to examine the detailed dose-response relationships between accelerometer-measured PA, sedentary time, and mortality among adults. Using a novel approach, an exposure harmonised meta-analysis, we examined the dose-response relations of total physical activity, different intensities of physical activity (light, low light, high light, moderate to vigorous, and vigorous) and sedentary time and all-cause mortality (Ekelund et al, BMJ 2019). This harmonized metanalysis includes data from eight studies and thus this several institutions contributed to the impact (The University of Sydney, Camperdown, NSW Australia, University of Vigo, Pontevedra, Spain, UiT the Arctic University of Norway, Tromsø, Norway, Uppsala University, Sweden, Mid Sweden University, Östersund, Sweden, Karolinska Institutet, Stockholm, Sweden, Columbia University Medical Center, New York, USA, University of Alabama at Birmingham, Birmingham, AL, USA, National Heart Lung Blood Institute, Bethesda, MD, USA, Harvard T H Chan School of Public Health, Boston, Massachusetts). The impact of this research did not only support the national and global strategies to improve public health through physical activity in populations, but findings from this consortium and in particular this paper informed the development of the current WHO PA guidelines launched in 2020. In particular, the research, provide evidence that physical activity of any bout duration is associated with improved health outcomes, including all-cause mortality. Based on this evidence, the recommendation for bouts of least 10 minutes duration has been removed.

Findings are important for policymakers and can inform future guideline development by also recognising the role of light intensity physical activity and hence total physical activity for reducing the risk of premature death. Further, we showed that all intensities of physical activity, including light intensity physical activity are associated with lower risk for all-cause mortality. Subsequent publications from the consortium have showed that physical activity of moderate intensity attenuate the detrimental association between sedentary time and risk for mortality (Ekelund BJSM 2020); and that total physical activity can mitigate the detrimental association between over-weight and obesity with risk for premature mortality.

5. Sources to corroborate the impact (indicative maximum of ten references)

Jostein Steene-Johannessen SAA, Mari Bratteteig, Emilie, Mass Dalhaug IDA, Oddbjørn Klomsten Andersen, Elin Kolle, Ulf, Ekelund KED. Kartlegging av fysisk aktivitet, sedat tid og fysisk form blant barn og unge 2018 (ungKan3). Norges idrettshøgskole; 2019.
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Bjørge Herman Hansen*, Jostein Steene-Johannessen*, Elin Kolle , Karine Udahl , Oda Bjørge Kaupang , Inge Dehli Andersen , Elisabeth Teinung , Ulf Ekelund, Wenche Nystad , Sigmund Alfred Anderssen. Kartlegging av fysisk aktivitet blant voksne og eldre 2020-22 (Kan3). Norges idrettshøgskole; 2023. https://www.fhi.no/publ/2023/kartlegging-av-fysisk-aktivitet-blant-voksne-og-eldre-2020-22-kan3/

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Hansen, Bjørge Hermann; Dalene, Knut Eirik; Ekelund, Ulf; Fagerland, Morten; Kolle, Elin; Steene-Johannessen, Jostein; Tarp, Jakob & Anderssen, Sigmund Alfred (2020). Step by step: Association of device-measured daily steps with all-cause mortality - A prospective cohort Study. *Scandinavian Journal of Medicine & Science in Sports*. ISSN 0905-7188. 30(9), s. 1705–1711. doi: 10.1111/sms.13726.

Hansen BH, Ommundsen Y, Holme I, Kolle E, Anderssen SA. Correlates of objectively measured physical activity in adults and older people: a cross-sectional study of population-based sample of adults and older people living in Norway. Int J Public Health. 2014 Apr;59(2):221-30. doi: 10.1007/s00038-013-0472-3. Epub 2013 Apr 26. PMID: 23619723.

Dalene KE, Kolle E, Steene-Johannessen J, Hansen BH, Ekelund U, Grydeland M, Anderssen SA, Tarp J. Device-measured sedentary time in Norwegian children and adolescents in the era of ubiquitous internet access: secular changes between 2005, 2011 and 2018. Int J Epidemiol. 2022 Oct 13;51(5):1556-1567. doi: 10.1093/ije/dyac063. PMID: 35362538;

Bull FC, Al-Ansari SS, Biddle S, Borodulin K, Buman MP, Cardon G, Carty C, Chaput JP, Chastin S, Chou R, Dempsey PC, DiPietro L, Ekelund U, Firth J, Friedenreich CM, Garcia L, Gichu M, Jago R, Katzmarzyk PT, Lambert E, Leitzmann M, Milton K, Ortega FB, Ranasinghe C, Stamatakis E, Tiedemann A, Troiano RP, van der Ploeg HP, Wari V, Willumsen JF. World Health Organization 2020 guidelines on physical activity and sedentary behaviour. Br J Sports Med. 2020 Dec;54(24):1451-1462. doi: 10.1136/bjsports-2020-102955. PMID: 33239350; PMCID: PMC7719906.

Ekelund, Ulf; Tarp, Jakob; Steene-Johannessen, Jostein; Hansen, Bjørge Hermann; Jefferis, Barbara; Fagerland, Morten; Whincup, Peter; Diaz, Keith M.; Hooker, Steven P.; Chernofsky, Ariel; Larson, Martin G.; Spartano, Nicole; Vasan, Ramachandran S.; Dohrn, Ing-Mari; Hagströmer, Maria; Edwardson, Charlotte; Yates, Thomas; Shiroma, Eric; Anderssen, Sigmund Alfred & Lee, I-Min. Dose-response associations between accelerometry measured physical activity and sedentary time and all cause mortality: systematic review and harmonised meta-analysis (2019). The BMJ. ISSN 1756-1833. 366. doi: 10.1136/bmj.l4570.

Tarp J, Fagerland MW, Dalene KE, Johannessen JS, Hansen BH, Jefferis BJ, Whincup PH, Diaz KM, Hooker S, Howard VJ, Chernofsky A, Larson MG, Spartano NL, Vasan RS, Dohrn IM, Hagströmer M, Edwardson C, Yates T, Shiroma EJ, Dempsey PC, Wijndaele K, Anderssen SA, Lee IM, Ekelund U. Device-measured physical activity, adiposity and mortality: a harmonized meta-analysis of eight prospective cohort studies. *Br J Sports Med* 2022;56:725-32

Ekelund U, Tarp J, Fagerland MW, Steene-Johannessen J, Hansen BH, Jefferis BJ, Whincup P, Diaz KM, Hooker SP, Howard WJ, Chernofsky A, Larson MG, Spartano ML, Vasan RS, Dohrn IM, Hagströmer M, Edwardson CL, Yates T, Shiroma EJ, Dempsey PC, Wijndaele K, Anderssen SA, Lee IM. The joint associations of accelerometer measured physical activity and sedentary time with all-cause mortality: A harmonized meta-analysis in more than 44,000 middle-aged and older individuals, *Br J Sport Med* 2020;54:1499-1506

Norwegian Institute of Public Health - Centre for Fertility and Health – impact case number 1

Institution: Norwegian Institute of Public Health
Administrative unit: Centre for Fertility and Health
Title of case study: Gender, education, and health
Period when the underpinning research was undertaken: 2017-2023
Period when staff involved in the underpinning research were employed by the submitting institution: 2017-2023
Period when the impact occurred: 2017-2023

1. Summary of the impact

Boys perform worse than girls in school, and men obtain lower education and have higher mortality than women. A group of researchers in our Centre has fundamentally changed how issues facing boys and men are viewed and discussed in the Norwegian society. They have brought attention to gender differences in school performance and education, created public awareness that biological differences in development contribute to these outcomes, raised concerns for health impacts of gender differences in schooling, and presented evidence-based solutions to the issues. The change has come about through wide-spread media participation, engagement with policymakers, and contributions to several government commissions and white papers.

2. Underpinning research

Boys perform worse than girls in school and men obtain lower education than women in Norway. This societal challenge has implications for health, one of many implications of which are the large and growing differences in male mortality by education and income.

Gender differences in school performance and education in Norway were well documented by the Stoltenberg commission (NOU 2019:3). Brandlistuen *et al.* (2021) in addition contributes with research on gender differences in early school performance, development, and behaviour among 5-year-old children. Using the Norwegian Mother, Father, and Child Cohort Study (MoBa), the researchers found gender differences favouring girls for all outcomes except internalising behaviour, including a .31 standard deviation difference in school readiness.

A second research endeavour has been to explore biological differences in development between the sexes. Using data on 13,477 British twins in the Twins Early Development Study (TEDS), Torvik *et al.* (2021) found that sex differences in pubertal maturation were important and accounted for up to half of the sex difference in academic achievement, whereas genetic influences on pubertal development explained 7-8% of the variation in academic achievement.

The third group of findings relates to impacts of gender differences in school performance and education on health and family formation. Beck *et al.* (2023) uses propensity score matching to study impacts of failing a final exam on mental health diagnoses in the following year. They find a 31% increased risk for boys compared to 11% for girls, and 64% of the impacted were male. Reme and Torvik *(forthcoming)* finds that males and females with low school grades have a three-to-fourfold higher mortality between ages 13 and 30 compared to children with high grades (0.06% vs 0.02%). Suicides, accidents, and overdoses are the main sources of excess mortality among males with low school grades. Bratsberg *et al.* (2023) find larger differences in fertility and childlessness by income for males than for females. Lack of family network may be one contributing factor to

excess male mortality. Taken together, this research suggests that school performance may affect men's health both in the short and the longer term.

Fourth, the group has been concerned with studying policies that can improve boys' performance in school. Flatø *et al.* (2023) evaluates effects of introducing school psychology offices in Norway, that promoted delayed school start for children based on a screening test in the 1960s and 1970s. They find positive effects of the offices during this period on adult income, and negative effects for male education when the practice was abandoned.

Key researchers:

- Camilla Stoltenberg, Director General NIPH (01.11.2017-01.07.2023)
- Fartein Ask Torvik, Senior Researcher (01.08.2018-today)
- Martin Flatø, Researcher (01.08.2018-today)
- Bernt Bratsberg, Senior Researcher II (29.06.2021-today)
- Thomas Kleppestø, Postdoc (01.11.2020-06.08.2023)
- Hans Fredrik Sunde, PhD Fellow (01.08.2020-30.09.2023), Researcher (01.10.2023-today)
- Magnus Nordmo, Postdoc (18.01.2021-today)
- Bjørn-Atle Reme, Postdoc/Researcher (01.11.2019-today)
- Jonathan Wörn, Postdoc/Researcher (09.12.2019-today)
- Kate Beck, PhD Fellow (15.08.2021-today)

3. References to the research

- Beck KC, Røhr HL, Reme BA & Flatø M. (2024). Distressing testing: A propensity score analysis of high-stakes exam failure and mental health. *Child Development,* 95(1), 242-260. https://doi.org/10.1111/cdev.13985
- Brandlistuen RE, Flatø M, Stoltenberg C, Helland SS & Wang MV. (2021). Gender gaps in preschool age: A study of behavior, neurodevelopment and pre-academic skills. *Scandinavian Journal of Public Health*, *49*(5), 503-510. https://doi.org/10.1177/1403494820944740
- Bratsberg B, Kotsadam A & Walther S. (2021). Male Fertility: Facts, Distribution and Drivers of Inequality. *IZA Discussion Paper*, No. 14506.
- Flatø M, Bratsberg B, Kotsadam A, Torvik FA, Røgeberg O & Stoltenberg C. (2023). Ready for School? Effects on School Starters of Establishing School Psychology Offices in Norway. *CESifo Working Paper*, No. 10352.
- Reme BA & Torvik F. (forthcoming). School performance and mortality in young adulthood: a register-based population study. *Unpublished, available upon request*.
- Torvik FA, Flatø M, McAdams TA, Colman I, Silventoinen K & Stoltenberg C. (2021). Early puberty is associated with higher academic achievement in boys and girls and partially explains academic sex differences. *Journal of Adolescent Health*, *69*(3), 503-510. https://doi.org/10.1016/j.jadohealth.2021.02.001

4. Details of the impact

The initiative started on 10 February 2017 with a newspaper column by Camilla Stoltenberg in Morgenbladet that highlighted the large gender differences in school performance and education at the disadvantage of boys and men, and launched the hypothesis that biological differences in development are contributing to these outcomes. It was followed up through two mutually reinforcing tracks. A *policy* track, in which the Ministry of Education on 25 August 2017 established a government commission on gender differences in school performance chaired by Stoltenberg, and a *research* track with the RCN-funded project "Health Gap: Health, Maturity, and Gender Gap in Education" which started on 1 May 2018. The research project was placed at the Centre for Fertility and Health (CeFH), which had several advantages. CeFH is an interdisciplinary centre, and

a combination of medical and social scientists were needed to properly address the research questions. Furthermore, it enabled studies of the role of reproductive maturation for school performance and impacts of education and income for male fertility.

Martin Flatø and Fartein Ask Torvik were hired in August 2018 and, together with Stoltenberg, the team worked closely with the Ministry of Education to contribute to the commission report and at the same time get input to develop research that would be relevant for policy. The close connection between policy and research has been key to achieving the impact in this case. The report made top headlines in most Norwegian news outlets when it was published, and the team gave more than 100 presentations on the work. This included dissemination to an audience outside Norway through Stoltenberg's presentations to Unesco and OECD, and her TED talk in 2019. The impact of changing the awareness in the general public as well as among policymakers can be dated to the 2017-2019 period.

After the turn of the decade, initial results and publications emerged from the group. Additional funding was secured, including the projects "Reproduction of socioeconomic differences and mental health across generations (REMENTA)" led by Torvik and "Lost in transition? Uncovering social and health consequences of sub-optimal transitions in the education system" as well as "Pubertal Timing and Inequalities in Education" led by Flatø. We were also partners in the project "Determined to Succeed? Maturation, Motivation and Gender Gaps in Educational Achievement" led by the Institute for Social Research. Kate Beck, Thomas Kleppestø, Magnus Nordmo, Bjørn-Atle Reme, Hans Fredrik Sunde and Jonathan Wörn were recruited, and the group expanded.

The findings from the Health-Gap project was presented at an open seminar attended by the Minister of Health and Social Affairs Ingvild Kjerkol on 16 March 2023, and followed up with a newspaper article in Morgenbladet on 17 March 2023 and with a presentation for all staff in the Ministry of Education on 3 May 2023. In addition to documenting the gender differences in school performance and their preschool origins, the group's research showed that differences in pubertal timing could partially explain the gender differences. The results also showed strong associations between school performance, boys' mental health, and mortality among young men. This widened the policy debate beyond the education sector and triggered interest within the health authorities in the school problems that are facing many boys. The group has also provided research on potential policies for a more maturity-sensitive and male-friendly school system.

The research is continuously being referred to and acted upon in policymaking. The Stoltenberg commission's report was followed up by Reports to the Parliament on early learning (Meld. St. 6 (2019–2020)) and upper secondary education (Meld. St. 21 (2020–2021)). Research from the group was presented in a parliamentary hearing on lower secondary school reform in 2022 and has thus uniquely impacted policies for all levels of education in Norway. The group has successfully managed to also communicate the gaps in current knowledge and called for further research that uses person-identifiable register data. This has been instrumental for a new government enquiry on improved data collection from schools and kindergartens, to which the group has contributed with expert advice. The group has also conveyed the research to the government commission on male equality where Stoltenberg is an appointed member, and the government commission on social differences in school performance where Torvik is member. Our research was cited by the Commission on quality assurance and development in schools (NOU 2023:27).

CeFH has spearheaded research and dissemination on gender, education, and health through leading several research projects, engaging in policy dialogue, and hosting several events. The research has been conducted in collaboration with other research organisations, in particular the Institute for Social Research and the The Ragnar Frisch Centre for Economic Research. The end

beneficiaries of our impact are boys in the Norwegian educational system, and girls who face similar problems as those that on average are affecting more boys. However, it will take years before any tangible impacts may be measured for boys, and it may not be likely that researchers will be able to identify research from the group as its cause. Nonetheless, the group has over a relatively short time period managed to fundamentally change public discourse on males in the education system and has engaged with policymakers to improve male equity in education and reduce adverse health consequences.

To our knowledge, no other country has had a similarly broad and balanced public debate and high number of policy processes addressing gender differences at the disadvantage of men. Nearly all OECD countries, and an increasing number of other countries, are facing similar gender differences in schools and education, family formation, health, marginalisation, and socioeconomic differences. At the moment, Norway appears to be at the forefront, however, the need for research and policies on these issues will hopefully soon be acknowledged internationally.

5. Sources to corroborate the impact

- Camilla Stoltenberg, CEO, Norce Research
- Ingvild Kjerkol, Minister of Health and Social Affairs
- Håkon Kavli, Deputy Director General, Section for Analysis and Research, Ministry of Education and Research
- Inga Bejer Engh, the Ombudsperson for children in Norway
- Claus Jervell, chairperson of the Men's Equality Commission, Ministry of Culture and Equality
- Richard Reeves, President, the American Institute for Boys and Men
- Arne Børke, president of MannsForum, a male rights NGO
- Are Saastad, president of Reform – resource center for men, a male rights NGO
- Omar Mekki, CEO, Guttas Campus, an educational programme for boys

Norwegian Institute of Public Health - Centre for Fertility and Health – impact case number 2

Institution: Norwegian Institute of Public Health
Administrative unit: Centre for Fertility and Health
Title of case study: Assisted reproductive technologies and impact on women's and children's health
Period when the underpinning research was undertaken: 2017 - 2023
Period when staff involved in the underpinning research were employed by the submitting institution: 2017 - 2023
Period when the impact occurred: 2018-2023

1. Summary of the impact

Women using Assisted Reproductive Technologies (ART) and children born after ART have been found to have increased risk of some adverse health outcomes. Our studies find that the actual ART procedures may play a role, and that some risks may vary with procedures, while others do not. Our research informs fertility clinicians and couples considering ART about potential risks, and helps clinicians and couples consider the safest ART method for them.

2. Underpinning research

With interdisciplinary teams, international collaborations and data from health registries and the Norwegian Mother, Father, and Child Cohort Study (MoBa), we have shown that (dates of when research was carried out in parentheses):

1) Women using ART differ in characteristics from women conceiving naturally (Jan 2019 to Jun 2020)
2) The long-term risk of cardiovascular diseases is not increased in women using ART (Jan 2021 to Sept 2023), and there are small cardiovascular differences in children born after ART (Jan 2020 – Jul 2022)
3) There is increased risk of preterm delivery and neonatal death after ART (Aug 2018 – Feb 2023)
4) ART-conceived children have increased risk of respiratory infections (Aug 2020 to Aug 2022) and are different in growth up to age 7 but not at age 18 (Mar 2020 – Mar 2021). The differences in birth weight were partly mediated through DNA methylation (Jun 2021 – Nov 2022)
5) ART-conceived offspring have fewer children as young adults, but not higher risks of pregnancy complications (Aug 2021 – Nov 2022)
6) ART conceived children have DNA methylation differences at birth in 176 known genes (Nov 2017 – Jul 2022), including differences in the BRCA promotor gene and in genes on the X chromosome (Jul 2020 – Jul 2022)

We are now following up and exploring if DNA methylation differences persist into childhood, and whether they are associated with RNA expression, sex differences in DNA methylation, and effects on outcomes.

Underpinning projects, funding and OUTPUT

Our work underpinning the impact of our ART research, is based on several research projects and funding:

1. The Norwegian Research Council's Centre of Excellence funding scheme (#262700)
   OUTPUT: Researcher time, PhD, Costs for analyses of DNA methylation
2. The European Research Council Starting Grant INFERTILITY (#947684)
   OUTPUT: Data collection, researcher time

3. The Norwegian Cancer Society) (#244291-2022)
   OUTPUT: Data collection, researcher time, analyses of RNA and DNA methylation
4. Norwegian Institute of Public Health (own funding)
   OUTPUT: Data collection, researcher time, infrastructure

NAME OF RESEARCHER	POSITION	DATE JOINING	DATE LEAVING
Siri Eldevik Håberg	Director	Nov 1, 2017	-
Per Magnus	Deputy Director	Nov 1, 2017	-
Øystein Kravdal	Principal Investigator	Nov 1, 2017	-
Liv Bente Romundstad	Researcher	Feb 1, 2018	-
Hans Ivar Hanevik	Researcher	Apr 8, 2019	-
Maria C Magnus	Senior Researcher	Aug 1, 2018	-
Astanand Jugessur	Senior Researcher	Nov 1, 2017	-
Håkon Gjessing	Principal Investigator	Nov 1, 2017	-
Yunsung Lee	Researcher	Nov 1, 2017	-
William Denault	PhD/Postdoc/Researcher	Jan 1, 2018	August 31, 2022
Haakon Nustad	Researcher	Jul 1, 2020	-
Christian Page	Researcher	Nov 1, 2017	-
Kristine Løkås Haftorn	PhD research fellow	Feb 1, 2019	June 30, 2023
Robert Lyle	Researcher	Apr 3, 2020	-
Ellen Øen Carlsen	PhD research fellow/Postdoc	Mar 4, 2019	-
Julia Romanowska	Postdoc/Researcher	Nov 1, 2017	-
Miriam Gjerdevik	PhD/Postdoc/Researcher	Nov 1, 2017	-

More than 10 million children have been born worldwide after ART. The number is rapidly increasing, also in Norway, where more than 50 000 children have been conceived through ART since 1984. Studies have found that these children have lower birthweight, higher risk of neonatal complications and increased risk of certain diseases, such as metabolic and neurodevelopmental disorders as well as some cancers.

It has been difficult to study whether these increased risks are related to the ART procedures or to the underlying conditions causing subfertility. Most studies have had methodological shortcomings, such as limited sample sizes and relatively short follow up time. A challenge in studying potential links between ART and risk of cancer beyond childhood is the relatively young age of the ART-conceived group. Although current evidence suggests a higher risk of some cancers in children born after ART it is emphasized that it is still unknown whether this is due to the ART treatment, to birth outcomes associated with ART, or to other factors associated with the use of ART, including parental subfertility. Our research is aimed at resolving these questions.

3. References to the research

1. Goisis A, **Håberg SE, Hanevik HI, Magnus MC, Kravdal Ø**. (2020). The demographics of assisted reproductive technology births in a Nordic country. *Hum Reprod,* 35(6), 1441-1450. https://doi.org/10.1093/humrep/deaa055
2. **Magnus MC**, Fraser A, **Håberg SE**, Rönö K, **Romundstad LB**, Bergh C, Spangmose AL, Pinborg A, Gissler M, Wennerholm UB, Åsvold BO, Lawlor DA, Opdahl S. (2023). Maternal Risk of Cardiovascular Disease After Use of Assisted Reproductive Technologies. *JAMA Cardiol,* 8(9), 837-845. https://doi.org/10.1001/jamacardio.2023.2324
3. **Magnus MC**, Wilcox AJ, Fadum EA, **Gjessing HK**, Opdahl S, Juliusson PB, **Romundstad LB, Håberg SE**. (2021). Growth in children conceived by ART. *Hum Reprod,* 36(4), 1074-1082. https://doi.org/10.1093/humrep/deab007

4. **Carlsen EØ, Lee Y, Magnus P, Jugessur A, Page CM, Nustad HE, Håberg SE, Lie RT, Magnus MC.** (2022). An examination of mediation by DNA methylation on birthweight differences induced by assisted reproductive technologies. *Clin Epigenetics,* 14(1), 151. https://doi.org/10.1186/s13148-022-01381-w
5. **Carlsen EØ**, Wilcox AJ, **Magnus MC, Hanevik HI, Håberg SE**. (2023). Reproductive outcomes in women and men conceived by assisted reproductive technologies in Norway: prospective registry based study. *BMJ Med,* 2(1), e000318. https://doi.org/10.1136/bmjmed-2022-000318
6. **Håberg SE, Page CM, Lee Y, Nustad HE, Magnus MC, Haftorn KL, Carlsen EØ, Denault WRP, Bohlin J, Jugessur A, Magnus P, Gjessing HK, Lyle R**. (2022). DNA methylation in newborns conceived by assisted reproductive technology. *Nat Commun,* 13(1), 1896. https://doi.org/10.1038/s41467-022-29540-w

4. Details of the impact

The nature and extent of the impact

The research increases knowledge about risk factors for cancer and consequences of ART treatments. More information on potential risks will enable couples to make more informed choices about reproduction and use of ART. This is important as use of ART is increasing. Our results identify risks according to different ART methods and in specific subgroups of women. This may guide medical practice and help tailor treatments.

The results increase the understanding of the role of genetics and epigenetics in breast cancer and other *BRCA*-associated cancers. Better knowledge on longer term health risks in persons conceived by ART will provide opportunities for closer follow-up and tailored screening and may inform preventive measures and early detection of cancer. This may improve the prognosis and potentially give rise to personalized treatment.

Researchers at our unit have collaborated with several institutions in the described work. One collaboration was through the CoNARTaS – the Committee of Nordic Assisted Reproductive Technology and Safety. Our collaborative work with ConARTAS has been presented at scientific conferences.

1. Magnus MC *et al.* Maternal risk of cardiovascular disease after use of assisted reproductive technologies: a Nordic registry linkage. *Society of Pediatric and perinatal Epidemiological Research, Chicago, June, 2022.* Poster Presentation 0093.
2. Westvik KJ *et al.* Maternal and treatment contributions to perinatal outcomes after transfer of fresh and cryopreserved embryos in assisted reproduction: A Nordic sibling study. *European Society of Human Reproduction (ESHRE) virtual meeting in 2020.* Oral Presentation O-029.

Our unit's work with epigenetics after ART have been disseminated at several scientific meetings as posters and oral presentations:

1. **Lyle R** *et al.* START: The STudy of Assisted Reproductive Technologies. *European Society of Human Genetics (ESHG) Conference* (2020). Interactive e-poster P01.005.B
2. **Lyle R** *et al.* DNA methylation in newborns conceived by assisted reproductive technology. *European Society of Human Genetics (ESHG) Conference* (2022). Hybrid Poster P01.024.D.
3. **Lyle R** *et al.* Assisted Reproductive Technology is associated with DNA Methylation in Newborns Conceived by Assisted Reproductive Technology. *Wellcome Genome Campus, UK,* November 2021. Oral Presentation.

4. **Lyle R** *et al.* DNA methylation in newborns conceived by assisted reproductive technology. *Genetics of Reproduction Meeting. The Royal Society, London* (2022). Poster P01.

Beneficiaries of the impact

Scientific community: Research findings has been communicated to the international scientific community through publications in high impact journals and by presentations at scientific conferences. The findings generate future research questions and collaborations with the obstetric community and perinatal epidemiologists, as well as with researchers in cancer, assisted reproduction, genetics, and epigenetics.

Policy makers: The Norwegian Institute of Public Health (NIPH) is in direct frequent contact with governmental agencies, and we communicate relevant findings to policy makers, such as the Directorate of Health and the Ministry of Health and Care Services. Our research has had an impact through public media. By identifying robust modifiable factors that influence the risk of breast cancer or other cancers after ART, this knowledge can be used to guide interventions and develop screening tools and treatments. The results from this project will help guide future research efforts in this direction.

Clinicians: We collaborate closely with two public and one private fertility clinic in Norway. These collaborators have central roles in the medical field of ART in Norway, and they ensure close contact wand communication of results to clinicians and obstetricians. Presentations have been given to clinicians participating in annual meetings of their National Association (NOFAB). We have also presented our work at a network conference to clinicians and researchers within breast cancer research (see dates and meetings below).

The general public: We participate in open popular science meetings to communicate research findings, for example the "Women's health conference". Also, we communicated our findings through open popular research websites specifically designed to communicate science to a general audience (project descriptions at www.fhi.no and www.cefh.no).

Subfertile women, women using ART and breast cancer patients: Our clinical collaborators are in close contact with representatives from the Norwegian Association for Fertility and Unwanted Childlessness "Ønskebarn" and will be involved in communicating results to women who struggle to conceive. This will ensure the right communication to those who consider ART or are treated with ART and to those who may face increased risk of adverse effects and adverse health conditions as a consequence of their infertility. Our results have been presented to patients through user participation at Women's health conference and NOFAB (see dates and meetings below).

5. **Sources to corroborate the impact**

Public popular science presentations for clinical and general audience:

1. Norwegian Association of Assisted Reproduction (NOFAB). Invited presentation. Annual meeting, Nov 2022. Håberg, SE. DNA methylation in newborns conceived by ART.
2. Norwegian Association of Assisted Reproduction (NOFAB). Invited presentation. Annual meeting, Nov 2019. Håberg, SE. Centre for Fertility and Health, studies on ART.
3. Women's Health Conference (Kvinnehelsekonferansen), Norwegian Research Council, Research on Women's Health, Dec 2022. Håberg, SE.
4. National Network Conference on Breast Cancer Research (research groups and breast cancer society), January 14, 2023, Trondheim, Norway. Invited presentation. Håberg SE. Risk of breast cancer in persons born after assisted reproductive technologies.

Norwegian Institute of Public Health - Centre for Fertility and Health – impact case number 3

Institution: Norwegian Institute of Public Health
Administrative unit: Centre for Fertility and Health
Title of case study: The role of chronological and biological aging in fertility
Period when the underpinning research was undertaken: 2018-2023
Period when staff involved in the underpinning research were employed by the submitting institution: 2017-2023
Period when the impact occurred: 2019-2023

1. Summary of the impact

Age is undoubtedly one of the most important factors in fertility. People age with different speed, and both the ability to become pregnant and health vary greatly within people of the same chronological age. Some genetic measures, including DNA methylation and telomere length, are surprisingly good indicators for biological aging. Accurate estimation of biological age can advance our understanding of biological mechanisms linking age to fertility, development, health and disease. Also, we have shown that gestational age can be predicted by genetic measures, which is particularly valuable in gauging fetal and newborn's development.

2. Underpinning research

Leveraging genetic, epigenetic and telomere data from the Norwegian Mother, Father, and Child Cohort Study (MoBa), we present here a selection of key findings from our research on the importance of chronological age, epigenetic aging and telomere length on fertility [dates in brackets]:

1) With Norwegian registry data we could show that the risk of miscarriage increases steeply with maternal age over 35 years, and around half of all pregnancies in women above age 40 end in a miscarriage. [2018 – 2019]
2) Building on previous work we show that an epigenetic gestational age clock built on DNA-methylation data from the more recent Illumina MethylationEPIC BeadChip (EPIC) platform estimates gestational age more precisely than previously published clocks based on data from earlier Illumina platforms. [2018-2022]
3) There were strong correlations between DNA-methylation and gestational age across seven main cell-types in cord blood, most of which was attributable to nucleated red blood cells (nRBCs). These correlations were closely related to genes involved in erythropoiesis, immune response, and the transition from fetal to adult hemoglobin. [2018-2022]
4) Our gestational age clock showed a similar performance when applied to samples from children born after assisted reproductive technologies and after natural conceptions. [2018-2022]
5) We found that telomere length is associated with 823 CpG sites using an epigenome-wide association study (2019) and have submitted a paper that shows that polygenic scores for telomere length predict the observed telomere length equally well for newborn children and adults.
6) We found a significant difference in the epigenetic age acceleration in adults calculated by the DunedinPoAm clock between in vitro fertilization (IVF) and non-ART mothers after adjustment for potential confounders. [2020 – 2022]

The above findings warrant further investigations and are already seeding new initiatives and exciting applications. Examples include the use of the Cytometry by time of flight (CyTOF) instrument at NIPH to disentangle specific contributions from different cell types to gestational

age. This will enable us to map the roles of different cell types in biological processes related to the postnatal period. Another application pertains to measuring DNA methylation levels of extracted cell-free fetal DNA in maternal blood as an alternative to cord-blood DNA, given the invasiveness and ethic-legal limitations of sampling biologic specimens before a baby is born.

The bulk of the work underpinning the impact of our research into gestational age and biological aging is based on funding from several research grants, including the following:

1. The Norwegian Research Council of Norway's Centre of Excellence funding Scheme (grant no. 262700)
   OUTPUT: Researcher time, PhD, Costs for analyses of DNA methylation
2. NIH: The National Institutes of Health (NIH; grant no. R01 1HL134840-01NIPH): "Telomeres and female fecundity."
   OUTPUT: Researcher time, PhD, Costs for analyses of telomere measurements
3. The Research Council of Norway's FRIPRO call (grant no. 262043): "Telomere length, epigenetic age and T cells in women who give birth at an older age."

Names of the key researchers and what positions they held at the administrative unit at the time of the research (where researchers joined or left the administrative unit during this time, these dates must also be stated).

NAME OF RESEARCHER	POSITION	DATE JOINING	DATE LEAVING
Siri Eldevik Håberg	Director	Nov 1, 2017	-
Per Magnus	Deputy Director	Nov 1, 2017	-
Astanand Jugessur	Senior scientist	Nov 1, 2017	-
Jon Bohlin	Senior scientist	Jan 1, 2020	-
Yunsung Lee	PhD/Researcher	Feb 1, 2018	-
Kristine L. Haftorn	PhD research fellow	Feb 1, 2019	June 30, 2023
Håkon Gjessing	Principal Investigator	Nov 1, 2017	-
William Denault	Postdoc	Jan 1, 2018	August 31, 2022
Julia Romanowska	Researcher	Nov 1, 2017	-
Maria C Magnus	Senior scientist	Aug 1, 2018	-
Haakon Nustad	Researcher	Jul 1, 2020	-
Christian Page	Researcher	Nov 1, 2017	-
Robert Lyle	Senior scientist	Apr 3, 2020	-

3. References to the research - Researchers in our unit in bold

1. **Magnus MC, Wilcox AJ,** Morken NH**,** Weinberg CR, **Håberg SE.** (2019). Role of maternal age and pregnancy history in risk of miscarriage: prospective register based study. *BMJ,* 364, l869. https://doi.org/10.1136/bmj.l869
2. **Lee Y,** Sun D, Ori APS, Lu AT, Seeboth A, Harris SE, Deary IJ, Marioni RE, Soerensen M, Mengel-From J, Hjelmborg J, Christensen K, Wilson JG, Levy D, Reiner AP, Chen W, Li S, **Harris JR, Magnus P,** Aviv A**, Jugessur A,** Horvath S**.** (2019). Epigenome-wide association study of leukocyte telomere length. *Aging (Albany NY)*, 11(16), 5876-5894. https://doi.org/10.18632/aging.102230
3. **Haftorn KL, Denault WRP, Lee Y, Page CM, Romanowska J, Lyle R**, Næss ØE, Kristjansson D, **Magnus PM, Håberg SE, Bohlin J, Jugessur A**. (2023). Nucleated red blood cells explain most of the association between DNA methylation and gestational age. *Commun Biol,* 6(1), 224. https://doi.org/10.1038/s42003-023-04584-w

4. **Lee Y, Haftorn KL, Denault WRP, Nustad HE, Page CM, Lyle R**, Lee-Ødegård S, Moen GH, Prasad RB, Groop LC, Sletner L, Sommer C, **Magnus MC, Gjessing HK, Harris JR, Magnus P, Håberg SE, Jugessur A, Bohlin J**. (2020). Blood-based epigenetic estimators of chronological age in human adults using DNA methylation data from the Illumina MethylationEPIC array. *BMC Genomics,* 21(1), 747. https://doi.org/10.1186/s12864-020-07168-8
5. **Lee Y**, Choufani S, Weksberg R, Wilson SL, Yuan V, Burt A, Marsit C, Lu AT, Ritz B, **Bohlin J, Gjessing HK, Harris JR, Magnus P**, Binder AM, Robinson WP, **Jugessur A**, Horvath S. (2019). Placental epigenetic clocks: estimating gestational age using placental DNA methylation levels. *Aging (Albany NY),* 11(12), 4238-4253. https://doi.org/10.18632/aging.102049
6. **Lee Y, Bohlin J, Page CM, Nustad HE, Harris JR, Magnus P, Jugessur A, Magnus MC, Håberg SE, Hanevik HI**. (2022). Associations between epigenetic age acceleration and infertility. *Hum Reprod,* 37(9), 2063-2074. https://doi.org/10.1093/humrep/deac147

4. Details of the impact

Our research has mainly focused on generating new knowledge to advance the field of chronological aging and biological aging in growth, development, fertility and health. Although it has been well known that women's age affects their ability to become pregnant, we were able to provide solid evidence quantifying the risk of miscarriage with maternal age. This study has proven valuable for other research groups around the world and has been highly cited in international publications since 2019.

We are in the forefront in developing and using biological aging clocks. Our team developed the first gestational age clock and have refined this gestational age clock and excelled the work around using DNA methylation in gestational age prediction. It has added significant value to both clinical and research settings by providing crucial insights into a newborn's developmental stage. Previous research has shown a link between preterm birth and several negative outcomes in neonates, extending into later life. The precise determination of gestational age is critical for effective perinatal care. Traditional methods, such as calculations based on the last menstrual period or ultrasound estimates, are fraught with limitations. With focus on cell-type specific relationships between gestational age and DNA methylation in cord blood we have identified strong correlations across seven main cell types found in cord blood, particularly in nucleated red blood cells (nRBCs). The DNA methylation markers (CpGs) we discovered were linked to genes crucial in the development of red blood cells, various developmental processes, and the preparation for birth and adaptation to life outside the womb. These findings not only contribute to our scientific understanding of these vital processes, but also highlight the potential for practical applications in neonatal care and developmental research. Promising new research based on our work in this field includes the potential of generating new methods for gestational age determination based on blood samples.

Our team has also worked extensively on refining and using DNA methylation clocks in adults as markers of accelerated biological aging and its implications for lower fertility and how the rate of biological aging in adults is relevant for later risk of disease. Prior to our work, a variety of epigenetic clocks had been developed and associated with various environmental exposures and diseases in the elderly, but these were mostly based on older methylation platforms. Our research, based on the newer methylation platform has provided numerous insights regarding the importance of the additional epigenetic marks included on this platform.

Several studies have suggested that epigenetic age acceleration in mothers who conceived using ART may be associated with low oocyte yield and poor ovarian response. However, the difference in epigenetic age acceleration between non-ART and ART mothers (or fathers) had not been examined previously. We filled this gap in knowledge by comparing epigenetic age derived from

various epigenetic clocks between non-ART and ART mothers and fathers. We found a significant difference in the epigenetic age acceleration between in vitro fertilization (IVF) and non-ART mothers after adjustment for potential confounders. A plausible biological mechanism for the observed association is that mothers who undergo IVF may be nearer to menopause compared to mothers who do not use ART.

We are now at a stage where it is possible to delve deeper into the significance of the findings in terms of their relevance for translational applications. Accordingly, we will seek funding to investigate cell-specific methylation profiles using state-of-the-art instruments (CyTOF) in-house at the NIPH, in addition to extracting cell-free fetal DNA in the maternal circulation to determine methylation profiles at an earlier stage than at birth.

5. Sources to corroborate the impact

Apart from peer-reviewed journal articles (a selection of which is provided above), we have also disseminated information about our research to the scientific community as oral or poster presentations at national and international venues, as well as popularized reports in news outlets to reach out to a non-technical audience. These include:

1) Epigenomics of Common Diseases 2022 conference at the Wellcome Trust in the UK (**Haftorn KL** *et al.* "Nucleated red blood cells explain most of the association between DNA methylation and gestational age").
2) The EPEC 2023 meeting in Stockholm, Sweden (**Haftorn KL** *et al.* "The epigenetic landscape of gestational age")
3) The 2023 European Society of Human Genetics (ESHG) Conference in Glasgow, UK (**Haftorn KL** *et al.* "Stability selection enhances feature selection and enables accurate prediction of gestational age using only seven DNA methylation sites").
4) The 2019 Annual Meeting of the Epigenomics of Common Diseases conference (Cambridge, United Kingdom)
5) The 2022 Annual Meeting of the European Society of Human Genetics in Vienna, Austria (**Haftorn KL** *et al.* "Epigenome-wide association study of gestational age at birth using DNA methylation data measured on the Illumina MethylationEPIC BeadChip microarray").
6) Science News DK. Interview of Kristine Haftorn by the Danish Novo Nordic, available at https://www.sciencenews.dk/en/newborns-dna-reveals-their-gestational-age

Norwegian Institute of Public Health - Centre for Fertility and Health – impact case number 4

Institution: Norwegian Institute of Public Health
Administrative unit: Centre for Fertility and Health
Title of case study: Understanding potential consequences of infection with and vaccination against Covid-19 during pregnancy
Period when the underpinning research was undertaken: 2020 - 2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2017 -
Period when the impact occurred: 2021 - 2024

1. Summary of the impact

During the Covid-19 pandemic, we conducted a range of studies looking into the potential consequences of infection with and vaccination against Covid-19 during pregnancy. These studies became very important in the generation and continuous update of national guidelines for vaccination of pregnant women during the pandemic and contributed to the international knowledge base on covid-19 and pregnancy. The findings were also communicated to the public through press releases and to important international stakeholder such as the World Health Organization and the European Medicines Agency.

2. Underpinning research

During the pandemic, we conducted a range of studies looking into the consequences of infection with and vaccination against Covid-19 during pregnancy. We used national health registries, and collaborated with researchers in Sweden and Denmark, to conduct high-quality studies and produce robust evidence using data from these three Nordic countries. With our unique registry linkages, we were able to perform research which is not possible in most other countries. Our work was made possible by the Emergency preparedness register for Covid-19 (BEREDT C19) at the Norwegian Institute of Public Health (NIPH). This register includes data from all the central health registries, including the Medical Birth Registry of Norway, the Norwegian Patient Registry, the Vaccination Registry, the Norwegian Surveillance System for Communicable Diseases and several other important data sources. In addition, with used rich data collected by questionnaires from participants in the Norwegian Mother, Father, and Child Cohort Study (MoBa) and the Norwegian Influenza Cohort (NorFlu). The regularly updated data in BEREDT C19 was invaluable to the conduction of this work. The research conducted within this topic at the CEFH has been funded by the Research Council of Norway and NordForsk. Some of our major findings include (the numbering of these main findings corresponds to the numbering of the references below):

1) In a study using information from Norwegian health registries, pregnant women were not more likely to be infected with the coronavirus SARS-CoV-2. Still, pregnant women with COVID-19, especially those born outside of Scandinavia, were more likely to be hospitalised. This supports the notion that pregnant women are at greater risk of severe disease from COVID-19 if they get infected. These findings supported vaccination of pregnant women (Oct 2020-Oct 2021)
2) The rate of fetal death (miscarriage and stillbirth) did not change after the implementation of COVID-19 pandemic mitigation measures in the three Nordic countries. This provided preliminary reassuring evidence that pandemic mitigation measures, or the general psychosocial stress throughout the pandemic, did not appear to impact the rate of fetal death (June 2021-Oct 2022)
3) Using unique population-based data on first-trimester miscarriages in Norway, we found no evidence of an increased risk of first-trimester miscarriage after Covid-19 vaccination,

which added to findings from smaller reports of more selected samples indicating no increased risk of early pregnancy loss following vaccination. (March 2021-Sept 2021)

4) Based on findings from a large population-based study of births in Sweden and Norway, vaccination against SARS-CoV-2 during pregnancy, compared with no SARS-CoV-2 vaccination during pregnancy, was not significantly associated with an increased risk of adverse birth outcomes, such as stillbirth, preterm birth, small-for-gestational age, low Apgar score etc. This study provided important evidence of the safety of vaccination against Covid-19 during pregnancy (July 2021-Feb 2022)
5) Results from Norway suggested a lower risk of a positive test for SARS-CoV-2 during the first 4 months of life among infants born to mothers who were vaccinated during pregnancy. Maternal COVID-19 vaccination may therefore provide important passive protection to young infants, for whom COVID-19 vaccines are not recommended. (Nov 2021-July 2022)
6) Using MoBa, we followed 70 000 participants with and without SARS-CoV-2 infection and found an excess risk of 13.6% for fatigue 12 months after infection. Two main underlying factors explained 50% of the variance in the 13 symptoms that were associated with infection (long COVID symptoms). Brain fog, poor memory, dizziness, heart palpitations, and fatigue had high loadings on the first factor, while shortness-of breath and cough had high loadings on the second factor.
7) Using questionnaire information from cohort participants we found that cigarette smoking, but not snus use, was negatively associated with SARS-CoV-2 infection in women. The lack of an association between snus use and SARS-CoV-2 infection in this population with prevalent snus use does not support the hypothesis of a protective effect of nicotine.

Names of key researchers

NAME OF RESEARCHER	POSITION	DATE JOINING	DATE LEAVING
Siri Eldevik Håberg	Director	Nov 1, 2017	-
Maria C Magnus	Researcher	Aug 1, 2018	-
Håkon Gjessing	Researcher	Nov 1, 2017	-
Ellen Øen Carlsen	PhD Student	Mar 4, 2019	-
Laura Oakley	Researcher	March 1, 2021	-
Jonas Minet Kinge	Researcher	Aug 1, 2018	-
Ida Caspersen	Researcher	March 1, 2021	
Per Magnus	Deputy Director	Nov 1, 2017	-

Grants:
We have received three grants to facilitate the completion of the described research. The research has primarily come out of a Nordic research collaboration funded by NordForsk, which enabled us to study the risk of more rare pregnancy complications.
NordForsk – Scandinavian studies of Covid-19 in pregnancy (SCOPE) : 105545
NordForsk – Scandinavian studies of Covid-19 in pregnancy 2 (SCOPE 2): 135876
NordForsk – Tobrisk-Cov grant no. 105544.
Research Council of Norway – Safety of Covid-19 vaccination in pregnancy (SAFETY): 324312

2. References to the research

1) **Magnus MC, Oakley L, Gjessing HK**, Stephansson O, Engjom HM, Macsali F, Juliusson PB, Nybo Andersen AM, **Håberg SE**. (2022). Pregnancy and risk of COVID-19: a Norwegian registry-linkage study. *BJOG*, 129(1), 101-109. https://doi.org/10.1111/1471-0528.16969

2) **Magnus MC, Gjessing HK**, Eide HN, Wilcox AJ, Fell DB, **Håberg SE**. (2021). Covid-19 Vaccination during Pregnancy and First-Trimester Miscarriage. *N Engl J Med*, 385(21), 2008-2010. https://doi.org/10.1056/NEJMc2114466
3) **Magnus MC**, Örtqvist AK, Dahlqwist E, Ljung R, Skår F, **Oakley L**, Macsali F, Pasternak B, **Gjessing HK, Håberg SE**, Stephansson O. (2022). Association of SARS-CoV-2 Vaccination During Pregnancy With Pregnancy Outcomes. *JAMA*, 327(15), 1469-1477. https://doi.org/10.1001/jama.2022.3271
4) **Carlsen EØ, Magnus MC, Oakley L**, Fell DB, Greve-Isdahl M, **Kinge JM, Håberg SE**. (2022). Association of COVID-19 Vaccination During Pregnancy With Incidence of SARS-CoV-2 Infection in Infants. *JAMA Intern Med*, 182(8), 825-831. https://doi.org/10.1001/jamainternmed.2022.2442
5) **Caspersen IH, Magnus P**, Trogstad L. (2022). Excess risk and clusters of symptoms after COVID-19 in a large Norwegian cohort. *Eur J Epidemiol*, 37, 539-548. https://doi.org/10.1007/s10654-022-00847-8
6) **Caspersen IH**, Trogstad L, Galanti MR, Karvonen S, Peña S, Shaaban AN, **Håberg SE, Magnus P**. (2023). Current tobacco use and SARS-CoV-2 infection in two Norwegian population-based cohorts. *BMC Public Health*, 23, 846 https://doi.org/10.1186/s12889-023-15822-5

4. Details of the impact

Description of relevant stakeholders

There are several important stakeholders regarding the described research.

1) Government agencies responsible for developing guidelines for vaccination of pregnant women against Covid-19 and monitoring of potential side effects.
2) Pregnant women contemplating vaccination.
3) General practitioners responsible for the routine antenatal care of pregnant women.
4) Other researchers.

Description of dissemination activities

1) Meetings with government agencies. Throughout the pandemic, we have continuously informed the **advisory group at the Norwegian Institute of Public Health (NIPH)** about our findings, in order to inform their development and updated recommendations for vaccination of pregnant women against Covid-19. The evidence that we have made available has been critically important to inform the existing national recommendations for vaccination of pregnant women. Therefore, we had regular meetings with the advisory group at the NIPH and informed them about our findings. Furthermore, we have presented our findings to a sub-committee at the **World Health Organization** responsible for their official guidelines of vaccination of pregnant women against Covid-19. Together with evidence from large-scale studies originating from other countries, our findings have therefore also contributed to the official WHO recommendations. Finally, we have presented findings from our studies on vaccination for the **Norwegian and European Medicines Agencies**. These agencies are responsible for monitoring all evidence regarding potential side effects of vaccines. Our reassuring findings of no adverse effects of vaccination during pregnancy based on Nordic data has been critically important both national and internationally for this purpose.
2) Our findings have been of interest to the **general population of pregnant women trying** to decide whether they should get vaccinated against Covid-19. We have been able to show that pregnant women appear to be at an increased risk of severe disease, and that there is no evidence of adverse effects of vaccination, supporting the general recommendation of vaccination for pregnant women. The described research has been disseminated widely through press releases and news articles to reach the general population of pregnant women. Specifically, we have written press releases together with the NIPH

communications department which has been published on our website. Furthermore, we have contacted/and been contacted by major national newspapers, which has further contributed to the wide dissemination of our findings to the general population.

3) Our findings have also been of interest to **all general practitioners responsible for the antenatal care of pregnant women**. As general practitioners are those who meet pregnant women and must answer their questions about whether or not they should get vaccinated against Covid-19, it has been vitally important to have evidence from large well-conducted studies that they can lean on when communicating with pregnant women. General practitioners heavily relied on the summary of evidence and existing recommendations from the NIPH, and as our findings contributed to these, they were also vitally important for these health-care workers.
4) Our findings have also been important for **other researchers both nationally and internationally**. For example, our analytical strategies to minimize bias leading to spurious findings have been adopted by other researchers on other/independent datasets. This has been important as similar evidence across different populations are necessary to increase confidence in the robustness of findings.

5. Sources to corroborate the impact (indicative maximum of ten references)

1. COVID-19: latest safety data provide reassurance about use of mRNA vaccines during pregnancy | European Medicines Agency (europa.eu)
2. Covid-19 vaksinering av gravide (nhi.no)
3. Ny studie blant gravide: – Koronavaksinen gir ikke økt risiko for komplikasjoner (aftenposten.no)
4. Vaksinestudie blant gravide: Ikke økt risiko for komplikasjoner (dagensmedisin.no)
5. Økt forekomst av menstruasjonsforstyrrelser hos unge kvinner etter vaksinasjon mot korona - FHI
6. Studie: Mors covid-19-vaksine under svangerskapet beskytter barnet etter fødsel (dagensmedisin.no)
7. Mors vaksine beskytter også barnet i magen - FHI
8. Covid-19 i graviditet – risiko for mor og barn | Tidsskrift for Den norske legeforening (tidsskriftet.no)
9. Meeting with the WHO Global advisory committee on Vaccine Safety, 31 May, 2022, https://www.who.int/groups/global-advisory-committee-on-vaccine-safety/topics/covid-19-vaccines/subcommittee

[FHI, KM] [1]

Institution: Norwegian Institute of Public Health (FHI/NIPH)
Administrative unit: Division of Climate and Environmental Health
Title of case study: New Approach Methodologies for use in the hazard identification and characterisation of chemicals – a case study on Developmental Neurotoxicity
Period when the underpinning research was undertaken: 2019-present
Period when staff involved in the underpinning research were employed by the submitting institution:
Period when the impact occurred: 2023

1. Summary of the impact

An increasing number of chemicals are entering the market and society demands that these chemicals are safe for human health. The public opinion (voiced by the European Parliament) demands to reduce the use of experimental animals in the safety testing of chemicals without compromising safety. New Approach Methodologies for hazard assessment have been proposed as a way forward. We have specifically worked on a model using human neural stem cell-based methods to study effects of environmental chemicals on neurodevelopmental processes vital for healthy brain development. This assay will be included in a revised DNT in vitro battery (https://one.oecd.org/document/ENV/CBC/MONO(2023)13/en/pdf).

2. Underpinning research

The developing nervous system is considered to be more susceptible to chemical perturbations than the adult brain, due to the complex processes that occur during brain development (Myhre and Hessel, 2022). These processes are typically time-sensitive and include differentiation of the neural progenitor cells into neurons and glial cells, synaptogenesis, neuronal network formation, etc. (Tal et al., 2023; Lauvås et al 2022). Disturbance of any of these processes may lead to adverse neurodevelopment. Information on the developmental neurotoxic potential of many chemicals is lacking and systematic testing for developmental neurotoxicity (DNT) is not mandatory in the EU for pesticides, biocides, pharmaceuticals, or industrial chemicals. Using animals as model organisms for human development is of limited value due to species differences in brain development as well as the associated difficulties with data interpretation and extrapolation. There is no formally accepted alternative to in vivo animal studies for the identification of the neurotoxic potential of chemicals for regulatory purposes. To protect children's healthy brain development, regulatory agencies need fast, affordable, versatile, ethical constraints-free New Approach Methodologies (NAMs) that can accurately evaluate substance toxicity to close the data gap on the DNT potential of untested compounds. The NAMs should allow both hazard identification as well as hazard characterisation and contribute to the next generation risk assessment. Over the past decades, there has been an intense focus on the development of alternatives to animal methods within the DNT community, resulting in the DNT in vitro battery (IVB) https://one.oecd.org/document/ENV/CBC/MONO(2023)13/en/pdf. The assays allow to studyseveral of the key neurodevelopmental processes vital for brain development. This major endeavour resulted in recently published OECD-supported guidance on the evaluation of data on DNT IVB, however, no guideline exists at this moment for the regulatory use of data produced with the DNT IVB. Therefore, NAMs for regulatory testing must be fully developed, recognized, and endorsed. The data gaps identified in the current DNT IVB are described in https://one.oecd.org/document/ENV/CBC/MONO(2023)13/en/pdf. NIPH has recently used human induced pluripotent stem cell (hiPSC)-derived NPC in a 2D culture system producing neurons and astrocyte mixed cultures. With this test system, a test method for studying synaptogenesis in addition to other neurodevelopmental processes that are gaps in the current DNT IVB was set up (Lauvås et al. 2022; Davidsen et al. 2021; Pistollato et al. 2017). Data gaps present in the current

DNT in vitro battery are addressed in ongoing projects like ONTOX and PARC with the aim to develop a 2nd generation DNT IVB.
It is quite unique that we have now established an IVB for DNT that was shown to deliver robust results for use in regulatory assessments. The developing brain is a complicated organ and the development of this IVB, and future improvements and refinements, is the result of the efforts of a dedicated group of researchers supported by funding agencies that are united in their willingness to make this happen. NIPH is proud to be part of this initiative and is now taking an even more prominent role in further work.

3. References to the research

To close existing gasps and develop in vitro DNT NAMS for a 2nd generation DNT IVB, the research unit has succeeded in acquiring external funding in the EU funded projects ONTOX and PARC, and recently an EFSA funded 4-years project to fill gaps in the current DNT IVB related to glia cell function in brain development and toxicity. The purposes in the EU projects are to develop developmental neurotoxicity in vitro NAMs to develop key events in the pathways to cognitive defects, and to develop a 2nd generation DNT IVB battery for improved risk assessment of chemicals. Employees from our department is highlighted bold letters in the selected publications below.

Tamara Tal, **Oddvar Myhre**, Ellen Fritsche, Joëlle Rüegg, Kai Craenen, Kiara Aiello-Holden, Caroline Agrillo, Patrick J. Babin, Beate I. Escher, **Hubert Dirven**, Kati Hellsten, Kristine Dolva, Harm J. Heusinkveld, Yavor Hadzhiev, Selma Hurem, Karolina Jagiello, Beata Judzinska, Nils Klüver, Anja Knoll-Gellida, Britta A. Kühne, Marcel Leist, **Malene Lislien**, Jan L. Lyche, Ferenc Müller, Winfried Neuhaus, Giorgia Pallocca, Bettina Seeger, Ilka Scharkin, Stefan Scholz, Ola Spjuth, Monica Torres-Ruiz, Kristina Bartmann (2023). New approach methods to assess developmental and adult neurotoxicity for regulatory use: A PARC Work Package 5 project (Frontiers in Toxicology (submitted).

Lauvås AJ, **Lislien M, Holme JA, Dirven H,** Paulsen RE, Alm IM, Andersen JM, Skarpen E, Sørensen V, Macko P, Pistollato F, Duale N, **Myhre O** (2022). Developmental neurotoxicity of acrylamide and its metabolite glycidamide in a human mixed culture of neurons and astrocytes undergoing differentiation in concentrations relevant for human exposure. *Neurotoxicology* 92, 33-48.

Myhre O, Hessel EVS (2022). Editorial: Toxicants and neurodevelopmental disorders. *ReproductiveToxicology* 110, 68-69.

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Myhre O, Låg M, Villanger G, Oftedal B, Øvrevik J, Aase H, Paulsen RE, Bal-Price A, **Dirven H** (2018). Early life exposure to air pollution particulate matter (PM) as risk factor for attention deficit/hyperactivity disorder (ADHD): Need for novel strategies for mechanisms and causalities. *Toxicology and Applied Pharmacology* **354**, 196-214.

Pistollato F, Canovas-Jorda D, Zagoura D, Price A (2017). Protocol for the Differentiation of Human Induced Pluripotent Stem Cells into Mixed Cultures of Neurons and Glia for Neurotoxicity Testing. *J Vis Exp* DOI: 10.3791/55702.

4. Details of the impact

Epidemiological data indicate that toxicant exposures in Europe contribute substantially to neurobehavioral deficits and diseases, with an estimated cost of >€150 billion /year, emphasising the advantages of developing new NAMs for testing and identifying hazards, get a mechanistic

understanding to explore causal relationships and introduction of knowledge-based regulations to control exposure.
New knowledge of risk factors and their underlying mechanisms is likely to be vital to minimise new cases of neurodevelopmental disorders and cognitive deficits. Our projects are therefore highly relevant and timely and has the potential to become a demonstrator how toxicological hazards could be addressed by NAMS, also for other health outcomes.
Animal experiments using mainly rats are currently the gold standard in DNT testing. DNT testing for a large number of environmental toxicants is not fit-for-purpose with the current guideline studies because i) they are time- and cost-intensive (1 year/compound may cost up to 1.000.000 EUR), ii) it is ethically questionable (testing one substance may require up to 140 dams and 1000 juveniles), iii) there are uncertainties in its methodologies, evaluation, and regulation; iv) their predictivity for protection of the human brain is questionable due to the differences in brain function/complexity, exposure, neurodevelopmental timing, toxicokinetics and toxicodynamics between rodents and humans.
To protect children's brains, regulatory agencies need fast, affordable, versatile, ethical constraint-free NAMs that can accurately evaluate substance toxicity in line with the Chemical Strategy Sustainability goals of the European Commission and the 3Rs-Principle (EUSAAT, https://eusaat.eu/), accesses 29th January 2024) to close the data gap on the DNT potential of untested compounds. The NAMs should allow both hazard identification as well as hazard characterization and contribute to the next generation risk assessment. Regulators should have high confidence that the proposed strategies substituting animal testing gives the same level of protection as animal studies.
Brain development is a highly complex procedure that covers time and a large variety of neurodevelopmental processes. Over the past decades, there has been an intense focus on the development of alternatives to animal methods, resulting in the DNT *in vitro* battery (IVB) https://one.oecd.org/document/ENV/CBC/MONO(2023)13/en/pdf. These assays model many, although not all, of the key neurodevelopmental processes vital for healthy brain development and employ cell models of mostly human origin. This major endeavor resulted in recently published OECD-supported recommendations on the evaluation of data on developmental neurotoxicity *in-vitro* battery, however, no guideline exists at this moment for the regulatory use of data produced with the DNT IVB. Therefore, to identify DNT alerts and prioritize substances for testing at a lower tier level in a more efficient and predictive manner to adhere to the domain of applicability, NAMs for regulatory testing must be fully developed, recognized, and endorsed.
Despite its complexity, key neurodevelopmental processes that are vital for brain development were identified (https://one.oecd.org/document/ENV/CBC/MONO(2023)13/en/pdf).
For testing if a substance exerts adverse effects on the developing brain without using whole animals, key neurodevelopmental processes known to be vital for healthy brain development are mimicked by assays in relevant test systems *in vitro*.
There are currently **biological gaps** in coverage of key neurodevelopmental processes in the DNT IVB that have been acknowledged, including

- assays for Neural Progenitor Cell (including radial glia) proliferation of different developmental stages
- Astrocyte development and function;
- Synaptogenesis (astroglia and microglia contribution, species)
- Myelination (astroglia and microglia contribution)
- Neural Network Formation (astroglia and microglia contribution, species);
- Microglia presence (microglia addition to existing test systems for synaptogenesis, neural network formation, myelination)

that produce uncertainty with regards to the biological applicability domain of the battery (Crofton and Mundy 2021 https://doi.org/10.2903/sp.efsa.2021.EN-6924). The hNPC model at our department aims to close the gaps in particular related to replacement of rat synaptogenesis in

the current DNT IVB with human based assay for synaptogenesis, and the role of astroglia and microglia cells for synaptogenesis in the EU funded projects PARC and ONTOX. Many countries world-wide, including several EU member states and EFSA as an EU agency as well as the US-EPA, have endorsed this activity and recognised its high priority.

5. Sources to corroborate the impact

Blum, J., S. Masjosthusmann, K. Bartmann, F. Bendt, X. Dolde, A. Dönmez, N. Förster, A. K. Holzer, U. Hübenthal, H. E. Keßel, S. Kilic, J. Klose, M. Pahl, L. C. Stürzl, I. Mangas, A. Terron, K. M. Crofton, M. Scholze, A. Mosig, M. Leist, and E. Fritsche (2022). Establishment of a human cell-based in vitro battery to assess developmental neurotoxicity hazard of chemicals, Chemosphere, 311: 137035.

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Davidsen, N., A. J. Lauvås, O. Myhre, E. Ropstad, D. Carpi, E. M. Gyves, H. F. Berntsen, H. Dirven, R. E. Paulsen, A. Bal-Price, and F. Pistollato (2021). Exposure to human relevant mixtures of halogenated persistent organic pollutants (POPs) alters neurodevelopmental processes in human neural stem cells undergoing differentiation. Reprod Toxicol, 100, 17-34.

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Lauvås, A. J., M. Lislien, J. A. Holme, H. Dirven, R. E. Paulsen, I. M. Alm, J. M. Andersen, E. Skarpen, V. Sørensen, P. Macko, F. Pistollato, N. Duale, and O. Myhre (2022). Developmental neurotoxicity of acrylamide and its metabolite glycidamide in a human mixed culture of neurons and astrocytes undergoing differentiation in concentrations relevant for human exposure, Neurotoxicology, 92, 33-48.

Masjosthusmann, S. et al (2020). Establishment of an a priori protocol for the implementation and interpretation of an in-vitro testing battery for the assessment of developmental neurotoxicity. EFSA Supporting Publications 17, 1938E, 1-152.

Myhre O, Låg M, Villanger G, Oftedal B, Øvrevik J, Aase H, Paulsen RE, Bal-Price A, Dirven H (2018). Early life exposure to air pollution particulate matter (PM) as risk factor for attention deficit/hyperactivity disorder (ADHD): Need for novel strategies for mechanisms and causalities. Toxicology and Applied Pharmacology 354, 196-214.

Pistollato, F., D. Canovas-Jorda, D. Zagoura, and A. Price (2017). Protocol for the Differentiation of Human Induced Pluripotent Stem Cells into Mixed Cultures of Neurons and Glia for Neurotoxicity Testing, J Vis Exp DOI: 10.3791/55702.

[FHI, KM] [2]

Institution: Norwegian Institute of Public Health (FHI/NIPH)
Administrative unit: Division of Climate and Environmental Health
Title of case study: Improved knowledge of health effects of low levels of air pollution and its contribution to guidelines and regulations
Period when the underpinning research was undertaken: 2012 - 2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2012-2022
Period when the impact occurred: 2012-2022

3. Summary of the impact

Air pollution is the number one environmental contributor to the burden of disease in Europe, and the fourth most important risk factor for premature death and disability worldwide according to the Global Burden of Disease Study 2019. Combining epidemiology and experimental research, our department contributes to a mechanistic and holistic understanding of the impact of air pollution on health. Our research has helped elucidating the main contributors and the mode of action for the health effects observed, as well as contributed new knowledge about health impacts of low levels of air pollution, ultimately underpinning changed air quality recommendations both nationally and internationally. Our research within this field has had an impact on national and international advisory and policy making to improve public health. More specifically, our research has contributed to newly updated air quality criteria in Norway.

2. Underpinning research

The research and knowledge of health effects of air pollution is based on both epidemiological and experimental studies. In our department we have both types of expertise. The department conducted large scale epidemiological studies in collaboration with leading research centers in Europe, and provided data, verified data, conducted statistical analysis, contributed to scientific discussions and critical review of manuscripts. Prior to the EU funded ESCAPE (European Study of Cohorts of Air pollution Effects) project, most studies providing evidence on exposure – response relationships were from North America. ESCAPE used refined assessments of residential long-term air pollution exposure linked to data from European cohorts and contributed new knowledge on exposure – response relationships and thresholds for health impacts. Our department provided data from the HUBRO cohort, contributing to the lowest exposure levels of air pollution. Although there were indications of adverse health effects below existing recommended limits in previous studies, knowledge of effects including the shape of exposure-response association at low exposure levels was still limited and uncertain. Studies were generally lacking sufficient data at the lower end of the exposure continuum. Further building on ESCAPE, ELAPSE (Effects of Low-level Air Pollution: A Study in Europe) aimed at contributing new knowledge of health effects at low levels of air pollution. Since Norway has low air pollution levels compared to most other countries, the department's contributions were crucial. The department established a national administrative cohort, NORCOHORT, composed of extensive registry data linked with improved air pollution exposures calculated for the individual home addresses of 2.6 million Norwegian citizens. Statistical analyses including adjustment for age, sex, and both individual and area level of socioeconomic factors provided exposure – response relationships showing health impacts below existing air pollution guidelines and limits. Results from several administrative cohorts across Europe were combined by means of meta-analysis, producing final results showing increased risk of mortality even at low levels of air pollution.

Since epidemiological studies show associations between air pollution and health effects, experimental studies have been used to support a possible causal relationship. To approach this challenge, our department explored the mechanisms of different air pollutants to study which of the components are the most critical. We have received three projects from the Norwegian

Research Council and one EU-project to elucidate this. The projects have mainly been focusing on PM (particulate matter) and the different chemical components attached, in addition to the relative contribution of different PM-sources and its impact on health. We have used animal- and clinical studies, but mostly cell models in monocultures and in advanced co-cultures exposed to different air pollutants. The mutual interactions between respiratory (epithelial and macrophages) and cardiovascular cells (endothelial, cardiomyocytes and fibroblasts) have been examined, with emphasis on cytotoxicity, inflammatory responses, cellular receptors and inter- and intracellular mediators involved.

We have studied the role of different particle sizes, traffic-related sources (exhaust particles and road abrasion particles), wood combustion particles and also several nanoparticles (NPs) as models for ultrafine particles. In particular, silica NPs and crystalline silica particles were compared, and cellular signaling pathways like involvement of inflammasome activation have been demonstrated. In addition, inflammatory processes induced by the PM-components like different minerals, metals, polycyclic aromatic hydrocarbons (PAH) and endotoxins have been studied regarding reactive oxygen species (ROS), CYP-enzymes and aryl hydrocarbon receptor (AhR) linked-mechanisms. Furthermore, effects of PM on other secondary organs than the cardiovascular system like nervous system, blood cells and liver have also been explored. A benefit was to develop advanced culture models to examine different air pollutants to complement and replace animal studies.

The breadth of research in the department with both epidemiological and experimental expertise is important for elucidating health effects of air pollution. Such knowledge and studies will complement each other with regard to dose-response relationships, causality and point out important sources and components inducing health effects.

The underpinning research was carried out throughout the whole evaluation period. Research output was numerous peer reviewed papers, news letters, and in communication in advisory work. The impact was a continuous process over the period, finally leading to the last revision of the Air Quality Criteria, starting 2022 and finalized 2023.

Per Everhard Schwarze, Department director, from 2015 to 2017
Bente Margaret Oftedal, Scientist (2012-2014) Senior Scientist (2014-)
Marit Låg, Senior Scientist (2012-)
Johan Øvrevik Scientist (2012-2013), Senior Scientist (2013-2016), Department Director (2017-2021)
Magne Refsnes, Senior Scientist (2012-2022)
Vegard Grytting Sæter, PhD (2017-2021), Scientist (2021-2022) Post doc (2022-)
Jørn Holme, Senior Scientist (2012 -2022)

4. References to the research

1. Author(s): Stafoggia M, **Oftedal B,** Chen J, Rodopoulou S, Renzi M, Atkinson RW et al.
- Title: Long-term exposure to low ambient air pollution concentrations and mortality among 28 million people: results from seven large European cohorts within the ELAPSE project
- Year of publication: 2022
- Lancet Planetary health, 6: e9-18. DOI: https://doi.org/10.1016/S2542-5196(21)00277-1

Evidence about the quality of the research: This paper was awarded the prize for "Best Environmental Epidemiology Paper (BEEP) published in 2022 at the ISEE (International Society for Environmental Epidemiology) conference the following year, with this rationale according to the Awards committee: "*The article makes an outstanding contribution to the knowledge of environmental epidemiology and was selected because of its quality, originality, importance and*

expected impact, particularly through its novel application of methodology."
(https://iseepi.org/beep.php)
Citations: 140
2. Author(s): Sophia Rodopoulou, Massimo Stafoggia, Jie Chen, Kees de Hoogh, Mariska Bauwelinck, Amar J. Mehta, Jochem O. Klompmaker, **Bente Oftedal** et al.
- Title: Long-term exposure to fine particle elemental components and mortality in Europe: Results from six European administrative cohorts within the ELAPSE project
- Year of publication: 2022
- Sci Total Environ 2022 Feb 25:809:152205. DOI: 10.1016/j.scitotenv.2021.152205.
Citations: 12
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- Title: Effects of long-term exposure to air pollution on natural-cause mortality: an analysis of 22 European cohorts within the multicentre ESCAPE project
- Year of publication: 2014
- Lancet 2014 Mar 1;383(9919):785-95. DOI:10.1016/S0140-6736(13)62158-3.
Citations: 1476
4. Authors: **Øvrevik J, Refsnes M, Låg M, Holme JA, Schwarze PE**.
-Title: Activation of Proinflammatory Responses in Cells of the Airway Mucosa by Particulate Matter: Oxidant- and Non-Oxidant-Mediated Triggering Mechanisms. Review
-Year of publication: 2015
- Journal: Biomolecules 5, Jul 2; 5 (3):1399-440
Citations: 221
5. Authors: **Låg M**, **Øvrevik J**, **Refsnes M**, **Holme JA.**
- Title: Potential role of polycyclic aromatic hydrocarbons in air pollution-induced non-malignant respiratory diseases Review
-Year of publication: 2020
-Journal: Respir Res.Nov 13;21(1):299. doi: 10.1186/s12931-020-01563-1.
-*Citations: 107*
6. Authors: **Skuland T, Låg M**, Gutleb AC, **Brinchmann BC**, Serchi T, **Øvrevik J, Holme JA, Refsnes M**
-Title: (2020). Pro-inflammatory effects of crystalline- and nano-sized non-crystalline silica particles in a 3D alveolar model.
-Year of publication: 2020
-Journal: Part Fibre Toxicol. Apr 21;17(1):13.
-*Citations: 42*

4. Details of the impact

Air pollution is a major threat to global health and prosperity, responsible for more than 6.5 million deaths each year globally (The Lancet Planetary Health, 2022). Air pollution can affect lung development and is implicated in the development of emphysema, asthma, and other respiratory diseases, such as chronic obstructive pulmonary disease (COPD). Increases in asthma prevalence and severity are linked to urbanization and outdoor air pollution. Other health effects from air pollution have been described such as cardiovascular diseases, diabetes, adverse birth outcomes and possibly neurological defects such as dementia and disturbed neurodevelopment in children.

Studying the health effects of air pollution in Norway and the Nordic countries has been an important contribution to help us understanding the impact on health even at low concentrations. These epidemiological studies together with experimental studies also help us identifying the different emission sources and chemical components of particulate matter, which pollutants are most harmful and develop strategies to reduce exposure to these harmful components. Norway

and Nordic countries have different emission sources of air pollution in different seasons of the year. The winter season contributes to high levels of particulate matter (PM10) from the use of spiked tires on icy roads and high levels of PM 2,5 from wood burning. Moreover, high air pollution levels can be measured in the cities with temperature inversions during cold temperature shifts. For the planning of healthy urban environments and the best measures, it is important to understand how other outdoor exposures possibly interact with and influence effects of air pollution. The department has expertise on all major outdoor exposures, and data on both noise and surrounding greenness are included in all recent studies (e.g. ELAPSE). The department's holistic research approach contributes to a broader understanding and improved knowledge of the health burden ascribed to air pollution and the most harmful components. Over the last years, the department has studied surrounding greenness, nature-based solutions and urbanisation (HELIX, Athlete, ELAPSE) and how climate change with emphasis on extreme temperatures may impact both exposure and vulnerability to air pollution (EXHAUSTION).

With this holistic view, we give knowledge-based advice to authorities and contribute to air quality criteria/guidelines and limit values, impacting policy regulations. Through international collaborating projects like ESCAPE and ELAPSE, our research has contributed with critical data and analyses to improve concentration response functions (CRFs) for low-level air pollution and health. The ELAPSE CRFs was used by the European Commission and contributed towards the EU Parliament voting for stricter regulation of air quality fully aligning with the WHO Air Quality Guidelines by 2035. The justifications for the WHO Air Quality Guidelines 2021 have been critically evaluated by our team and taking into account our own and others research from Norway and Nordic countries (ELAPSE, NordicWelfAir). In evaluating Norwegian requirements, we have in close collaboration with the Environmental Directorate published the Air Quality Criteria for Norway. Norwegian air quality criteria were revised in 2013, 2016, 2020 and during 2022 until 2023. The last ten years, these guidelines have been using Norwegian and Nordic cohort data. The criteria are regularly updated based on the departments' research and knowledge (see ref 5). These criteria are used as national targets for reduction of air pollution. Furthermore, the guidelines are used in forecasting by the Norwegian Meteorological Institute (YR.no, https://www.yr.no/en/other-conditions/1-72837/Norway/Oslo/Oslo/Oslo), and Air Quality in Norway (https://luftkvalitet.miljodirektoratet.no/) to classify air pollution levels of different components according to risk of possible health hazard. Vulnerable groups are specified in the health recommendations. In addition, the air quality criteria are used in Planning Guidelines for the municipalities' Agency for Planning and Building Services. In the revision of the Norwegian limit values for particular matter (PM10 and PM2.5), burden of disease and cost estimated by our department together with the cost of the measures were included in a cost-benefit analysis. A socioeconomic gain favored the restriction of the legally binding national limit values for both PM10 and PM2.5 in 2022.

Through regular meeting seminars called "Luftsamarbeidet" ["Air quality cooperation"] with the Environmental Directorate, Health Directorate, Norwegian Public Roads Administration and The Norwegian Meteorological Institute, held at different levels of authority (from researchers and advisors to senior management) we discuss and agree on efficient regulations and measures to bring forward to the ministry, and ways of communicating to the public on air quality and possible health impact. The aim is to take care of life, health, and environment through reducing emissions to the air and exposure to local air pollution. A report of the work accomplished is published yearly. This cooperation between important actors in knowledge and regulation of air pollution has been important for the large reduction of air pollution levels observed in Norway during the last 10-15 years (https://miljostatus.miljodirektoratet.no/tema/forurensning/lokal-luftforurensning/)

IMPACT of the research: The revision and restriction of important Air Quality Criteria (PM2,5 and NO_2) that are used as national targets for reduction of air pollution, in the health recommendation in forecasting of air pollution and in area planning.

5. Sources to corroborate the impact

1. Fuller et al. Pollution and health: a progress update. The Lancet Planetary Health 2022 June; 6(6):e535-e547. DOI: https://doi.org/10.1016/S2542-5196(22)00090-0.(https://www.thelancet.com/journals/lanplh/article/PIIS2542-5196(22)00090-0/fulltext)
2. Wolf K, Hoffmann B, Andersen ZJ, Atkinson RW, Bauwelinck M, Bellander T ::: **Oftedal B**, ::: Schwarze P, :::, Ljungman PLS. Long-term exposure to low-level ambient air pollution and incidence of stroke and coronary heart disease: a pooled analysis of six European cohorts within the ELAPSE project. Lancet Plan Health 2021;5:e620-32. https://www.thelancet.com/action/showPdf?pii=S2542-5196%2821%2900195-9
3.
4. About the EXHAUSTION project, examining air pollution in the context of climate change: https://www.exhaustion.eu/
5. Berit Granum, **Bente Oftedal**, Lydiane Agier, Valerie Siroux, Philippa Bird, Maribel Casas, Charline Warembourg ::: Martine Vrijheid. Multiple environmental exposures in early-life and allergy-related outcomes in childhood. Eviron Int 2020 Nov; 144:106038. DOI: 10.1016/j.envint.2020.106038. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8768577/
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[FHI, KM] [3]

Institution: Norwegian Institute of Public Health (FHI/NIPH)
Administrative unit: Division of Climate and Environmental Health
Title of case study: PFAS – from research to regulation
Period when the underpinning research was undertaken: 2009-2017
Period when staff involved in the underpinning research were employed by the submitting institution: 1995-present
Period when the impact occurred: 2018-2022

5. Summary of the impact

PFAS, "forever chemicals", are prevalent in the environment and a human health concern. The Division has led PFAS research for over 15 years. Our multidisciplinary approach: identifying exposure sources, assessing PFAS levels and the association between exposure and health, and *in vitro* experiments to find mechanisms of action and support causality. We contributed to European impact through research findings and involvement of our experts in EFSA risk assessments, resulting in tolerable weekly intakes, food and drinking water legal limits and EU bans on some PFAS. Global impact is supporting evidence for the Stockholm Convention on PFAS.

2. Underpinning research

Per- and Polyfluoroalkyl Substances (PFAS), are used in consumer products for their water/grease-resistant properties. These "forever chemicals" persist in the environment and living organisms, raising health concerns. Before 2010, in Europe, restrictions were focused on the most prevalent PFAS – PFOS, regulating manufacture and use, with little attention to human exposure. The Division discovered key insights allowing a more accurate assessment of PFAS exposure and health effects.

Exposure

Although PFAS was widely detected in the environment and wildlife, prior to Haug et al. (2010, 2011) human exposure sources were not well described.

Food, particularly seafood, is an important source of PFAS (Haug et al. 2010). Seafood was identified as a significant dietary source by comparing food frequency questionnaire data and PFAS food level databases to individuals' blood levels. ***However, there are multiple pathways including house dust*** (Haug et al. 2011). In 2011, the group estimated PFAS intake from various sources, including dust, in the individual's environment and compared these to their blood levels, highlighting the indoor environment as another key exposure source.

Poothong et al. (2017) determined 25 PFAS in blood and described for the first time in so many PFAS how these partition into the different matrices ("parts") of blood. A new insight was also that some PFAS are in the red blood cell part, and not just the serum/plasma ("liquid" part). This provided conversion factors, important for comparing data from different studies.

Pregnant women and their young children

While previous studies focussed on adults, Haug et al (2011), Brantsæter et al. (2013), Gützkow et al. (2012), and Papadopoulou et al. (2016) provided new data on the vulnerable subpopulations of pregnant women and children.

Maternal concentrations of PFAS are most influenced by pregnancy and lactation *(Brantsæter et al. 2013).* Mothers who had previously given birth had lower concentrations of various PFAS compared to first time mothers. Breastfeeding was linked to reduced PFAS levels, and time since the last pregnancy with increased levels. This demonstrated for the first time that PFOA bioaccumulates in humans.

PFAS are differentially transferred from mother to child during pregnancy *(Gützkow et al. 2012).* Several PFAS were detected in both maternal and cord blood, showing a correlation between them. The levels in cord blood were 30% to 79% of the maternal levels, indicating placental transfer.

Breast milk is the most important source of PFAS for breastfed infants, although breast milk concentrations are a fraction of maternal blood concentrations *(Haug et al. 2011*). ***By the age of 3 years, 98% of toddlers had higher levels of PFAS than their mothers*** *(Papadopoulou et el. 2016).* Every month of breastfeeding was associated with a 4 % increase in toddlers.

Health effects

The Division's research on PFAS health effects is extensive, with study of immune response having the most impact.

Increased exposure to PFAS leads to lower vaccine response (Granum et al. 2013). Higher maternal levels of two PFAS were negatively associated with infant's rubella antibody response at 15 months. This suggested an impact of PFAS on the immune response in children post-vaccination even at low levels.

Three of these studies used data from the Norwegian Mother, Father and Child Cohort Study (MoBa).

Research projects: BROFLEX, A-TEAM, MoBa-substudies
Research carried out: 2009-2017
Key researchers, position (years in the Division):
Anne Lise Brantsæter, PhD student (2002-2007), Postdoc (2007-2009), Scientist (2009-2012), Senior Scientist (2012—)
G Brunborg, Department of Chemicals and Radiation, Director (2010-2015)

Berit Granum, PhD student (1996-2000), Postdoctoral fellow (2000-2005), Scientist (2005-2011), Senior Scientist (2011—)
Kristine B Gützkow, Postdoc (2007-2010), Scientist (2010-2015), Senior scientist (2016-2021) Department director (2021—)
Line S. Haug, PhD student (2007-2011), Scientist (2011-2013), Senior Scientist (2013—)
Helle K. Knutsen, PhD student (1989-1995), Postdoc (1996-1999), Senior Scientist (1999-)
Unni C Nygaard, PhD student (1999-2005), Scientist (2005-2011), Senior Scientist (2011-2020)
Eleni Papadopoulou, postdoc (2013-2016)
Somrutai Poothong, PhD student (2013-2018), Engineer (2018-2019)
Azemira Sabaredzovic, Engineer (2009-2013), Over Engineer(2013-2017), Senior Engineer(2017-)
Cathrine Thomsen, PhD student (1997-2002), Postdoctoral fellow (2002-2004), Scientist (2004-2007), Senior Scientist (2007-2014), Department Director (2014—)

3. References to the research (indicative maximum of six references)

Authors: **Brantsaeter AL**, Whitworth KW, Ydersbond TA, **Haug LS**, **Haugen M**, **Knutsen HK**, **Thomsen C**, **Meltzer HM**, **Becher G**, **Sabaredzovic A**, Hoppin JA, Eggesbø M and Longnecker MP
Title: Determinants of plasma concentrations of perfluoroalkyl substances in pregnant Norwegian women
Year: 2013
Journal: Environment International, 54, 74–84
https://doi.org/10.1016/j.envint.2012.12.014 *146 Citations*
Authors: **Haug LS**, **Thomsen C**, **Brantsaeter AL**, **Kvalem HE**, **Haugen M**, **Becher G**, **Alexander J**, **Meltzer HM** and **Knutsen HK**
Title: Diet and particularly seafood are major sources of perfluorinated compounds in humans
Year: 2010

Journal: Environment International, 36, 772–778
https://doi.org/10.1016/j.envint.2010.05.016 *244 Citations*
Authors: **Haug LS**, Huber S, **Becher G** and **Thomsen C**
Title: Characterisation of human exposure pathways to perfluorinated compounds — Comparing exposure estimates with biomarkers of exposure
Year: 2011
Journal: Environment International, 37, 687–693
https://doi.org/10.1016/j.envint.2011.01.011 *274 Citations*
Authors: **Granum B**, **Haug LS**, **Namork E**, **Stølevik SB**, **Thomsen C**, Aaberge IS, van Loveren H, **Løvik M** and **Nygaard UC**
Title: Pre-natal exposure to perfluoroalkyl substances may be associated with altered vaccine antibody levels and immune-related health outcomes in early childhood
Year: 2013
Journal: Journal of Immunotoxicology, 10, 373–379
https://doi.org/10.3109/1547691X.2012.755580 *203 Citations*
Authors: **Gützkow KB**, **Haug LS**, **Thomsen C**, **Sabaredzovic A**, **Becher G** and **Brunborg G**
Title: Placental transfer of perfluorinated compounds is selective – A Norwegian Mother and Child sub-cohort study
Year: 2012
Journal: International Journal of Hygiene and Environmental Health, 215, 216–219
https://doi.org/10.1016/j.ijheh.2011.08.011 *152 Citations*
Authors: **Papadopoulou E**, **Sabaredzovic A**, **Namork E**, **Nygaard UC**, **Granum B** and **Haug LS**
Title: Exposure of Norwegian toddlers to perfluoroalkyl substances (PFAS): the association with breastfeeding and maternal PFAS concentrations
Year: 2016
Journal: Environment International, 94, 687–694
https://doi.org/10.1016/j.envint.2016.07.006 *62 Citations*
Authors: **Poothong S**, **Thomsen C**, **Padilla-Sanchez JA**, **Papadopoulou E** and **Haug LS**
Title: Distribution of Novel and Well-Known Poly- and Perfluoroalkyl Substances (PFASs) in Human Serum, Plasma, and Whole Blood
Year: 2017
Journal: Environmental Science & Technology, 51, 13388–13396
https://doi.org/10.1021/acs.est.7b03299 *106 Citations*

4. Details of the impact (indicative maximum 750 words)

Impact 1: Tolerable weekly intakes (TWIs) for PFAS
→Drinking water limits for PFAS
→Maximum levels of PFAS in certain food stuffs
Beneficiaries: General population of Europe, pregnant women, infants
Dates: 2018 (TWIs PFOA and PFOS), 2020 (TWIs sum four PFAS), 2021 (drinking water limits), 2022 (maximum levels in certain food).

The European Food Safety Agency (EFSA) sets safety thresholds to improve food safety by conducting risk assessments to set TWIs for chemicals in food. A substantial part of the European population exceeded the TWIs for PFAS, so the European Commission acted to reduce exposure in food and water. The Drinking Water Directive took effect on 16 January 2021 and included a limit for all PFAS. The Maximum levels of PFAS in certain food stuffs took effect on 7 December 2022.

Process

The research above is highly cited and disseminated widely in reputable journals, at conferences, and directly for national authorities including the Norwegian Food Safety Authority. In addition, individual researchers, Dr Line S. Haug and Dr Helle K. Knutsen are recognised PFAS experts. Dr Knutsen was the chair of the CONTAM Panel at EFSA, 2015—2018. Dr Haug was a member of the

EFSA working group on PFAS under the CONTAM Panel that assessed research, performed the risk assessment, and developed the Scientific Opinions. The research described above in Section 1 (except Poothong et al. 2017), were included in the evaluation of PFOA and PFOS, contributing to setting TWIs (EFSA 2018). Fish and seafood were highlighted as key exposure sources and a decreased immune response as a critical effect for children. This research documented that levels in Norway were comparable to the levels in Europe, and that for a considerable proportion of the population exposure exceeds the TWIs.

Between 2018 and 2020, EFSA extended the PFAS evaluation, including PFNA and PFHxS in a new TWI for the sum of four PFAS (EFSA 2020). Dr Haug and Dr Knutsen were members of the EFSA working group and all above research contributed to the assessment and Scientific Opinion. In addition, original data from Granum et al. (2013) was included in the benchmark dose modelling for setting the TWI. EFSA emphasised that toddlers and other children are the most exposed population groups, and exposure during pregnancy and breastfeeding is the main contributor to PFAS in infants (Haug et al. 2011, Brantsæter et al. 2013, Gützkow et al. 2012, Papadopolou et al. 2016).

In all risk assessments, many sources of data are assessed, however, research described here were novel findings and important for the assessment. The Scientific Opinions were the direct driver for risk management and stricter regulation of PFAS in food and drinking water.

Impact 2: Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH)
→The European Commission set a ban for use of long-chain PFCAs, PFOA and PFHxS
Beneficiaries: General population of Europe
Dates: 2020 (PFOA), 2021 (long-chain PFCAs), 2022 (PFHxS)
Process

Dr Haug and Dr Kristine Gützkow contributed to the PFOA restriction proposal, which came from Norway (Norwegian Environment Agency) and Germany. They developed the background document on human health, with Brantsæter et al. (2013) key in showing that PFOA bioaccumulates in humans.

Some research was included in the documentation for the ban for use of long-chain PFCAs: breast milk as the main source for infants (Haug et al., 2011), and monitoring and trend data (Haug et al. 2011), and human biomonitoring data (Papadopoulou et al. 2016).

Norway drafted the PFHxS restriction proposal. Dr Haug quality assured the text on human exposure. Supporting documents referred to breastmilk as an important exposure pathway to PFHxS for infants (Brantsæter et al. 2013), the importance of the indoor environment for exposure (Haug et al. 2011) and included data on cord blood levels (Gützkow et al. 2012).

The impact continues with a restriction on all PFAS in Europe expected in 2025 (ECHA, 2024).

Impact 3: Stockholm Convention on POPs – PFOA and PFHxS
→Global regulation/restrictions for use of PFOA and PFHxS
Beneficiaries: Global
Dates: 2019 (PFOA), 2022 (PFHxS)
Process

PFOA and PFHxS were proposed for inclusion in the Stockholm Convention on POPs. Background documents highlighted the role of indoor environment (Haug et al., 2011), PFOA bioaccumulation and breastfeeding as an important pathway (Brantsæter et al. 2013), levels increase with age and diet is the most important source (Haug et al. 2010, 2011). For PFHxS, Brantsæter et al. 2013, Granum et al. (2013), Gützkow et al (2012) were all cited.

The PFAS case illustrates the synergy between research and advisory roles in public health prevention.

5. Sources to corroborate the impact (indicative maximum of ten references)

Impact 1: Tolerable Weekly Intakes for PFAS

First PFOA and PFOS TWI, 2018

Authors: EFSA Panel on Contaminants in the Food Chain (CONTAM), **Knutsen HK**, Alexander J, Barregård L, Bignami M, Brüschweiler B, Ceccatelli S, Cottrill B, Dinovi M, Edler L, Grasl-Kraupp B, Hogstrand C, Hoogenboom LR, Nebbia CS, Oswald IP, Petersen A, Rose M,
Roudot AC, Vleminckx C,Vollmer G, Wallace H, Bodin L, Cravedi JP, Halldorsson TI, **Haug LS**, Johansson N, Loveren Hv, Gergelova P, Mackay K, Levorato S, Manen Mv, Schwerdtle T.
Risk to human health related to the presence of perfluorooctane sulfonic acid and perfluorooctanoic acid in food. 2018. EFSA Journal https://efsa.onlinelibrary.wiley.com/doi/full/10.2903/j.efsa.2018.5194

Second PFAS TWI, 2020

Authors: EFSA Panel on Contaminants in the Food Chain (EFSA CONTAM Panel); Schrenk D, Bignami M, Bodin L, Chipman JK, Del Mazo J, Grasl-Kraupp B, Hogstrand C, Hoogenboom LR, Leblanc JC, Nebbia CS, Nielsen E, Ntzani E, Petersen A, Sand S, Vleminckx C, Wallace H, Barregård L, Ceccatelli S, Cravedi JP, Halldorsson TI, **Haug LS**, Johansson N, **Knutsen HK**, Rose M, Roudot AC, Van Loveren H, Vollmer G, Mackay K, Riolo F, and Schwerdtle T. Risk to human health related to the presence of perfluoroalkyl substances in food. 2020. EFSA Journal https://efsa.onlinelibrary.wiley.com/doi/full/10.2903/j.efsa.2020.6223
p.346 K.2. Benchmark dose modelling: Vaccination response: "Data on rubella are from the study by Granum et al. (2013) and obtained from the authors. Analysis performed by the CONTAM Panel."
Press release: EFSA News, 17 Sept 2020. PFAS in food: EFSA assesses risks and sets tolerable intake.
https://www.efsa.europa.eu/en/news/pfas-food-efsa-assesses-risks-and-sets-tolerable-intake

Drinking Water Directive

DIRECTIVE (EU) 2020/2184 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 December 2020 on the quality of water intended for human consumption.
https://eur-lex.europa.eu/eli/dir/2020/2184/oj
COMMISSION REGULATION (EU) 2022/2388 of 7 December 2022 amending Regulation (EC) No 1881/2006 as regards **maximum levels of perfluoroalkyl substances in certain foodstuffs**
https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32022R2388

Impact 2: Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH)

PFOA

ECHA, 2018. Committee for Risk Assessment (RAC), Committee for Socio-economic Analysis (SEAC) Background document to the Opinion on the Annex XV dossier proposing restrictions on Perfluorooctanoic acid (PFOA), PFOA salts and PFOA-related substances
https://echa.europa.eu/documents/10162/e40425c6-590f-8df7-2cd9-0eef79527685

PFHxS

ECHA, 2020. Committee for Risk Assessment (RAC), Committee for Socio-economic Analysis (SEAC) Background document to the Opinion on the Annex XV dossier proposing restrictions on perfluorohexane sulfonic acid (PFHxS), its salts and PFHxS-related substances
https://echa.europa.eu/documents/10162/4e84f904-7cd7-9be6-dd9b-2cc711c0859b

Long Chain PFCAs

ECHA, 2018. Committee for Risk Assessment (RAC) Committee for Socio-economic Analysis (SEAC) Background document to the Opinion on the Annex XV dossier proposing restrictions on C9-C14 PFCAs including their salts and precursors
https://echa.europa.eu/documents/10162/02d5672d-9123-8a8c-5898-ac68f81e5a72

All PFAS restriction

ECHA, 2024. Registry of restriction intentions until outcome
https://echa.europa.eu/registry-of-restriction-intentions/-/dislist/details/0b0236e18663449b

Impact 3: Stockholm Convention on POPs (PFAS)

PFOA https://www.pops.int/Implementation/IndustrialPOPs/PFAS/Overview/tabid/5221/Default.aspx
Document name: UNEP/POPS/POPRC.12/11/Add.2: Risk profile for PFOA, its salts and PFOA-related compounds (opens as pdf)

PFHxS https://chm.pops.int/Implementation/IndustrialPOPs/PFAS/Overview/tabid/5221/Default.aspx
Document name: UNEP/POPS/POPRC.14/6/Add.1: Risk profile for PFHxS, its salts and PFHxS-related compounds (opens as pdf)

Norwegian Institute of Public Health, Division for Health Services: Impact case 1

Institution: Norwegian Institute of Public Health
Administrative unit: Division of Health Services
Title of case study: Informed health choices by individuals, professionals, and policy makers.
Period when the underpinning research was undertaken: 2012-2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2012-2022
Period when the impact occurred: 2014-2022

1. Summary of the impact

We have developed, evaluated, and disseminated:

- EDUCATIONAL RESOURCES EDUCATIONAL RESOURCES to teach people how to assess health claims.

- TOOLS TO IMPROVE THE USE OF RESEARCH EVIDENCE in guideline development and policy decisions:
  - Evidence to Decision-frameworks that facilitate structured and transparent decision making.
  - Approachhttps://www.cerqual.org/ for assessing confidence in findings from qualitative research and using that evidence to inform decisions.

This research has improved the use of research evidence in healthcare decisions.

2. Underpinning research

EDUCATIONAL RESOURCES

In a project funded by the Research Council of Norway from 2013-2018 (Supporting informed healthcare choices in low-income countries), we collaborated with colleagues in Uganda, Rwanda, and Kenya and other members of the Informed Health Choices network to develop and evaluate tools for teaching primary school pupils and their parents how to critically assess health claims. The project resulted in widely disseminated educational resources. The resources were developed through extensive user testing employing human-centred design. They included a cartoon book story about 12 key concepts (principles) for deciding what to believe and what to do for our health. The resources were evaluated in a cluster-randomized trial and a parallel process evaluation. We found that the educational resources were highly effective in improving the children's ability to assess health claims. A podcast for parents was also shown to be effective. (Researchers: Andy Oxman, Astrid Dahlgren, Sarah Rosenbaum, Simon Lewin, Jenny Moberg, Matt Oxman, Atle Fretheim)

TOOLS TO IMPROVE THE USE OF RESEARCH EVIDENCE

We initiated the GRADE Working group in 2000. Together with other members of the group, we led the development and evaluation of Evidence to Decision-frameworks. This work included consultation with stakeholders, an international survey of policy makers, workshops, and user testing. The frameworks provide a structured and transparent approach to support policy making informed by the best available research evidence, while making the basis for decisions accessible to those whom they will affect. This work was funded in part by the EU from 2011-15. (Researchers: Andy Oxman, Signe Flottorp, Claire Glenton, Simon Lewin, Sarah Rosenbaum, Jenny Moberg).

We also led the development and evaluation of GRADE-CerQual for assessing confidence in qualitative evidence and using qualitative evidence to inform decisions. This work took place between 2012 to 2022. We employed a pragmatic and iterative approach that included talking to experts in the field of qualitative evidence synthesis, developing consensus through multiple face-to-face meetings and teleconferences, and seeking feedback from ongoing engagement with the qualitative evidence synthesis community and organisations that commission, produce, or use systematic reviews. (Researchers: Simon Lewin, Claire Glenton, Heather Munthe-Kaas).

Key researchers involved in the research underpinning the impact case:

- Andy Oxman, Senior Researcher
- Simon Lewin, Senior Researcher
- Claire Glenton, Senior Researcher (until 2022)
- Heather Munthe-Kaas, Researcher
- Sarah Rosenbaum, Senior Researcher
- Signe Flottorp, Senior Researcher
- Astrid Dahlgren, Researcher (until 2018)
- Jenny Moberg, Researcher
- Matt Oxman, Researcher/PhD-student (2016–)
- Atle Fretheim, Senior Researcher (Head of Unit)

3. References to the research

1. Nsangi A, Semakula D, Oxman AD, Austvoll-Dahlgren A, Oxman M, Rosenbaum S, Morelli A, Glenton C, Lewin S, Kaseje M, Chalmers I, Fretheim A, Ding Y, Sewankambo NK. Effects of the Informed Health Choices primary school intervention on the ability of children in Uganda to assess the reliability of claims about treatment effects: a cluster-randomised controlled trial. ***Lancet***. 2017 Jul 22;390(10092):374-388. doi: 10.1016/S0140-6736(17)31226-6.
2. Semakula D, Nsangi A, Oxman AD, Oxman M, Austvoll-Dahlgren A, Rosenbaum S, Morelli A, Glenton C, Lewin S, Kaseje M, Chalmers I, Fretheim A, Kristoffersen DT, Sewankambo NK. Effects of the Informed Health Choices podcast on the ability of parents of primary school children in Uganda to assess claims about treatment effects: a randomised controlled trial. ***Lancet***. 2017;390(10092):389-98. doi: 10.1016/s0140-6736(17)31225-4
3. Oxman AD, Aronson JK, Barends E, Boruch R, Brennan M, Chalmers I, Chislett J, Cunliffe-Jones P, Dahlgren A, Gaarder M, Haines A, Heneghan C, Matthews R, Maynard B, , Oxman M, Pullin A, Randall N, Roddam H, Schoonees A, Sharples J, Stewart R, Stott J, Tallis R, Thomas N, Vale L. Key concepts for making informed choices. ***Nature***. 2019;572(7769):303-6. doi: 10.1038/d41586-019-02407-9.

4. Rosenbaum SE, Moberg J, Glenton C, Schunemann HJ, Lewin S, Akl E, et al. Developing Evidence to Decision frameworks and an Interactive Evidence to Decision tool for making and using decisions and recommendations in health care. ***Glob Chall***. 2018;2(9):1700081. doi: 10.1002/gch2.201700081.
5. Lewin S, Glenton C, Munthe-Kaas H, Carlsen B, Colvin CJ, Gülmezoglu M, Noyes J, Booth A, Garside R, Rashidian A. Using qualitative evidence in decision making for health and social interventions: an approach to assess confidence in findings from qualitative evidence syntheses (GRADE-CERQual). ***PLoS Med***. 2015 Oct 27;12(10):e1001895. doi: 10.1371/journal.pmed.1001895.
6. Lewin S, Glenton C. Are we entering a new era for qualitative research? Using qualitative evidence to support guidance and guideline development by the World Health Organization. ***Int J Equity Health***. 2018 Sep 24;17(1):126. doi: 10.1186/s12939-018-0841-x.

4. Details of the impact

EDUCATIONAL RESOURCES

The primary school resources that we developed enabled children, teachers, and parents to think critically about health choices, as documented by a randomized trial with over 10,000 pupils (published in 2017), a process evaluation (published in 2019), and a one-year follow-up study (published in 2020). The process evaluation found that teachers, children, their parents, and education authorities liked the educational resources and felt that the content was important. This and the children's enthusiasm motivated the teachers. Nearly everyone interviewed thought that the children learnt something important and many thought that it improved their decision-making. The follow-up study found that children retained what they learned for at least one year. These resources were the first of their kind and received substantial media attention. This included, for example, a BBC documentary. The resources have been translated to 14 languages and adapted versions have been (or are being) introduced and tested in schools in other countries between 2017 and 2022. The Informed Health Choices (IHC) Network, which grew out of this work, includes people from 26 countries who are developing, evaluating, or contextualising educational resources for thinking critically about health choices.

We developed an item bank of multiple-choice questions that assess an individual's ability to think critically about health choices and used that as the basis for developing and evaluating the outcome measure used in randomized trials of the primary school resources and the podcast for parents. Questions from the item bank have been used to develop other evaluation tools and have also been translated to other languages.

The IHC Key Concepts serve as the basis for developing educational resources. The concepts are principles for deciding what to believe and what to do for our health. They help people to recognise unreliable claims, recognise reliable evidence, and make well-informed choices. Our research has inspired colleagues in agriculture, education, environmental policy, international development, management, nutrition, policing, social welfare, veterinary medicine, and other disciplines to adapt and use the IHC Key Concepts as a framework for supporting critical thinking about the effects of interventions.

IHC Key Concepts are included in the curriculum for bachelor students at the Faculty of Health Sciences, Oslo Metropolitan University, as part their training in knowledge-based practice. As part of this subject, they also receive training in breaking myths and exposing unreliable claims they

encounter in the media and other parts of society that deal with the effect of various forms of treatment. The University also hosts Behind the Headlines, which is an interdisciplinary teaching and research project aimed at raising the students' competence in critically appraisal of health claims.

We currently are completing a second project funded by the Research Council of Norway (2019 to 2024) which built on the first project. As part of this research, we developed educational resources for lower secondary school students and evaluated the resources in randomized trials in Kenya, Rwanda, and Uganda.

TOOLS TO IMPROVE THE USE OF RESEARCH FINDINGS

Our research group took the lead on developing Evidence to Decision (EtD) frameworks as part of the EU-funded DECIDE project (2011-2015). This led to EtD frameworks tailored for clinical practice guidelines (2016), public health and policy decisions (2018), coverage decisions (2017), and tests (2016). More than 110 organizations around the world, including the World Health Organization (WHO), now use GRADE (and GRADE EtD frameworks) to assess the certainty of evidence and strength of recommendations in guideline development and decision-making processes. Our team also led the development of the interactive EtD tool and guidance for populating and using EtD frameworks.

The GRADE-CERQual approach provides a transparent and systematic method for assessing confidence in the evidence from reviews of qualitative research and communicates this to end users, such as guideline panels or decision makers. The approach was first published in an article in 2015 and has been refined since. WHO is a partner in the GRADE-CERQual-project and the WHO has included GRADE-CERQual-assessments in their guideline development processes and policy recommendations. A literature search conducted in August 2020 identified 233 studies that had applied the GRADE-CERQual approach – a figure that is likely to have at least doubled by now. Cochrane recommends that authors of qualitative evidence syntheses apply the GRADE-CerQUAL approach.

5. Sources to corroborate the impact

1. Bermudez LG, Grilo SA, Santelli JS, Ssewamala FM. Informing health choices in low-resource settings. Lancet. 2017;390(10092):336-8. https://doi.org/10.1016/s0140-6736(17)31290-4

2. This researcher may have discovered the antidote to health bullshit

Julia Belluz and Alvin Chang, Vox 2017

3. The Documentary: How children are fighting misinformation *(video, 3 minutes)*

BBC World Service, with Sir David Spiegelhalter and producer Sandra Kanthal 2019

4. Muller L-M, Morris A, Sharples JM, Chislett J, Rose N, Chalmers H. How to assess claims about cognition and learning: The ACE Concepts. Impact J R Coll Teach. 2020;18:19. https://impact.chartered.college/article/how-to-assess-claims-cognition-learning-ace-concepts/

5. Informed Health Choices Newsletter 2023

6. Informed Health Choices, il corso che insegna il pensiero scientifico in medicina ai bambini- Corriere.it

Corriere Dela Sera (Italian daily newspaper), reporting on use of Informed Health Choices teaching resources in schools in Italy.

7. The World Health Organization: Evidence, policy, impact: WHO guide for evidence-informed decision-making (this WHO-document includes 30 references to publications from our research group).

8. Vestrheim DF, Iversen BG, Flottorp SA, Denison EM-L, Oxman AD. Should individuals in the community without respiratory symptoms wear facemasks to reduce the spread of Covid-19?– Update 1. Oslo, Norway: Norwegian Institute of Public Health; 2020. https://hdl.handle.net/11250/2722757

9. Glenton C, Lewin S, Norris S. Using evidence from qualitative research to develop WHO guidelines. WHO handbook for guideline development. 2014. https://iris.who.int/bitstream/handle/10665/145714/9789241548960_chap15_eng.pdf

10. Wainwright, M., Zahroh, R.I., Tunçalp, Ö. et al. The use of GRADE-CERQual in qualitative evidence synthesis: an evaluation of fidelity and reporting. Health Res Policy Sys 21, 77 (2023). https://link.springer.com/article/10.1186/s12961-023-00999-3

Norwegian Institute of Public Health, Division for Health Services: Impact case 2

Institution: Norwegian Institute of Public Health
Administrative unit: Division for Health Services
Title of case study: Development and impact of the GRADE approach for assessing the confidence in effect estimates to make the findings of systematic reviews more useable in evidence-based decision-making processes
Period when the underpinning research was undertaken: 2000- current date
Period when staff involved in the underpinning research were employed by the submitting institution: 2000- current date
Period when the impact occurred: 2004-current date

1. **Summary of the impact**

In this impact case we describe the participation of our employees in the global working group who developed and implemented the use of GRADE (Grading of Recommendations Assessment, Development and Evaluation). GRADE is a methodological approach for assessing the quality of the evidence/ confidence in the results of a systematic review and the strength of recommendations in a guidelines process. We then describe the impact that the implementation of GRADE has had on increasing the transparency of reporting of findings for systematic reviews, and in guidelines processes. Furthermore, GRADE has become the gold standard for systematic reviews in international groups such as the Cochrane Collaboration, the WHO and the National Institute for Health Care and Excellence (NICE) in the United Kingdom.

This impact case will focus on the impact of using GRADE to assess the confidence in the results from a systematic review.

2. **Underpinning research**

Before GRADE there were many different ways to assess the confidence in findings from a systematic review. These approaches were not transparent and were less systematic.

Methodological work to develop GRADE started in 2000 and continues to this day. Implementation of the GRADE approach in systematic reviews and guidelines started in approximately 2004.

The GRADE working group took the following approach to developing GRADE:

1. The GRADE working group started by mapping and assessing the current ways of assessing the confidence in the quality of the evidence.
2. The team used an evidence-based approach to develop the new tool through an iterative process of surveys, and user testing of examples. Everything that was included in the final tool worked well in user testing and had been understood by participants in multiple tests before being included.

The final GRADE assessment tool encourages researchers to make transparent, systematic and consistent assessments. After implementing the initial tool with evidence profiles where researcher decisions are explained, the GRADE working group introduced Summary of Findings (SoF) tables. This further increased the level and detail of decision reporting and communication. GRADE also provides a transparent and equal approach for decision makers to understand the findings of systematic reviews and how much trust they can place in the effect estimates when making informed decisions.

The development of the GRADE tool led to the publication of scientific articles, a handbook and a multitude of freely available teaching materials. These include:

- GRADE Handbook
- GRADEpro
- Two chapters in the Cochrane handbook for systematic reviews of interventions
- More than 30 academic publications (including a series of 6 articles in BMJ followed by a still ongoing series in J clin epi)
- Thousands of published systematic reviews that have implemented GRADE assessments
- Webinars, teaching materials, integrated into systematic review teaching, website, included in Cochrane training

GRADE has also encouraged further methods development to assess the confidence in the findings of qualitative evidences synthesis (GRADE CERQual), software to support the assessment process (GRADEpro, iSoQ), support for guidelines processes (MAGIC) and a project to make systematic review findings available to the general public (SUPPORT summaries (kort oppsummert)). There is currently a worldwide network of researchers using and further developing these methods.

GRADE has also been used in hundreds of guidelines processes across a large number of institutions, for example, the WHO. Since 2009, the WHO has had mandatory use of GRADE in systematic reviews underpinning their recommendations, as well as standard use of the GRADE evidence-to-decision framework for determining the strength of recommendations. More than 110 organizations from 19 countries around the world have endorsed or are using GRADE.

The GRADE working group is a global network with global collaboration amongst members and institutions. Our employees played a key role in the development, testing and implementation of the method.

- Signe Flottorp and Andy Oxman were the initiators of the idea that led to the collaboration that became the GRADE working group. The informal meeting in 2000 with several other international collaborators where this discussion started is considered the first meeting, Gunn Vist joined at the second meeting later in 2000. All three are still employed in the Area for Health Services.
- Annhild Mosdøl (employed until 2019) was a member of the GRADE Equity Group.
- A number of current employees are members of GRADE Scandinavia.
- GRADE inspired GRADE CERQual for use in qualitative evidence synthesis. Many researchers in the Area for the Health Services at NIPH have been involved in its development since 2012; Claire Glenton (employed until 2022), Simon Lewin (employed until 2022), Signe Flottorp, Andy Oxman, Rigmor Berg and Heather Munthe-Kaas.
- GRADE also inspired the MAGIC app development led by Per Olav Vandvik (employed until 2024). Stijn van der Velde (employed until 2023) joined the MAGIC group a short time later.

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4. Details of the impact

The GRADE Working Group is a network of international collaborators who participated in discussions and testing of examples while developing this methodological approach (see table below). Three of our employees were key members of the core working group during the formative years of the development of the approach. In addition to participating in the discussions and tests, our people were deeply involved in making progress through planning, developing, preparing and conducting the tests, assessing and writing. The examples used for developing and testing the GRADE approach were selected from discussions and suggestions from within this group and therefore often by default relevant to the participating institutions.

Table over key participating institutions

American University of Beirut, Lebanon	Hospital de Sant Pau, Universidad Autonoma de Barcelona, Spain	The Swedish Agency for Health Technology Assessment and Assessment of Social services (SBU), Sweden
Bond University, Australia	Kyoto University Graduate School of Medicine/School of Public Health, Japan	Universidad San Sebastian, Chile
Case Western Reserve University, USA	Manchester University NHS Foundation Trust, UK	University Hospital Basel, Switzerland
Copenhagen University Hospital, Denmark	Mayo Clinic, USA	University Medical Center Freiburg, Germany
Duke University Medical Center and Durham Veterans Affairs Center for Health Services Research in Primary Care, USA	McMaster University, Canada	University of Florida, College of Medicine, USA

German Hospital, Argentina	Oregon Health and Science University, USA	University of Modena and Reggio Emilia, Italy
Guide2Guidance, The Netherlands	State University of New York at Buffalo, USA	University of Toronto, Canada
Harvard Medical School, USA		West China Second University Hospital, Sichuan University and Key Laboratory of Birth Defects and Related Disease of Women and Children, China

The participation of many different organizations with employees focused on different aspects of the systematic review and guidelines process (systematic review producers, guideline produces, and global networks across medical and public health disciplines) was helpful for implementing and disseminating of the GRADE approach.

A key dissemination activity was workshops at Cochrane Colloquium. These provided access to the target user group for the GRADE approach as well as an arena for feedback on implementation of GRADE and its ease of use. The active participation of anyone interested in GRADE at workshops during Cochrane Colloquiums encouraged the participation of relevant people and expertise as well as aiding dissemination to and input from experienced systematic review methodologists. As a result of these workshops, implementation of the GRADE approach in Cochrane systematic reviews was made easier.

Beneficiaries

The clear beneficiaries of the GRADE tool are the producers of, and users of systematic reviews and guideline recommendations. These groups benefit from the increased transparency, systematic approach, and consistency in judgements around the confidence in the results of a systematic review that using the GRADE tool provides. A further beneficiary is the general public as GRADE has increased the transparency of the decision-making process for guidelines in implementation of new methods in the health care sector and beyond. GRADE allows for end users to follow the decision trail of a recommendation back to the original evidence and see which other factors influence the guideline panel's decision.

Nature of the impact

Impact of the GRADE approach began about 2004 and continues to grow, both in systematic reviews and guidelines processes. The GRADE working group continues to explore new methodological innovations linked to using the GRADE tool allowing the tool to adapt to the changing landscape of systematic reviews and guidelines. As GRADE has become standard practice in leading institutions worldwide (WHO, NICE), other institutions have become aware of the benefits of transparent and systematic evaluation of the evidence and begun to implement the approach. This continued implementation has happened at the country level and is also happening at the municipal level in Norway through the *Supporting municipalities to make informed decisions* project at the NIPH.

Evidence or indicators of the extent of the impact (with dates)

- Since 2004 it has become standard practice to use GRADE in systematic reviews
- GRADE has been used in Norwegian guidelines processes, for example related to changes in treatment for multiple sclerosis, the dangers of using snus and e-cigarettes, or how best to communicate about children's weight status to parents.

- GRADE is a required component of all systematic reviews contributing to WHO guidelines. Most recently employees in our cluster contributed key evidence to a guideline on non-surgical management of chronic primary low back pain in adults in primary and community care settings.

5. Sources to corroborate the impact (indicative maximum of ten references)

An example with considerable impact in Norway is the HTA-report with a network meta-analysis on disease modifying treatment for relapsing remitting multiple sclerosis (using GRADE).

An international example involving the use of GRADE with a global impact are the WHO living guidelines on Covid 19 drugs

The impact from the GRADE working group is clearly demonstrated by the inclusion of this methodological approach in the assessment of the confidence in results from systematic reviews by the Cochrane collaboration's Handbook for Systematic Reviews of Interventions, chapter 14 and 15, Cochrane Handbook for Systematic Reviews of Interventions | Cochrane Training

Another clear demonstration of impact and uptake is the adoption of the GRADE approach by leading international guideline producers such as
-The WHO Handbook for Guideline Development, GRC Handbook - second edition (who.int) chapter 9 and 10.
-WHO Guidelines handbook that clearly describes and highlights GRADE as a mandatory part of the process: https://www.who.int/publications/i/item/9789241548960
-NICE, Developing NICE guidelines: the manual, chapter 6.
- Canada's Drug and Health Technology Assessment Agency (CADTH) requires the ues of GRADE in their reports.

Finally, our national Directorate of Health has adopted the use of GRADE in Norwegian guidelines processes through the Norwegian National Guide for Developing Guidelines (Veileder for utvikling av kunnskapsbaserte retningslinjer (fullversjon).pdf (helsedirektoratet.no). This guidance on the use of GRADE (from page 28), is only available in Norwegian. However, we think it has had an important impact in Norway and has improved the methodology used for Norwegian National Guidelines for Health.

Norwegian Institute of Public Health, Division for Health Services: Impact case 3

Institution: Norwegian Institute of Public Health
Administrative unit: Division for Health Services
Title of case study: eRegistries: Digital Health Interventions for Public Health Systems Strengthening
Period when the underpinning research was undertaken: 2009 – 2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2009 – 2022
Period when the impact occurred: 2011 – 2022

1. Summary of the impact

This impact case features a multifaceted initiative that integrates science and policy, with strong local and global collaborations for comprehensive health impact. We strive to establish good quality health data and facilitate real-time utilization of data by health workers in low- and middle-income countries (LMIC), as well as for monitoring LMIC health systems over time. This is achieved through a streamlined approach, utilizing longitudinal data in digital registries (*eRegistries*) from a single source at the point of generation, that is, health facilities.

Our scientific endeavors span global scoping reviews, concept development, and intervention science, implementing global guidelines and a Lancet series. Policy contributions include WHO guidelines, taxonomy, and classification for digital health interventions. Locally, we have demonstrated significant impact on health systems and health information systems, healthcare delivery, and human resources, for example, in Palestine. We operate with a strong focus on research and capacity strengthening in LMIC, fostering infrastructure and personnel development from entry-level to senior scientists. The *eRegistries* initiative has contributed to global goods such as District Health Information Software 2 (DHIS2) used in 80 LMIC, user-friendly Apps for health workers, and global guidelines for digital health interventions.

2. Underpinning research

The *eRegistries* initiative emerged as the result of several NIPH-led global scholarly collaborations – including both academia, governmental and UN agencies – to address the lack of quality data and unhelpful classification systems for stillbirth prevention. This work became an integral part of our 2011 Lancet Stillbirth Series, acclaimed by the Editors for its global impact (box).

> "*Its powerful mix of advocacy and hard data attracted more media attention than perhaps any other [Lancet] Series, and made waves on numerous levels, from the individual to the intergovernmental.*"
> Zoë Mullan, Editor

The NIPH and the World Health Organization (WHO) partnered in the *eRegistries* initiative as "*a direct response to The Lancet Stillbirth Series to strengthen health information systems, specifically electronic health registries tracking women and children across the continuum of care*". The *eRegistries* initiative developed concepts through three influential papers on data collection principles for health information systems (Frøen et al., 2016), technology and system needs, legal and ethical aspects, and clinical indicators for health systems. Notably, global scoping reviews revealed the absence of essential Health Information Systems (HIS) in LMIC and revealed the need to challenge the status quo.

Representing a new paradigm for public health surveillance in LMIC, implementing and studying the effectiveness of *eRegistries* in such settings was "high risk, high gain" and was awarded a

European Research Council grant, HEALTHMPOWR, for cluster-randomized controlled trials in the West Bank of Palestine. With co-funding from the Research Council of Norway, WHO, Norad, and Centre for Intervention Science in Maternal and Child Health (CISMAC, National Center of Excellence) implementations and trials expanded to national scale including Gaza. Notably in our first hands-on implementation project in Palestine, we defied skeptics who claimed that radical transformations of health systems and health information systems in LMIC "cannot be done" or "will not work." Implementation science played a crucial role, where we employed co-design with users to drive necessary changes in the health system (Bogale et al., 2020).

The eRegistries projects in-country demonstrated immediate policy impact, which allowed us to contribute with conceptual as well as practical insights to our 2016 Lancet Series on Ending Preventable Stillbirth. Our research and implementations were also contributing steadily to global infrastructures like the District Health Information Software (DHIS2), specifically to guidance on individual-level data collection systems in LMIC.
Intervention science has been our focus across different country settings and projects, addressing the need for high-quality evidence of impactful digital health interventions highlighted by the WHO. A first-of-its-kind cluster-randomized controlled trial in Palestine demonstrated that a digital registry with clinical decision support is effective in improving quality of care for pregnant women (Venkateswaran, Ghanem, et al., 2022). A unique cluster-randomized controlled trial in Bangladesh showed that a digital registry is effective in improving health outcomes (Venkateswaran et al., 2024).
Policy-oriented research of changes in data showcased how enhanced data transforms indicators of healthcare quality, deepens understanding of population-scale health conditions, and influences priority setting in public health (Venkateswaran, 2019). Such approaches to policy-relevant research helped allay preconceived notions about the infeasibility of implementing relatively radical interventions in LMIC.
Our work has not only addressed data needs but also positioned LMIC as key players in driving impactful change. With strategic partnerships and a commitment to science, the project successfully navigated challenges, leveraging local expertise to influence global policies. By demonstrating the feasibility of improving data infrastructure in LMIC, the initiative not only debunked myths but also contributed valuable insights to the global health community.
In summary, this comprehensive effort spans scholarly groundwork, project implementations and research evaluations in real world health systems, and policy impact research. As a result, we have been able to challenge conventional beliefs about feasibility, benefits, and limitations of data-driven interventions in LMIC.

3. References to the research

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4. Essential project researchers from our research unit

Alphabetically, project and work package leads in **bold**: Akuba Dolphyne, Binyam Bogale, Brian O'Donnell, **Eleni Papadopoulou**, Hollie Stone, **Ingrid K Friberg**, **J. Frederik Frøen**, Jagrati Jani Bolstad, Kim Frost, **Kjersti Mørkrid**, Linda Nyanchoka, **Mahima Venkateswaran**, Marie Hella Lindberg, Michael J Frost, Socheat Cheng, **Sonja Myhre**, **Victoria Nankabirwa**, Åse Pay.

5. Details of the impact

The intersection of science, policy, and local capacity building has given rise to this transformative eRegistries initiative. Our endeavour encompasses various facets, each contributing to a holistic approach to address critical health and health system challenges, as outlined below. Our projects and work represent a paradigm shift in health information systems in global health. By seamlessly integrating science, policy, local impact, capacity development, and the creation of global goods, our work exemplifies a model for comprehensive and sustainable data-driven digital health interventions and use of data.

Scientific Advancements:

At the core of this initiative lies a commitment to advancing scientific knowledge. We have employed a range of approaches – global scoping reviews of registries and data collection systems in LMIC, concept development to demonstrate the novelty of health system indicators (Flenady et al., 2016), implementation science and intervention science. Our research projects involve close collaborations and hands-on implementations with partners in LMIC, and end users of health information systems. This approach responds to top-priority research questions from authoritative bodies like the WHO while also responding to local needs. Our approach and methods have set a precedent for others to pursue similar challenging yet impactful research.

Policy Influences:

Our work extends its reach into the realm of policy, and we have contributed directly to the development of the WHO guidelines, taxonomy, and classification for digital health interventions, including leading the development of eleven systematic reviews for the WHO. We have contributed to the FIGO (The International Federation of Gynecologists and Obstetricians) position paper (Frøen et al., 2021) on data for the prevention of preterm birth and the WHO framework for mHealth Evidence Reporting and Assessment (mERA) (Agarwal et al., 2016). We have strived to ensure that the latest advancements in science are translated into tangible guidelines and frameworks that can guide global health efforts.

Local Impact in Country:

The impact on the ground has been clear and pronounced, particularly in Palestine, where we implemented a digital registry for antenatal, postnatal, and newborn care in all public primary healthcare clinics. The accompanying research demonstrated positive impacts on the health information system, care delivery, quality of care, and the optimal use of human resources (Venkateswaran, Nazzal, et al., 2022). This large-scale implementation provides a good example of localized impact of global guidelines and recommendations, underscoring the adaptability and relevance digital health interventions in diverse settings.

LMIC Capacity Development:

Recognizing the importance of strengthening sustainable capacity in LMIC, our projects align with the societal mandate of the NIPH, and its long history of involvement with capacity strengthening

initiatives, the latest being the Building Stronger [Public Health] Institutions and Systems. We have leveraged such capacity strengthening initiatives and bridged them with research projects to maximize impact on infrastructure development and personnel training. Over the years our collaborations have fostered entry-level positions, and senior scientists and professors in LMIC institutions.

Real-Time Data Infrastructure:

A notable achievement of the initiative is the creation of a robust infrastructure for real-time, real-life data assessments. The ongoing project (Evidence-based policies and health systems interventions for antenatal care) in Uganda funded by the Research Council of Norway exemplifies this, allowing for the evaluation of the impact of policy or guideline changes in health systems. Specifically, we are examining what it takes for the health system to transition from 4 antenatal care (ANC4) visits to 8 antenatal care (ANC8) contacts. The emphasis on data and digital health in this project to support the delivery of the intervention is directly in response to WHO's priority research question on the implementation of ANC8. The approach of implementing longitudinal data collection systems, integrated into the existing health information system, provides an opportunity to study data in real-time and provide policy recommendations.

Global Goods and Pandemic Response:

All our software and implementation guidance are global public goods, free for all to use at DHIS.org. We have contributed to and curated "ready-made" meta-data packages that include implementation guidance, fostering communities of practice for shared learning and collaboration. Examples include the Reproductive, Maternal, Newborn, and Child Health (RMNCH) and childhood immunization, and the DHIS2 Tracker for Antenatal Care based on WHO's Digital Adaptation Kit (DAK). Our work with the DHIS2 developers over a decade to transition from their traditional aggregate data sources to individual-level registries has made such tools available for the 80+ LMIC using DHIS2. The snowballing impact of these contributions on a global scale is particularly evident in the realm of pandemic response and readiness; individual-level data health information systems played a crucial role in the COVID-19 response with over 40 countries repurposing "Tracker" systems of individual-level data from other programs towards COVID-19 response.

5. Sources to corroborate the impact

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Norwegian Institute of Public Health, Division for Health Services: Impact case 4

Institution: Norwegian Institute of Public Health
Administrative unit: Division for Health Services
Title of case study: Beredt-C19 – the foundation and enablement of a system producing scientifically founded real time knowledge to handle the covid-19 pandemic
Period when the underpinning research was undertaken: April 2020-Dec 2023
Period when staff involved in the underpinning research were employed by the submitting institution: April 2020-Dec. 2023
Period when the impact occurred: April 2020-Dec 2023.

1. Summary of the impact

The research unit was responsible for establishing and daily operation of NIPHs Preparedness Registry (Beredt-C19). Beredt C19 played a crucial role in Norway's response to the pandemic through real time data driven decisions enabling targeted infectious disease measures. The legal basis was the Health Emergency Preparedness Act, which allows NIPH to collect extensive amounts of health/administrative data and link them at an individual level. The result was an innovative analytical platform giving real time knowledge of spread, causation and hospitalizations of covid-19, covid-19 vaccine coverage, effect and side effects. The research group enabled preparation of unstructured, real-time data, in addition to producing substantial amounts of knowledge and research. Beredt-C19 represents a unique, innovative and significant step forward using real time data both in and between crises.

2. Underpinning research

The urgent need for information for both the public and policy makers during the covid-19 pandemic implied that research and analysis had to be available for decisions-makers exceptionally fast. Preliminary results were shared with both the media and relevant policy makers before publication. The research was all carried out between April 2020, when the first data sources were included, up until December 2023.

The research insights were all related to the covid-19 pandemic, and their importance and relevance were characterized by the short period between preliminary results and decision-making, to implement or adjust measures and advice. Research on infection spread, hospitalization and health care use, vaccine uptake, side effects and vaccine effectiveness were all conducted simultaneously with the ongoing pandemic and Beredt C19 made real time evaluation of measures possible. Moreover, studies showing unintended effects of restrictions and infection prevention measures, such as use of health services due to mental health or changes in planned surgeries were also produced. A wide body of research explored differential effects according to migrant and social background. Complications, rehabilitation and post covid symptoms were also areas of research. The rapid research conducted, and the knowledge produced were policy relevant on a day-to-day basis for handling the pandemic.

The research unit's long-standing experience with analysing large data from health registries and other administrative data, combined with a broad range of scientific, analytical methods and legal insight, made it possible to develop an infrastructure to make data available for analytical purposes for the rest of the institute. A flexible infrastructure was developed to allow including new data sources as the knowledge need increased.

The data sources were administrative registries for administration and financing purposes, health registries etc (over 20 data sources were included, see Emergency preparedness register for COVID-19 (Beredt C19) - NIPH (fhi.no)). Due to the daily data flow from the majority of data

sources, there was limited time for regular data quality assurance routines in each registry. To produce research from unpolished data depend on skilled researchers, who can manage a vast quantitative of unstructured data and exploit them to answer research questions necessary to underpin decisions and information needs. To produce high quality research from the available data material at the fast pace that was necessary was challenging, but rapid knowledge production is crucial in a crisis. Beredt C19 has effectively demonstrated the valuable insights from real time surveillance and science in a health crisis, and was awarded a price from the Norwegian Data Association FHI vant Innsiktsprisen – Dataforeningen (in Norwegian).

Essential project researchers from our research unit

- Anja Schou Lindman: Department director Health Service Research Unit, project leader for Beredt C19 (data processor according to GDPR, responsible for legal and technical operations)
- Kjetil Telle: Executive director for the Division of Health Services, Beredt C19 Research manager
- Jon Helgeland: Senior researcher
- Mari Grøsland: Junior researcher
- Karin Magnusson: Senior researcher, research leader for analytical team
- Anna Godøy: Senior researcher, research leader for analytical team
- Katrine Skyrud: Senior Researcher
- Vilde Bergstad Larsen: Junior researcher
- Torill Alise Rotevatn: Senior researcher
- Jonas Gjesvik: Junior researcher
- Sigurd Storehaug Arntzen: Junior researcher
- Lema Hussaini: Junior researcher
- Fredrik Methi: Junior researcher
- Bjørn Atle Reme: Senior researcher

The Beredt C19 analytical resources included researchers from the whole of NIPH but was led and administrated from our unit. During the pandemic over 25 analytical teams with different analytical purposes were active, led by dedicated team leaders. Beredt C19 was the central data source for the covid-19 surveillance in Norway. Several impact cases from NIPH are based on Beredt C19.

2. **References to the research** (indicative maximum of six references)

Our research group's contribution:

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2. **Katrine Skyrud, Kjetil Telle, Karin Magnusson**. Impacts of mild and severe COVID-19 on sick leave/*International Journal of Epidemiology/2021/ https://doi.org/10.1093/ije/dyab182 / https://academic.oup.com/ije/article/50/5/1745/6359516?login=false*
3. Silje Jørgensen, Karin Nygård, Oliver Kacelinik and **Kjetil Telle.** Secondary Attack Rates for Omicron and Delta Variants of SARS-CoV-2 in Norwegian Households/*JAMA/2022/ doi:10.1001/jama.2022.3780 / https://jamanetwork.com/journals/jama/fullarticle/2789920*
4. **A Rotevatn, Vilde Bergstad Larsen**, Tone Bjordal Johansen, Elisabeth Astrup, Pål Surén, Margrethe Greve-Isdahl and Kjetil Elias Telle. Transmission of SARS-CoV-2 in Norwegian schools during academic year 2020-21: population wide, register based cohort study/*BMJ Medicine/2022/ doi: 10.1136/bmjmed-2021-000026 / https://bmjmedicine.bmj.com/content/1/1/e000026.abstract*
5. **Karin Magnusson, Katrine Damgaard** Skyrud, Pål Suren, Margrethe Greve-Isdahl, Ketil Størdal, **Doris Tove Kristoffersen, Kjetil Telle.** Health care use for 6 months after COVID-19 in 700.000 children and adolescents: a pre-post register-based cohort study /BMJ/2021/

https://doi.org/10.1136/bmj-2021-066809 / https://www.bmj.com/content/376/bmj-2021-066809

6. **Fredrik Methi** , **Kjetil Telle** , **Karin Magnusson**. COVID-19 among bartenders and waiters before and after pub lockdown. */Occupational and Environmental Medicine/2022/ DOI: 10.1136/oemed-2021-107502/https://oem.bmj.com/content/79/1/46/*

4. Details of the impact

A health emergency has the potential to be followed by an information emergency. Nevertheless, the availability of extensive data, a flexible infrastructure, and the body of research and analyses conducted within Beredt-C19 ensured that the swiftly evolving knowledge requirements could be addressed through the development of the registry and research efforts. New knowledge was continuously communicated to decision makers, media and the public trough NIPHs surveillance team - weekly reports, risk assessments, modelling reports etc. Beredt-C19 contributed to decisions and advice being data driven and helped shed light on potential risks or benefits of the continuously changing measures, and also target interventions towards the population with the highest risk.

The weekly reports were expanded as knowledge production increased. Risk assessments were regularly published during the pandemic and a vital part of the data behind them was the ongoing analysis from Beredt-C19. Research on the Omicron variant, later published in Jørgensen et al (2022), was for example essential in the risk assessment of December, 2021, which formed an important knowledge base in measures put in place with the arrival of Omicron.
In Norway several immigrant groups had higher risk for infection and hospitalizations, and this knowledge and statistic was important to communicate. However, as stated in the report of the Norwegian Korona commission (NOU 2022:5), the fear of stigmatizing migrants through targeted interventions was stronger in the public administration than in the migrant groups and organizations themselves. Moreover, municipalities responsible for local measures, informed the commission that it was first when data and statistics from NIPH documented that the migrants were more severely hit of the pandemic, that it became legitimate to aim interventions specifically at this group. Indseth and Lindman (2021) writes more extensively on this topic (COVID-19 among immigrants in Norway, assessment of measures, and experiences from the field, report 1, chapter 4).

One example is regarding infection rates in certain professions and following infection prevention measures. The 4th of November, preliminary results of infection rates for a range of professions were published, showing particularly high rates for bartenders and waiters. The results were also distributed in Norwegian media, including VG, one of the main newspapers in Norway. Infection prevention measures ('skjenkestopp') were in place already 7th of November, with restrictions in serving of alcohol (https://www.stortinget.no/no/Saker-og-publikasjoner/Publikasjoner/Referater/Stortinget/2020-2021/refs-202021-11-05?all=true). In addition, real-time data in Beredt C19 allowed simultaneously evaluation of measures, and on the 5th of February, new results were made available, showing a decline in infection rates for these professions.

An example of the flexibility of the system was demonstrated when there an urgent need for knowledge on cross-border virus spread through travels to Norway. New data on border crossings was included in Beredt C19 17th of March, 2021. Just a few days later, 23rd of March, preliminary results were published showing that imported infections mainly arrived from Africa and Asia.

Based on these results, NIPH came with updated advice on quarantine measures, and this was followed by new regulations from the government 26th of March. See the following link for background on the intervention from the government.
https://www.regjeringen.no/no/tema/Koronasituasjonen/begrunnelser-for-endringer-i-covid-19-forskriften/begrunnelse-for-endringer-28.-april-2021-i-covid-19-forskriften-5-om-oppholdssted-for-innreisekarantene/id2862154/
There are some examples where a direct link between the knowledge produced, and the policy impact is evident. 11th of march, the vaccine from Astra Zeneca were put on hold due to reports of adverse events with high mortality, VITT. Together with Danish researchers, researchers in Beredt C19 reported an increased incidence of blood clots post-vaccination, as found in cases of VITT, which led to the NIPH recommending excluding vector vaccines from the vaccination program in April 2021, implemented as policy from May 2021.
The Beredt C19 was a large-scale project, which included making sure legal restrictions were met, such as DPIA, data collection and data collection infrastructure, infrastructure for access, access control and data analysis, in addition to researcher teams for analyzing the data and conducting research. Researchers all across NIPH were involved in conducting research and analysis in this project, and the methodological competencies in our research unit were essential for the development of both the infrastructure and the research made. In total, more than 150 researchers contributed to the research output, and organization of this structure was thus a major task.

5. Sources to corroborate the impact (indicative maximum of ten references)

Surveillance examples

- Weekly reports from NIPH: https://www.fhi.no/publ/statusrapporter/luftveisinfeksjoner/#alle-ukerapporter-2020-2023
- Risk assessments from NIPH: https://www.fhi.no/publ/2020/covid-19-epidemien-risikovurdering/
- Covid-19 modelling reports: https://www.fhi.no/ss/korona/koronavirus/koronavirus-modellering/

Migration health examples

- Indseth, T., Elgersma, I. H., Strand, B. H., Telle, K. E., Labberton, A. S., Arnesen, T. M., ... & Godøy, A. A. (2021). Covid-19 blant personer født utenfor Norge, justert for yrke, trangboddhet, medisinsk risikogruppe, utdanning og inntekt. Rapport Folkehelseinstituttet 2021.
- Indseth, T., Kjøllesdal, M. K. R., Jacobsen, C. C., Nygård, K. M., & Godøy, A. A. (2020). Covid-19 i Oslo etter fødeland: Personer testet, bekreftet smittet og relaterte innleggelser. Rapport Folkehelseinstituttet 2021.
- Expert group report. Immigrant Population During the COVID-19 Pandemic Infection, Vaccine, and Consequences for Integration Oslo, June 23, 2021. Report from an expert group
- Myndighetenes håndtering av koronapandemien – del 2. Rapport fra Koronakommisjonen. NOU 2022:5, s.407

Occupational risk

- Fredrik Methi, Kjetil Telle , Karin Magnusson. COVID-19 among bartenders and waiters before and after pub lockdown. Occupational and Environmental Medicine 2021. Doi: 10.1136/oemed-2021-107502

- Magnusson Karin, Nygård Karin, Methi Fredrik, Vold Line, Telle Kjetil. Occupational risk of COVID-19 in the first versus second epidemic wave in Norway, 2020. Euro Surveill. 2021;26(40):pii=2001875. https://doi.org/10.2807/1560-7917.ES.2021.26.40.2001875

Astra Zeneca example

- Pottegård A, Lund LC, Karlstad Ø, Dahl J, Andersen M, Hallas J, Lidegaard Ø, Tapia G, Gulseth HL, Ruiz PL, Watle SV, Mikkelsen AP, Pedersen L, Sørensen HT, Thomsen RW, Hviid A. Arterial events, venous thromboembolism, thrombocytopenia, and bleeding after vaccination with Oxford-AstraZeneca ChAdOx1-S in Denmark and Norway: population based cohort study. BMJ. 2021 May 5;373:n1114. doi: 10.1136/bmj.n1114. PMID: 33952445; PMCID: PMC8097496.

Norwegian Institute of Public Health, Division of Infection Control, Case number 1

Institution: Norwegian Institute of Public Health
Administrative unit: Division of Infection Control
Title of case study: COVID-19 vaccines and menstrual disturbances
Period when the underpinning research was undertaken: 2020-2023
Period when staff involved in the underpinning research were employed by the submitting institution: 2012-2023
Period when the impact occurred: 2022-2023

1. Summary of the impact (indicative maximum 100 words)

Menstrual irregularities are very common, and affect women's health, wellbeing, and daily life. Following the launch of the covid-19 vaccination campaign, signals of heavy menstrual bleedings were reported. We took advantage of existing population-based cohorts and confirmed positive associations between COVID-19 vaccination and heavy menstrual bleeding in different age groups. The findings were part of the evidence evaluated by the European Medicines Agency, which resulted in the recommendation that heavy menstrual bleeding should be added to the mRNA vaccines' product information as a side effect of unknown frequency.

2. Underpinning research (indicative maximum 500 words)

Menstrual irregularities are very common, and affect women's health, wellbeing, and daily life. Before the covid-19 vaccination roll-out, menstrual changes after vaccination had rarely been reported to spontaneous reporting systems for adverse events following immunization (AEFIs), and no associations between vaccination and menstrual features had been noted. After the initiation of the covid-19 vaccination campaigns, unforeseen signals of menstrual changes as possible side effects of the vaccines were detected by spontaneous reporting systems in many countries, including Norway.

The first research effort was to explore the potential association between covid-19 vaccination and menstrual disturbances in 18-30 year old women, using population-based questionnaire data from 3972 cohort participants (YoungAdult cohort, see below).[1] The prevalence of any menstrual disturbance was high: 36.7% in the last menstrual cycle *prior* to the first vaccine dose. We observed increased risk of heavier menstrual bleeding than usual in the first cycle after the first vaccine dose as compared to the last cycle prior to vaccination, RR = 1.90 (95 % CI: 1.69-2.13). Increased risks were also observed for prolonged bleeding, shorter interval between menstruations, and stronger period pain. The results were unaffected by vaccine brand, contraception/hormone use, or presence of existing gynecological condition(s), and were similar in women who were tracking their menstruation using an app or other method.

The second research effort was to explore the association between vaccination and menstrual disturbances in 7 565 adolescent girls aged 12-15 years using maternal questionnaire responses in a large population-based cohort (MoBa, see below).[2] Menstrual irregularities were common also in this age group, independent of vaccination and infection status. The proportion of vaccinated girls reporting one or more menstrual irregularities in their last period *prior* to vaccination was 22.6%, while 25.1% of this group reported at least one event for the first cycle *after* vaccination. Unusually heavy bleeding was reported by 4.7% prior to vaccination and 7.3% after vaccination, RR = 1.61 (95 % CI 1.43 to 1.81). The effect sizes were similar in girls who were tracking their menstruation using an app or other method.

The third effort aimed at exploring the risk of unexpected vaginal bleeding in women who were not menstruating due to hormone use or menopause. Through electronic questionnaires issued

during the pandemic, a total of 22,000 women in a cohort of Seniors (see below) and the Norwegian Mother, Father and Child Study (MoBa) were asked if they had experienced unexpected vaginal bleeding in 2021, the year when the vast majority received their first COVID-19 vaccine dose.[3] Among the women who reported of such bleeding, close to 50% stated that the change had occurred within four weeks of COVID-19 vaccination. Across all three groups of women, we found an 2-4 times increased risk of unexpected vaginal bleeding in the first month following vaccination.

Key researchers (from the research unit SMHB):

Kristine Blix, Researcher (15.03.2022-today)
Berit Feiring, Senior Adviser (01.03.1989-today)
Ida Laake, Senior Researcher (05.08.2013 – today)
Anna H Robertson, Senior Adviser (01.09.2013-today)
Siri Mjaaland, Senior Researcher (-1.10.2007-today)
Lill Trogstad, Head of Section (13.07.2009-today)

3. References to the research (indicative maximum of six references)

1. **Trogstad L, Laake I, Robertson AH, Mjaaland S,** Caspersen IH, Juvet LK, Magnus P, **Blix K, Feiring B.** Heavy bleeding and other menstrual disturbances in young women after COVID-19 vaccination. Vaccine. 2023 Aug 14;41(36):5271-5282. doi: 10.1016/j.vaccine.2023.06.088. Epub 2023 Jul 3. PMID: 37451876. https://pubmed.ncbi.nlm.nih.gov/37451876/
2. **Trogstad, Lill.** Increased Occurrence of Menstrual Disturbances in 18- to 30-Year-Old Women after COVID-19 Vaccination (January 1, 2022). Available at SSRN: https://ssrn.com/abstract=3998180 or http://dx.doi.org/10.2139/ssrn.3998180 Preprint
3. **Blix K, Laake I,** Juvet L, **Robertson AH,** Caspersen IH, **Mjaaland S**, Skodvin SN, Magnus P, **Feiring B, Trogstad L**. Unexpected vaginal bleeding and COVID-19 vaccination in nonmenstruating women. Sci Adv. 2023 Sep 22;9(38):eadg1391. doi: 10.1126/sciadv.adg1391. Epub 2023 Sep 22. PMID: 37738335; PMCID: PMC10516485 https://pubmed.ncbi.nlm.nih.gov/37738335/
4. Caspersen IH, Juvet LK, **Feiring B, Laake I, Robertson AH, Mjaaland S,** Magnus P, **Trogstad L.** Menstrual disturbances in 12- to 15-year-old girls after one dose of COVID-19 Comirnaty vaccine: Population-based cohort study in Norway. Vaccine. 2023 Jan 9;41(2):614-620. doi: 10.1016/j.vaccine.2022.11.068. Epub 2022 Dec 2. PMID: 36517325; PMCID: PMC9715483. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9715483/
5. **Trogstad L**, Juvet L, **Feiring B, Blix K**. Covid-19 vaccines and menstrual changes. BMJ Med. 2022 Oct 21;1(1):e000357. doi: 10.1136/bmjmed-2022-000357. PMID: 36936587; PMCID: PMC9951358. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9951358/

4. Details of the impact (indicative maximum 750 words)

Since March 2020, biweekly questionnaires were issued to participants in two already ongoing population based cohort studies at the NIPH, namely The Norwegian mother, father and child study (MoBa, https://www.fhi.no/en/ch/studies/moba/) and the Norwegian Influenza Cohort Study (NorFlu, https://www.fhi.no/en/id/studies/norflu/). The MoBa and NorFlu cohorts are pregnancy cohorts and have followed parents and children since pregnancy in 1998 and 2009, respectively. During the SARS-CoV-2 pandemic, a YoungAdult cohort (ages 18-30, https://www.fhi.no/en/id/corona/studies/ungvoksen/) and a Senior cohort (ages 65-80, https://www.fhi.no/en/id/corona/studies/the-senior-cohort/) were recruited to provide data for age groups not covered in the MoBa/NorFlu. Similar questionnaires were issued in all cohorts and linked to individual, national registry data on SARS-CoV-2 vaccination and infection. The overall objective is to understand the course and consequences of health crises like pandemics, encompassing short- and long-term consequences of infections and vaccination: We monitor

vaccine effectiveness, immune responses and adverse reactions, and the course of SARS-CoV-2 infection. The results are applied in public advice and decision-making, with emphasis on optimized vaccination strategies, and published scientifically.

The specific research initiative on menstrual disturbances following COVID-19 vaccination started in spring of 2021, after the launch of the COVID-19 vaccination campaign in Norway in late December of 2020. In the questionnaire free-text fields, many participants noted that they experienced heavy menstrual bleeding following vaccination. This led us to include structured questions on unexpected vaginal bleeding and menstrual disturbances in questionnaires to female participants. During the summer of 2021, the Norwegian Medicines Agency, NMA received many reports of heavy menstrual bleeding after COVID-19 vaccination.

Preliminary results from the cohort analyses were shared in confidentiality with the NMA. Based on these results and the high number of spontaneously reported bleeding episodes, the NMA decided to report heavy menstrual bleeding as a potential side effect of COVID-19 vaccines to the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA).

The cohort studies among 12-15- year- old adolescents and 18-30- year- old women were referred to the EU regulatory network (EMA and the national competent authorities in the EU/EEA countries) by the Norwegian PRAC Rapporteur, for discussion in PRAC's June7-10 plenary, 2022. On May 23, 2022, Lill Trogstad was contacted by the Signal Management Lead at the Pharmacovigilance Office of EMA, Irina Caplanusi, and asked to present the preliminary study results at the PRAC June plenary meeting under a confidentiality commitment. The presentation to PRAC was held on June 7, 2022.

On October 27, 2022, the PRAC recommended to include "heavy menstrual bleeding" as a side effect of unknown frequency to Spikevax.[4,5] On November 10, 2022, the PRAC Committee recommended that heavy menstrual bleeding should be added also to the Comirnaty product information as a side effect of unknown frequency.[6] The publications and the recommendations from PRAC/EMA received much media attention. In Norway, 128 media articles were published in 2021- 2023. The preprint publication that was available at this time received more than 20 000 views/downloads, 4 international policy citations and 19 international news stories.[7]

Post menopausal bleeding has also been reported following COVID-19 vaccination. Our third publication, on unexpected vaginal bleeding in non-menstruating women, has been referred to EMA by the NMA for the current evaluation of post-menopausal bleeding as a side effect to COVID-19 vaccination. This paper is in the top 5% of all research outputs scored by Altmetric and was viewed/downloaded more than 53 000 times the first 30 days after publication, and a total 40 news stories from 27 outlets are listed.[8]

Given the novelty and the magnitude of the spontaneously reported menstrual changes after COVID-19 vaccination, exploration of the associations of sex-specific outcomes after vaccination is imperative. Well-designed studies can inform the female population, secure transparency in vaccine safety issues, and contribute to maintaining public trust in vaccination programmes and surveillance systems. Blinded, randomised controlled trials are best suited to address this issue. However, menstrual changes are unaddressed in such trials to date.

A mass-vaccination setting with such high coverage and rapid roll-out, leaves limited opportunity to retrospectively compare the frequency of adverse events in vaccinated and unvaccinated individuals. While severe reactions can be captured by health registries, non-severe outcomes may go undetected without active real-time monitoring. We have demonstrated that dynamic data

collection within existing cohorts is a powerful tool in gaining timely, new insights during an ongoing health crisis.

6. Sources to corroborate the impact (indicative maximum of ten references)

[1]https://www.fhi.no/en/id/corona/studies/ungvoksen/increased-incidence-of-menstrual-changes-among-young-women/
[2] https://www.fhi.no/en/news/2022/increased-incidence-of-menstrual-disturbances-after-coronavirus-vaccination/
[3]https://www.fhi.no/en/news/2023/vaginal-bleeding-after-covid-19-vaccination-among-non-menstruating-women/
[4]https://www.ema.europa.eu/en/documents/prac-recommendation/signal-assessment-heavy-menstrual-bleeding-covid-19-mrna-vaccine-spikevax_en.pdf
[5]https://www.ema.europa.eu/en/documents/prac-recommendation/new-product-information-wording-extracts-prac-recommendations-signals-adopted-24-27-october-2022-prac-meeting_en.pdf
[6]https://www.ema.europa.eu/en/documents/covid-19-vaccine-safety-update/covid-19-vaccines-safety-update-10-november-2022_en.pdf
[7]https://plu.mx/ssrn/a/?ssrn_id=3998180 [8]
[8]https://scienceadvances.altmetric.com/details/154536038

Irina Caplanusi, Signal Management Lead at the Pharmacovigilance Office, EMA
Irina.Caplanusi@ema.europa.eu
Unni Hjelmaas, Head of Unit, Department for regulatory affairs and better use of medicines, NMA,
Unni.Hjelmaas@legemiddelverket.no

Norwegian Institute of Public Health, Division of Infection Control, Case number 2

Institution: Norwegian Institute of Public Health (NIPH)
Administrative unit: Division for Infection Control
Title of case study: Impact of vaccination on meningococcal disease
Period when the underpinning research was undertaken: 2012-2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2012-2022
Period when the impact occurred: 2012-2022 and ongoing into 2023-2024

1. Summary of the impact (indicative maximum 100 words).

The rollout of a new polysaccharide-conjugated vaccine against serogroup A meningococcal disease in countries of sub-Saharan Africa, with more than 300 million people vaccinated is estimated to have avoided 300,000 cases and 30,000 deaths. Our research on the transmission of the pathogen and on its genetic evolutionary capability, as well as on the ability of the vaccine to induce mucosal immunity, has contributed to demonstrate how the vaccine generated herd protection of the populations and prevented serogroup A epidemics since its introduction. In Norway, our studies have pin-pointed the need for introducing meningococcal vaccine among teenagers, impacting national guidelines.

2. Underpinning research (indicative maximum 500 words)

Meningococcal disease, a public health threat in all countries of the world, is caused by the bacterium *Neisseria meningitidis* (the meningococcus). Research on meningococcal disease and vaccines have been a focus area at NIPH for several decades. NIPH is a World Health Organization (WHO) Collaborating Centre for Meningococci.

Meningococci are harboured only by humans, who are normally colonized asymptomatically in the oropharynx. Occasionally, the bacterium can reach the bloodstream and/or the meninges and cause severe disease. Six serogroups (A, B, C, W, X and Y) of *N. meningitidis* are responsible for nearly all cases globally. Various vaccines have been developed.

The highest burden of the disease is in sub-Saharan Africa (the meningitis belt) where large serogroup A epidemics have occurred for many decades. An effective and affordable polysaccharide-conjugated vaccine against serogroup A (MenAfriVac) was developed and introduced in sub-Saharan Africa from 2010. Polysaccharide-conjugated vaccines can potentially hinder carriage acquisition, reducing transmission of the bacterium in the population, and thus also providing protection of the non-vaccinated individuals (herd protection). This is a most significant public health impact of the use of conjugate vaccines.

To demonstrate that herd protection was provided by MenAfriVac, we performed, in collaboration with WHO and the Centers for Disease Control and Prevention in the United States (CDC), large carriage studies at multiple sites in Burkina Faso, before and after the vaccine introduction (Kristiansen et al., 2013). These studies were in large part supported by grants from the Research Council of Norway (RCN). Oropharyngeal samples were collected from nearly 50,000 people in the age-group 1 to 29. In-depth analyses of the isolated bacteria were performed at the NIPH using cutting-edge methods, including sequencing of selected genes. From 2016 whole genome sequencing was established and applied to all meningococcal isolates recovered from the surveys (Brynildsrud et al., 2018).

Furthermore, genetic loci involved in protein glycosylation were analysed in collections of isolates from meningococcal patients and carriers, as protein glycosylation is thought to play a significant role in adaptation of the bacteria in response to the environment. Large degree of

microheterogeneity in protein glycan structure was evidenced, possibly contributing to the ability of *N. meningitidis* to resist the bactericidal activity of human serum (Børud et al., 2020). To evaluate the immunological effect of conjugate vaccines in both serum and saliva, a rapid and simple multiplex microsphere assay for the quantification of specific IgG and IgA antibodies against meningococcal serogroup A, C, W, and Y capsular polysaccharides was developed. The assay was found to be reproducible, showing a good correlation with standard methods to measure antibodies, while requiring less time and workload (Bårnes et al., 2015). In Norway, adolescents are at increased risk of meningococcal carriage and disease, as in many other countries. Our study showed that meningococcal carriage is high among older teenagers and the ACWY vaccine would protect against most circulating disease-causing strains (Watle et al., 2020). Cost-effectiveness analysis evidenced that introducing the vaccine for adolescents in the national immunisation program would likely be cost-effective (Watle et al., 2021).

Key researchers, position (years of employment)

- Ola Brynildsrud, scientist (2015-ongoing)
- Bente Børud, senior scientist (2013-ongoing)
- Guro Bårnes, PhD student (2012-2017)
- Dominique A. Caugant, chief scientist (2012-ongoing)
- Hannah Jørgensen, scientist (2013-2016)
- Paul Kristiansen, PhD student/scientist (2012-2019)
- Lisbeth M. Næss, senior scientist (2012-ongoing)
- Gro Tunheim, senior scientist (2017-ongoing)
- Sara V. Watle, senior physician/PhD student (2017-ongoing)

3. References to the research (indicative maximum of six references)

Watle SV, Næss LM, Tunheim G, Caugant DA, Wisløff T. Cost-effectiveness of meningococcal vaccination of Norwegian teenagers with a quadrivalent ACWY conjugate vaccine. Hum Vaccin Immunother. 2021 Aug 3;17(8):2777-2787. doi: 10.1080/21645515.2021.1880209.

Watle SV, Caugant DA, Tunheim G, Bekkevold T, Laake I, Brynildsrud OB, Næss LM. Meningococcal carriage in Norwegian teenagers: strain characterisation and assessment of risk factors. Epidemiol Infect. 2020 Mar 31:148:e80. doi: 10.1017/S0950268820000734.

Brynildsrud OB, Eldholm V, Bohlin J, Uadiale K, Obaro S, Caugant DA. Acquisition of virulence genes by a carrier strain gave rise to the ongoing epidemics of meningococcal disease in West Africa. Proc Natl Acad Sci U S A. 2018 May 22;115(21):5510-5515. doi: 10.1073/pnas.1802298115.

Børud B, Bårnes GK, Brynildsrud OB, Fritzsønn E, Caugant DA. Genotypic and Phenotypic Characterization of the *O*-Linked Protein Glycosylation System Reveals High Glycan Diversity in Paired Meningococcal Carriage Isolates. J Bacteriol. 2018 Jul 25;200(16):e00794-17. doi: 10.1128/JB.00794-17.

Bårnes GK, Kristiansen PA, Caugant DA, Næss LM. Development and Evaluation of a Multiplex Microsphere Assay for Quantitation of IgG and IgA Antibodies against Neisseria meningitidis Serogroup A, C, W, and Y Polysaccharides. Clin Vaccine Immunol. 2015 Jul;22(7):697-705. doi: 10.1128/CVI.00087-15.

Kristiansen PA, Diomandé F, Ba AK, Sanou I, Ouédraogo AS, Ouédraogo R, Sangaré L, Kandolo D, Aké F, Saga IM, Clark TA, Misegades L, Martin SW, Thomas JD, Tiendrebeogo SR, Hassan-King M, Djingarey MH, Messonnier NE, Préziosi MP, Laforce FM, Caugant DA. Impact of the serogroup A meningococcal conjugate vaccine, MenAfriVac, on carriage and herd immunity. Clin Infect Dis. 2013 Feb;56(3):354-63. doi: 10.1093/cid/cis892.

4. Details of the impact (indicative maximum 750 words)

It was essential to determine whether MenAfriVac was also providing herd protection, as was the case for a monovalent serogroup C conjugate vaccine introduced in the UK in 1999. MenAfriVac has been introduced gradually since 2010 in mass vaccination campaigns in 24

countries of the meningitis belt and 15 countries have introduced the vaccine into the national immunisation programmes. Since 2017 there have been no confirmed cases of serogroup A disease in countries of the meningitis belt. Our studies on carriage showing the dramatic effect of the vaccine on transmission were crucial in explaining the impact of the vaccination campaigns. Since the introduction of MenAfriVac, the overall incidence of meningitis in the meningitis belt has decreased steadily and no serogroup A cases occurred either in the unvaccinated population younger than 1 year and older than 30 years that were not eligible for vaccination.

Although serogroup A epidemics have been eliminated, a serogroup C epidemic broke out in Nigeria starting in 2013. In 2015 the epidemic spread to Niger resulting in about 10,000 cases that year. The epidemic is still ongoing in the region in spite of reactive vaccination campaigns. We showed that this serogroup C epidemic was caused by a strain, not known to have caused disease previously, that originated from an ancestor previously circulating asymptomatically in carriers in the African population. The ancestral strain acquired several virulence factors, including a serogroup C polysaccharide capsule. Whole genome sequencing allowed to pin-point to the genetic events that had occurred in the ancestral strain, resulting into this emerging highly virulent pathogen. A pentavalent conjugate vaccine (ACYWX) that might cover this new strain, as well as others, is now WHO pre-qualified and carriage studies to assess the herd protection impact of this new vaccine are under planning.

Currently available meningococcal vaccines protect against most disease-causing strains, but not all, and duration of protection is not lifelong. Glycosylation is an important protein modification system displayed by bacteria that is used to evade the human immune response. Ongoing studies (2019-present) will determine whether glycan-specific antibodies can confer protection against meningococcal infection. This could be important for the development of new, improved neisserial vaccines, including vaccines against gonococcal infection.

The multiplex microsphere immunoassay developed for antibody detection in serum and saliva was used to test the effect of both the monovalent serogroup A MenAfriVac and a tetravalent serogroup A, C, W and Y conjugate vaccine in Ethiopian volunteers. With the use of this assay, we could show that serogroup-specific IgG antibody levels in serum increased with both vaccines. In addition, we could show that vaccination with MenAfriVac elicited specific salivary antibodies, giving a biological explanation for the vaccine's effectiveness against carriage. The multiplex method was also used to show that natural protection against meningococcal disease is low among unvaccinated Norwegian adolescents.

In Norway, vaccination with a serogroup ACWY polysaccharide conjugate vaccine has been recommended for teenagers since 2011, when an increase in meningococcal disease was observed in this age group. While recommended, the vaccine is not included in the national immunisation programme, potentially contributing to social inequity in health. Serogroup Y was the predominant serogroup circulating in this age-group, as determined by our carriage surveys, but unvaccinated adolescents had low natural immunity against this serogroup. Use of Swedish snus (smokeless tobacco), kissing and partying were associated with carriage. These results have had consequences for Norwegian guidelines, underpinning the need for vaccination of this age group, and have been communicated to the public and health care personnel involved in meningococcal vaccination of adolescents. The results will also be important for evaluating whether meningococcal vaccination should be included for teenagers in the national immunisation program. Therefore, our studies in Norway have been the basis for moving forward such a recommendation to the Ministry of Health.

Our studies on meningococcal vaccines and vaccination have a significant impact on public health both nationally and globally. Our contribution to the projects in Africa has been

important to explain how the vaccines are working and to give confidence in new development and implementation. Altogether our research is a support to the WHO global road map for defeating meningitis by 2030 through the elimination of bacterial meningitis epidemics.

5. Sources to corroborate the impact (indicative maximum of ten references)

The impact of our studies has been acknowledged by international stakeholders such as the WHO https://iris.who.int/bitstream/handle/10665/342010/9789240026407-eng.pdf?sequence=1 and the Meningitis Research Foundation https://www.meningitis.org/blogs/using-technology-to-defeat-meningitis. We demonstrated for the first time that MenAfriVac was highly effective in reducing transmission of serogroup A meningococci by preventing carriage https://pubmed.ncbi.nlm.nih.gov/22607898/. This indicated that if vaccination was given to all countries of the meningitis belt, epidemics of serogroup A disease could be eliminated. The findings were essential to give confidence to the international community to invest and accelerate the introduction of the vaccine. Four years after the beginning of the introduction significant reduction of the disease burden was evidenced, linked to nearly elimination of the bacterium in the populations having introduced the vaccine https://pubmed.ncbi.nlm.nih.gov/26553676/. The results have been pivotal in evaluating strategies for introduction of MenAfriVac in the national immunisation programmes of the countries of the meningitis belt https://pubmed.ncbi.nlm.nih.gov/29364884/. For planning the introduction of the pentavalent (ACWXY) vaccine, the results are essential to determine the age-group of the population to vaccinate to attain the maximum impact at the lower cost.

The results from the NUSS-study have been disseminated to the public in Norway through a dedicated website https://www.fhi.no/ss/studier/nuss-studien/publikasjoner-fra-nuss-studien/ and national media (newspapers, radio, television) https://www.tv2.no/nyheter/innenriks/sykdommen-kan-vaere-dodelig-likevel-far-ikke-alle-vaksinen-gratis/15272031/, as well as at national and international conferences for health care personnel and researchers working in the meningococcal field https://www.fhi.no/globalassets/bilder/vaksine/vaksinedagene-2019-forelopig-program.pdf, https://emgm.eu/meetings/emgm2019/emgm2019_abstracts.pdf, https://www.ipnc2022.co.za/.The results have also been included in a health technology assessment initiated in 2022, evaluating whether meningococcal vaccine for teenagers should be included in the national immunisation programme in Norway. A new recommendation from the NIPH is now under evaluation by the Norwegian Ministry of Health and Care Services.

Norwegian Institute of Public Health, Division of Infection Control, Case number 3

Institution: Norwegian Institute of Public Health
Administrative unit: Division for Infection Control
Title of case study: Stimulating innovation of and access to new antibiotics – DRIVE-AB
Period when the underpinning research was undertaken: 2014-2018
Period when staff involved in the underpinning research were employed by the submitting institution: 2014 to present
Period when the impact occurred: 2016 and ongoing

1. Summary of the impact (indicative maximum 100 words)

Bacteria are becoming increasingly resistant to many antibiotics, and too few antibiotics are developed to combat them. DRIVE-AB provided foundational evidence about how to stimulate the innovation of and access to novel antibiotics through economic incentives. Not only did DRIVE-AB publish (50+) and present (30+) widely, its results informed the implementation of incentives in Sweden and the UK, started in 2019, as well others in progress (Canada, EU, Japan, and US). DRIVE-AB continues to influence European policy with a recent publication in Nov-23. Countries now see the incentives developed by DRIVE-AB as vital to manage the growing threat of AMR.

2. Underpinning research (indicative maximum 500 words)

The key research findings that underpinned the impact were:

- New economic models are needed as incentives for the discovery and development of novel antibiotics, especially for infections with too few patients today to justify private sector research and development (R&D) investments. These models should focus on rewarding the innovation, not the use of the antibiotic since stewardship of the antibiotic make the potential for a profitable business model unlikely. DRIVE-AB recommended the implementation of a delinked pull incentive (where revenues are based on innovation and accessibility rather than consumption). These findings were based upon extensive stakeholder interviews, primary data analyses, and computer simulations.
- New economic models represent potential sizeable public investments. These must be protected to ensure that the resulting antibiotics have a lengthy and positive impact on human health. DRIVE-AB developed stewardship and access requirements based upon extensive stakeholder interviews, then current stewardship policies, timelines regarding the development of resistance, and data on the availability of existing antibiotics.
- Innovation of new antibiotics is important, but it is worthless if the antibiotics are not accessible to the patients who need them. DRIVE-AB found that there is great variation in geographic availability of antibiotics. These findings were based upon analyses of sales data (IQVIA) for antibiotics approved globally between 1999-2014.
- Other technologies (peptides, bacteriophages, etc.) are also being developed to treat antibacterial infections. Yet DRIVE-AB found that whereas these technologies are promising, they will not displace the need for new antibiotics in the short and medium terms. These findings were based on a literature review and a multi-criteria decision analysis exercise.

This research was performed in work package 2 of DRIVE-AB –co-led by John-Arne Røttingen (Director, Division for Infection Control, NIPH, 2014-2016) and Christine Årdal (Senior Researcher, NIPH) with 50 participating researchers from about 10 organizations including pharmaceutical companies. DRIVE-AB was funded by the EC's Innovation Medicines Initiative, meaning that public

sector researchers were funded through the EC and companies were funded through their own financing. NIPH had a team of 11 researchers working on DRIVE-AB (including Røttingen and Årdal): Jostein Johnsen, Cecilia Kållberg, Lene Martinsen (2017-2018), Ejike Nwokoro (2015-2016), Elizabeth Peacocke, Jens Plahte, Miloje Savic (2016-2018), Live Storehagen Dansie (2016-2018), and Dimitrios Gouglas. All contributed to the research on economic models. Kållberg contributed mainly on the areas of access and stewardship, which were the focus of her PhD, financed by DRIVE-AB. NIPH was paid € 919,100 from IMI for DRIVE-AB.

3. References to the research (indicative maximum of six references)

1. Årdal C, Findlay D, Savic M, Carmeli Y, Gyssens I, Laxminarayan R, Outterson K, Rex JH. DRIVE-AB Final Report: Revitalizing the antibiotic pipeline, 2018. http://drive-ab.eu/wp-content/uploads/2018/01/CHHJ5467-Drive-AB-Main-Report-180319-WEB.pdf
2. Årdal C, Baraldi E, Theuretzbacher U, Outterson K, Plahte J, Ciabuschi F, Røttingen J-A. Insights into early stage antibacterial development in small and medium sized enterprises: a survey of targets, costs, and durations. *Journal of Pharmaceutical Policy and Practice* 201811:8. https://doi.org/10.1186/s40545-018-0135-0
3. Kållberg C, Årdal C, Salvesen Blix H, Klein E, M. Martinez E, Lindbæk M, et al. Introduction and geographic availability of new antibiotics approved between 1999 and 2014. *PLoS ONE* (2018) 13(10): e0205166. https://doi.org/10.1371/journal.pone.0205166.
4. Theuretzbacher U, Årdal C, Harbarth S. Linking sustainable use policies to novel economic incentives to stimulate antibiotic research and development. *ID Reports* 2017;9(1). https://doi.org/10.4081/idr.2017.6836
5. Kållberg C, Hudson J, Salvesen Blix H, Årdal C, Klein E, Lindbæk M, Outterson K, Røttingen J-A, Laxminarayan R. The effect of generic market entry on antibiotic prescriptions in the United States. *Nat Commun* **12,** 2937 (2021). https://doi.org/10.1038/s41467-021-23049-4
6. Nwokoro E, Leach R, Årdal C, Baraldi E, Ryan K, Plahte J. An assessment of the future impact of alternative technologies on antibiotics markets. *Journal of Pharmaceutical Policy and Practice* 2016;9:34. https://doi.org/10.1186/s40545-016-0085-3

4. Details of the impact (indicative maximum 750 words)

The research of DRIVE-AB has paved the way to today's situation where countries are rapidly implementing delinked pull incentives, as DRIVE-AB recommended. Both the UK and Sweden have already implemented delinked pull incentives. Canada, EU, Japan, Switzerland, US, and others are in the process of implementation. All have used evidence from DRIVE-AB as well as other sources where DRIVE-AB collaborated closely including the UK AMR Review (led by Lord Jim O'Neill). Our results have been recognized in several G7 and G20 communiques calling for new incentives, starting in 2017 after DRIVE-AB published a call in *The Lancet Infectious Diseases*.

DRIVE-AB academic authors continue to contribute to the discussion, including with a *Lancet* editorial in 2023 advising the EU to rethink an alternative incentive. We recently published a policy brief in November 2023 taking account of the EU Council recommendations from June 2023 and suggesting a detailed pan-European pull incentive. This policy brief was presented on December 14, 2023, at the Swedish Mission in Brussels to Member State representatives.

DRIVE-AB has led to new leadership roles and financing for NIPH. It directly led to the next project and role within the EU Joint Action on AMR and Healthcare-Associated Infections (EU-JAMRAI-1)

where NIPH co-led the work package on access and innovation as well as the work package on stewardship (2017-2021). In this Joint Action the next step of DRIVE-AB was pursued – to work with Member State stakeholders to understand the barriers to implementation of pull incentives for antibiotics, allowing for continuity of the implementation of DRIVE-AB recommendations. Feedback from Member States demonstrated the need to include older antibiotics with vulnerable supply in the mandate of pull incentives, since shortages of older antibiotics are common and create problems for healthcare systems. DRIVE-AB's incentives were thus adjusted to improve accessibility for both old and new antibiotics.

NIPH will continue to lead on accessibility in EU-JAMRAI-2 (2024-2027), including working with DG HERA as a discussion forum for countries and relevant European organizations regarding access to new technologies and implementation of incentives.

5. Sources to corroborate the impact (indicative maximum of ten references)

1. Årdal C, Baraldi E, Ciabuschi F, Outterson K, Rex JH, Piddock LJV, Findlay D. To the G20: incentivising antibacterial research and development. *The Lancet Infectious Diseases*, Volume 2017, Issue 8, 799 – 801. https://drive.google.com/file/d/15dX3DY4R0_mgoGHtAbGaeQmFoRmAfKFc/view
2. Årdal C, Lacotte Y, Ploy M-C. Financing pull mechanisms for antibiotic-related innovation: Opportunities for Europe. *Clinical Infection Diseases* (2020). https://doi.org/10.1093/cid/ciaa153
3. Årdal, C.; Lacotte, Y.; Edwards, S.; Ploy, M.-C.; on behalf of the European Union Joint Action on Antimicrobial Resistance and Healthcare-Associated Infections. National Facilitators and Barriers to the Implementation of Incentives for Antibiotic Access and Innovation. *Antibiotics* 2021, 10, 749. https://doi.org/10.3390/antibiotics10060749
4. Årdal C, Baraldi E, Beyer P, Cooke E, Lacotte Y, Larsson DGJ, Ploy M-C, Røttingen J-A, Smith I. Supply chain transparency needed to enable sustainable and continuous supply of essential medicines. *Bull World Health Organ* 2021 March 10 https://doi:10.2471/BLT.20.267724
5. Årdal C, Baraldi E, Busse R, Castro R, Ciabuschi F, Cisneros JM, Gyssens IC, Harbarth S, Kostyanev T, Lacotte Y, Magrini N, McDonnell A, Monnier AA, Moon S, Mossialos E, Peñalva G, Ploy M-C, Radulović M, Alonso Ruiz A, Røttingen J-R, Sharland M, Tacconelli E, Theuretzbacher U, Vogler S, Wolff Sönksen U, Åkerfeldt K, Cars O, O'Neill J. Transferable exclusivity voucher: a flawed incentive to stimulate antibiotic innovation. The Lancet, Feb 8, 2023, https://doi.org/10.1016/S0140-6736(23)00282-9
6. Årdal C, Baraldi E, Bettiol E, Ciabuschi F, Colson A, Gyssens I, Monnier A, Morel C, Outterson K, Røttingen J-A, Tacconelli E, Harbarth S. Policy Brief: A Pan-EU/EEA Pull Incentive for Antimicrobial Innovation and Access, https://drive-ab.eu/news/drive-ab-policy-brief-a-pan-eu-eea-pull-incentive-for-antimicrobial-innovation-and-access/

Norwegian Institute of Public Health, Division of Infection Control, Case number 4

Institution: NIPH
Administrative unit: Division of infection control
Title of case study: COVID-19 modelling
Period when the underpinning research was undertaken: 2015-2019
Period when staff involved in the underpinning research were employed by the submitting institution: 2015-2022
Period when the impact occurred: 2020-2022

1. Summary of the impact

Since early 2020, we collaborated with UiO, Norwegian Computing Center and Telenor to develop and implement mathematical and statistical models tailored to manage the COVID-19 pandemic in Norway. These models served multiple purposes, including (i) estimating effective reproduction numbers to assess the current situation, (ii) generating short-term projections to estimate hospital and ICU bed requirements, and (iii) conducting scenario analyses for policy decisions related to vaccine deployment, infection control, risk assessments, and long-term strategies.

Our results were pivotal in providing COVID-19 policy advice and supporting Norwegian national and local health authorities throughout the complex and highly dynamic pandemic with high-profile media coverage.

2. Underpinning research

Contribution 2015-2019

NIPH's aim to build a strong infectious disease modelling group, led to partnership through BigInsight SFI and two PhD projects that became essential for our COVID-19 modelling work:

R1. Development of a spatio-temporal, stochastic model for the spread of influenza informed by mobile phone data, using an Approximate Bayesian Computation (ABC-SMC) calibration technique (PhD Solveig Engebretsen UiO/NIPH; 2019 moved to NR).

R2. Development of a fine-grained individual-based model for MRSA transmission in Norway, closely mimicking the sociodemographic (PhD Francesco Di Ruscio UiO/NIPH; from 2019 NIPH).

Contribution 2020-2022

In February 2020, we quickly mobilised a COVID-19 modelling team with our partners in BigInsight: UiO, NR and Telenor. We provided weekly situational awareness and forecasting reports from March using Norwegian real-time registry data (BEREDT C19). We conducted short-deadline scenario modelling at requests from the government and internally at NIPH. We also received informal requests from hospitals and other stakeholders.

The complexity and breadth of the modelling and data analytics increased over time due to changes in data quality, new knowledge, arrival of novel strains, vaccines, shifts in policy questions, etc., necessitating constant developments. The workload was high and intense throughout. Key methods and deliveries include:

Situational awareness and forecasting (165+ reports March 2020-2022) (C1/C2):

- *National/Regional Changepoint Model:* We adjusted R1 to SARS-CoV-2 and county-level geography of Norway, informed by real-time Norwegian mobility data. The models assumed constant reproduction numbers within specific periods, offset by manually chosen "changepoints", linked to intervention changes. We developed a novel split-ABC-SMC inference technique for high-dimensional calibration(R3).

- *National/Regional Sequential Monte Carlo (SMC) Model:* Using a similar metapopulation structure, we developed a model providing daily-varying reproduction numbers nationally and regionally. The models were fitted adopting an SMC inference technique using resampling of weighted particles for faster calibration (R4).
- *Key outputs: R-numbers, hospital capacity needs, case counts, county mobility trends*

Scenario modelling (40+ reports from May 2020 – 2022):

- *Individual-based model (IBM):* We adapted R2 to model SARS-CoV-2 transmission in Norway using a geolocated grid of 13,521 cells with 5.4 million individuals having multiple attributes, including age, household size, and occupation, based on census data. (R5).
- *Metapopulation model:* In tandem, we developed an age- and risk-structured model for Norway separated into 10-25 regions representing Norway with age-specific mixing based on Norwegian contact matrices and mobile phone data for travel between regions (R5).
- *Key output:*
    - Modelling age- and geographic prioritisation of vaccines (C3)
    - Modelling for health-economic evaluations, Holden Utvalg (II-IV) (C4)
    - Modelling long-term strategies/risk evaluations as a knowledge base into NIPH's advising on policies (C1)
- We produced results on specific aspects of the COVID-19 epidemiology and behaviour relevant to managing COVID-19. For example, analyses of contact tracing data showing increased household transmission and effects of vaccination on Delta and Omicron transmission(R6).

Contribution post COVID-19:

- We continue to document our work through publications, including quantifying the drop in social contacts in Norway in 2020 using Norwegian adult panel data (C6)
- We make methodological developments of IBM calibration (PhD started 2023 in collaboration with Dept. of Physics UiO).
- We extend and use our models through participation in international forecasting hubs ECDC RespiCast and CDC FluSight.

NIPH: Birgitte Freiesleben de Blasio (leader/ 20% OCBE UiO), Francesco Di Ruscio (researcher), Gunnar Rø (reseacher), Alfonso Diz-Lois Palomares (researcher), Jonas Christopher Lindstrøm (researcher), Anja Bråthen Kristoffersen (researcher, started May 2020), Louis Yat Hin Chan (postdoc 2020-2022); Jørgen Midtbø (researcher, started March 2021), Neda Jalali (postdoc 2021-2022), *infrastructure* Richard White (researcher), Gry Grøneng (researcher), Chi Zhiang (researcher/PhD OCBE).
UiO: Oslo Centre for Biostatistics and Epidemiology (OCBE) Arnoldo Frigessi (co-lead), Chi Zhiang (researcher/PhD), David Swanson (researcher May-June 2020); Geir Storvik (senior researcher), Department of Mathematics. Norwegian Computing Centre (NR) Solveig Engebretsen (researcher); Telenor Research Kenth Engø-Monsen

3. References to the research (indicative maximum of six references)

R1: Engebretsen, S., Engø-Monsen, K., Aleem, M.A., Gurley, E.S., Frigessi, A. and De Blasio, B.F., 2020. Time-aggregated mobile phone mobility data are sufficient for modelling influenza spread: the case of Bangladesh. *Journal of the Royal Society Interface*, *17*(167), p.20190809.

R2: Di Ruscio, F., Guzzetta, G., Bjørnholt, J.V., Leegaard, T.M., Merler, S. and De Blasio, B.F., 2019. Quantifying the transmission dynamics of MRSA in the community and healthcare settings in a low-prevalence country. *Proceedings of the National Academy of Sciences*, *116*(29), pp.14599-605.

R3: Engebretsen, S., Diz-Lois Palomares, A., Rø, G., Kristoffersen, A.B., Lindstrøm, J.C., Engø-Monsen, K., Kamineni, M., Hin Chan, L.Y., Dale, Ø., Midtbø, J.E. and Stenerud, K.L., Di Ruscio, F., White, R., Frigessi, A., De Blasio, B.F., 2023. A real-time regional model for COVID-19: Probabilistic situational awareness and forecasting. *PLOS Computational Biology*, *19*(1), p.e1010860.

R4: Storvik, G., Diz-Lois Palomares, A., Engebretsen, S., Rø, G.Ø.I., Engø-Monsen, K., Kristoffersen, A.B., de Blasio, B.F. and Frigessi, A., 2023. A sequential Monte Carlo approach to estimate a time-varying reproduction number in infectious disease models: the Covid-19 case. With discussion. *Journal of the Royal Statistical Society Series A*, *186*(4), pp.616-632.

R5: Chan, L.Y.H., Rø, G., Midtbø, J.E., Di Ruscio, F., Watle, S.S.V., Juvet, L.K., Littmann, J., Aavitsland, P., Nygard, K.M., Berg, A.S. and Bukholm, G., Kristoffersen, A.B., Engø-Monsen, K., Engebretsen, S., Swanson, D., Diz-Lois Palomares, A., Lindstrøm, J.C., Frigessi, A. De Blasio, B.F.,2023. Modeling geographic vaccination strategies for COVID-19 in Norway. Accepted by PLOS *Computational Biology*, available on *medRxiv*

R6: Jalali, N., Brustad, H.K., Frigessi, A., MacDonald, E.A., Meijerink, H., Feruglio, S.L., Nygård, K.M., Rø, G., Madslien, E.H. and De Blasio, B.F., 2022. Increased household transmission and immune escape of the SARS-CoV-2 Omicron compared to Delta variants. *Nature Communications*, *13*(1), p.5706.

3. Details of the impact

Our modelling team provided continuous and timely support to the government and health authorities to inform policy decisions throughout the COVID-19 pandemic in Norway. The instrumental policy impact spanned from early 2020 to the spring of 2022. However, the effect of the research reaches beyond this day, contributing to enhanced preparedness for future pandemics.

Our success was facilitated by collaborations with research institutions in Oslo, leveraging existing modelling partnerships to swiftly scale up activity during the crisis. We also benefited from unique access to real-time Norwegian registry data at NIPH (Beredt C19), and in-house expertise in infection control, surveillance, virology, and vaccination critically supported the development of our models.

The team was responsible for data curation, methodology development, and infrastructure pipeline management, utilising high-performance computing clusters at UiO (Sigma2/USIT) for model execution, visualisations, and report writing. Typically, models for assessment of the SARS-CoV2 transmission were launched on Monday mornings to use the most recent day for the weekly reports that were published at noon on Wednesdays. The latter part of the week was focused on developments and test runs. Reports were written in English for accessibility, featuring results with uncertainty intervals about regional and national developments, county mobility trends, and foreign roamers. Alongside, on requests, scenario modelling involving major model developments and testing had to be planned and executed with short deadlines. We also addressed questions from hospitals regarding staff planning, and from health authorities regarding stockpiling of medical equipment.

Our results were included in presentations to the government, and we presented results in meetings with health authorities, including municipal doctors. The modelling outcomes and the uncertainties were part of the public discourse. Our results commonly made headlines in national newspapers and were commented on by researchers, e.g. on Twitter. Team members were often approached directly by journalists or via the communication department at NIPH.

The Koronakommisjonen evaluating the Norwegian authorities' handling of the COVID-19 pandemic states in their second report, April 2022: "*The country's population and its authorities have handled the pandemic well overall. Norway has had one of Europe's lowest mortality rates, least restrictive infection control regimes and smallest declines in economic activity*". NIPH contributed to this success, including through modelling.

To further corroborate, the final evaluation report by the Koronautvalget, June 2023,(C9) concludes on mathematical modelling: "*Throughout the pandemic period, projections of infections, admissions and sickness absence were an important part of the authorities' decision-making. Projections [..] can take the form of "forecasts" -thought to be most likely future development - and "scenarios", i.e. different more or less realistic outcomes based on various assumptions, such as the virus's contagiousness. The purpose of scenarios is often to show a possible outcome space, not to*

predict the most likely development. The committee believes such projections have clear utility value as a basis for decision-making and therefore should be employed in future crises".

The Koronautvalget report further highlights challenges in effectively communicating modelling uncertainties. We experienced difficulties conveying the meaning of scenarios, often misinterpreted as forecasts (C7). We made our short-term forecasts by keeping the most recent trend in data constant, i.e. assuming a "no-change policy" to support policy decisions, which led to misconceptions. Critiques emerged when our forecasts retrospectively were perceived as too high or too low when policy measures had changed (C7). Furthermore, the lack of critical Norwegian seroprevalence data gave rise to uncertainties and potential biases in our results.

Concerning impact within the research community, we regularly met with modellers at our Nordic sister organisations during the crisis to discuss models and relevant data to inform policies. We also participated in international and national scientific meetings (C8), contributing to discussions, and providing results when possible. However, given the time pressure, contacts with other Norwegian academic modelling teams were limited. In November 2022, we arranged a 2-day network modelling workshop with the Norwegian Science Programme on COVID-19 with participation from UiO, UiB, NTNU and NORCE and NMBU. Norwegian modellers presented their work, and we initiated discussions on collaborating and building modelling capacity for the next pandemic, data sharing problems, etc.

Another impact of our work is an improved understanding of infectious disease epidemiology, like reproduction numbers, and the usefulness of infectious disease modelling in the broader public.

Finally, on long-term impact, we are working on several papers to bolster preparedness for future pandemics, including studies on modelling the Omicron wave in Norway with exit strategies around the start of 2022 and a health-economic evaluation to optimise non-pharmaceutical interventions during pandemics.

4. Sources to corroborate the impact

C1: NIPH COVID-19 modelling webpage with links to reports:
https://www.fhi.no/en/id/corona/coronavirus/coronavirus-modelling-at-the-niph-fhi/

C2: Example of situational awareness report, 24 March 2021
https://www.fhi.no/contentassets/e6b5660fc35740c8bb2a32bfe0cc45d1/vedlegg/nasjonale-og-regionale-rapporter/2021.03.24-national_regional_model.pdf

C3: Example of scenario modelling report for geographic prioritisation March 2021 (In Norwegian)
https://www.fhi.no/contentassets/e6b5660fc35740c8bb2a32bfe0cc45d1/vedlegg/nasjonale-og-regionale-rapporter/oppdrag_8_2303_bfdblasio.pdf

C4: Example of modelling for health economic evaluations (Holden Utvalg III – part 2 -March 2021
https://www.helsedirektoratet.no/rapporter/samfunnsokonomisk-vurdering-av-smitteverntiltak-covid-19/Samfunns%C3%B8konomiske%20vurderinger%20av%20smitteverntiltak%20-Tredje%20rapport%20%20del%202%20(15.%20mars%202021).pdf/_/attachment/inline/d543e9b0-907e-4de887594ca5061fa1d9:f1cb9a46c5015eac6f01693e91b3eefa71a12bd9/Samfunns%C3%B8konomiske%20vurderinger%20av%20smitteverntiltak%20-Tredje%20rapport%20-%20del%202%20(15.%20mars%202021).pdf

Further articles to corroborate our impact:

C5: Use of Norwegian mobile phone data reveals different effects of non-compulsory and mandatory COVID-19 interventions in urban vs rural areas in Norway
https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2023.28.17.2200382

C6: We participated in the pan-European COMIX study, providing information on behaviour and social mixing during the pandemic for use in models:
https://www.medrxiv.org/content/10.1101/2023.11.18.23298731v1

C7: Selections from the media (In Norwegian):
-Interview with Solveig Engebretsen, "The Corona hunter" Dagens Næringsliv 5 May 2020
www.dn.no/d2/ledestjerner/ledestjerner-2020-koronajegeren/7-1-obyurjfq
-Interview with Gunnar Rø and Alfonso Diz-Lois Palomares in Computer World, 6 January 2021
https://www.cw.no/jakten-pa-en-presis-beskrivelse-av-epidemien/506145
-Aftenposten makes mistakes on forecasts. Again and again. Aftenposten, 18 June 2021,
https://www.aftenposten.no/meninger/kronikk/i/7KbAKo/aftenposten-bommer-om-prognoser-igjen-og-igjen, our answer to the article on Aftenposten of 15 June 2021:
https://www.aftenposten.no/norge/i/0KLBLG/prognosene-bommet-fullstendig-paa-antallet-pasienter-igjen-og-igjen
-No a single calculation did not keep Norway closed. Aftenposten, 4 February, 2022.
https://www.aftenposten.no/meninger/kronikk/i/8QLwbW/nei-eit-reknestykke-held-ikkje-noreg-stengt, our answer to the article on Aftenposten of 1 February 2022
https://www.aftenposten.no/norge/i/ALWwEj/her-er-regnestykkene-som-holdt-norge-stengt-enda-lenger
In English: COVID-19: The Norwegian model, The UNESCO Courier, 15 December 2022,
https://courier.unesco.org/en/articles/covid-19-norwegian-model

C8: Selection of talks at virtual conferences/events:
Talk 17 March 2022 at The Turing Institute by Birgitte F de Blasio and Arnoldo Frigessi:
https://www.turing.ac.uk/events/probabilistic-approach-situation-awareness-and-forecasting-covid-19-pandemics-norway
Talk 8 June 2022 on the Norwegian experience with use of mobile phone data in modelling at the National Academies of Sciences USA Workshop by Birgitte F de Blasio
https://nap.nationalacademies.org/catalog/26645/location-data-in-the-context-of-public-health-research-and-law-enforcement-an-exploration-of-governance-frameworks
and later contributions:
Talk 15 March 2023 by Alfonso Diz-Lois Palomares at Bayes Comp on use of Bayesian computation to track the COVID-19 pandemic
https://bayescomp2023.com/programme
Talks at the Nordita workshop 23-27 May 2023 on the COVID-19 modelling work by Francesco Di Ruscio and Jørgen Midtbø
Unifying the Epidemiological and Evolutionary Dynamics of Pathogens (29 May 2023 - 23 June 2023): Main Page · Agenda (Indico) (su.se)

C9: The Koronautvalget report on the evaluation of the management of the pandemic in Norway
https://www.regjeringen.no/no/dokumenter/nou-2023-16/id2982388/

C10: Camilla Stoltenberg, former head of Norwegian Institute of Public Health, thanks BigInsight for the collaborative modelling work during the pandemic (video with English translation):
https://www.biginsight.no/news/2023/11/21/biginsight-celebration-day-was-fun

[Norwegian Institute of Public Health, Division of Mental and Physical Health] [1]

Institution: Norwegian Institute of Public Health
Administrative unit: Division of Mental and Physical Health
Title of case study: Disease burden analyses
Period when the underpinning research was undertaken: 2010 - 2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2012 - 2022
Period when the impact occurred: 2015 - 2022

1. Summary of the impact

Our disease burden analyses provide the overview needed by policy makers to monitor progress towards the public health targets, promote an evidence-based public health policy and adjust the capacity in the health system. We have generated knowledge on the comparative disease burden impact from fatal and non-fatal causes and avoidable risk factors, forecasted the future disease burden, demonstrated socioeconomic differences in disease burden, and monetized the effect of reducing disease burden due to air pollution. This knowledge serves as evidence-base of policy plans, strategies, programs and reforms aimed to meet current and future needs in the health and welfare systems.

2. Underpinning research

The Centre of Disease Burden has since its establishment in January 2017 served as the Norwegian arm of the Global Burden of Disease (GBD) study, a large-scale international collaboration that provides comprehensive overviews of causes of mortality and disability, as well as the impact of risk factors, across geographies, time, age-groups and sex. We also do our own research on disease burden beyond what is done by GBD.

Disease burden analyses

Since 2013, GBD has released country-wise estimates on disease burden, providing a complete overview of the relative and absolute impact from sources of health loss in the Norwegian population. Important insights include the contribution from non-fatal health outcomes such as mental disorders on the total disease burden, as well the burden attributable to avoidable risk factors (source 1). A collaborative effort between the Centre and the GBD resulted in the integration of disease burden results by Norwegian counties in the GBD 2019 release, highlighting large similarities overall, while noting some important differences between counties (source 2). Analyses led by the Centre also identified crucial differences in life expectancy, disease burden and risk factor attribution across the Nordic region (source 3).

Forecasting

Forecasting future disease burden is a strategic target area for both the GBD project and NIPH, and our close collaboration has given the Centre unique access to GBD forecasting results on disease burden in Norway (up till 2050). Published in 2022, the results demonstrated changes in future disease burden due to aging of the population (source 4).

Analyses based on primary data

The Centre expands the knowledge produced by GBD by employing disease burden methodology on Norwegian and Nordic primary data. We have documented large socioeconomic differences in disease burden in Norway (source 5), and quantified associated costs and productivity losses with disease burden. Further, we have estimated the disease burden due to air pollution and

transportation noise, and calculated the cost-effectiveness of interventions reducing exposure to air pollution (source 6).

Key researchers

Professor Stein Emil Vollset (2013 – 2018). Founder and first director of the Centre. Has led the work on Future Health Scenarios in GBD since 2018. Returned to NIPH in 2023 to establish the GBD Collaborating Unit on Future Health Scenarios.

Professor Simon Øverland (2018 – 2021). Director of the Centre, and member of GBD Scientific Council. Key in incorporating Norwegian counties into GBD.

Senior researcher Ann Kristin Knudsen (2014 – td). Researcher and current director of the Centre, member of GBD Scientific Council. Active in the dissemination of GBD results to Norwegian policy makers and in establishing the Nordic Burden of Disease collaborating network.

Senior researcher Jonas Minet Kinge (2013 – td). Researcher on economic costs and socioeconomic differences in disease burden, which have had great policy impact.

Researcher Benjamin Clarsen (2019-2023). Led the work on county differences in disease burden, and diet related disease burden in the Nordic and Baltic countries.

Senior researchers Gunn Marit Aasvang and Anette Kocbach Bølling (2018-td). Lead the work on environmental related disease burden.

2. References to the research (indicative maximum of six references)

Research group members are highlighted in bold.

1) GBD 2013 DALYs and HALE Collaborators*. Global, regional, and national disability-adjusted life years (DALYs) for 306 diseases and injuries and healthy life expectancy (HALE) for 188 countries, 1990-2013: quantifying the epidemiological transition. Lancet. 2015 Nov 28;386(10009):2145-91. doi: 10.1016/S0140-6736(15)61340-X.
2) **Clarsen B,** Nylenna M, **Klitkou ST, Vollset SE, Baravelli CM, Bølling AK, Aasvang GM, Sulo G,** Naghavi M, Pasovic M, Asaduzzaman M, Bjørge T, Eggen AE, Eikemo TA, Ellingsen CL, Haaland ØA, Hailu A, Hassan S, Hay SI, Juliusson PB, Kisa A, Kisa S, Månsson J, Mekonnen T, Murray CJL, Norheim OF, Ottersen T, Sagoe D, Sripada K, Winkler AS, **Knudsen AKS.** Changes in life expectancy and disease burden in Norway, 1990-2019: an analysis of the Global Burden of Disease Study 2019. Lancet Public Health. 2022 Jul;7(7):e593-e605. doi: 10.1016/S2468-2667(22)00092-5.
3) **Knudsen AK**, Allebeck P, **Tollanes MC,** Skogen JC, Moesgaard Iburg K, McGrath JJ, Juel K, Agardh EE, Ärnlöv J, Bjorge T, Carrero JJ, Cederroth CR, Eggen AE, El-Khatib Z, **Ellingsen CL,** Fereshtehnejad SM, Gissler M, Hadkhale K, Havmoeller R, Johansson L, Juliusson PB, Kiadaliri AA , Kisa S, Kisa A, Lallukka T, Mekonnen T, Meretoja TJ, Meretoja A, Naghavi M, Neupane S, Nguyen TT, Petzold M, Plana-Ripoll O, Shiri R, Sigurvinsdottir R, **Skirbekk V**, Skou ST, Sigfusdottir ID, Steiner TJ, **Sulo G**, Truelsen TC, Vasankari TJ, Weiderpass E, **Vollset SE**, Vos T, **Overland S.** Life expectancy and disease burden in the Nordic countries: results from the Global Burden of Diseases, Injuries, and Risk Factors Study 2017. Lancet Public Health. 2019 Dec;4(12):e658-e669. doi: 10.1016/S2468-2667(19)30224-5.
4) **Knudsen AK, Sulo G, Klikou S, Vollset SE.** Disease burden in Norway 2050. In the Public Health Report Thematic Publication 2022: Future Public Health Challenges in Norway [Sykdomsbyrde i Norge i 2050. Folkehelserapportens temautgave 2022. Framtidens utfordringer for folkehelsen.] Report. 2022. Oslo: Norwegian Institute of Public Health. https://www.fhi.no/he/fremtidens-utfordringer-for-folkehelsen/del-1-3/sykdomsbyrde-i-norge-i-2050/?term=
5) **Kinge JM,** Modalsli JH, **Øverland S,** Gjessing HK, **Tollånes MC, Knudsen AK, Skirbekk V,** Strand BH, Håberg **SE, Vollset SE.** Association of Household Income With Life Expectancy

and Cause-Specific Mortality in Norway, 2005-2015. JAMA. 2019 May 21;321(19):1916-1925. doi: 10.1001/jama.2019.4329.

6) Norwegian Environment Agency, the Norwegian Public Roads Administration, **the Norwegian Institute of Public Health** and the Norwegian Meteorological Institute. Limit values for particulate matter: revision of Norwegian limit values for PM10 and PM2.5. [Grenseverdier for svevestøv. Forslag til reviderte grenseverdier for PM10 og PM2,5.] Report 2020. https://www.miljodirektoratet.no/globalassets/publikasjoner/m1669/m1669.pdf, and the NIPH

* The Centre for Disease Burden at NIPH is the Norwegian arm of the Global Burden of Disease (GBD) project. All GBD results are updated in each iteration of GBD, and published on the project website, as well as in capstone papers in the Lancet. Members of the Centre are co-authors on these publications.

3. Details of the impact

Disease burden analyses are highly warranted by policy makers, and as part of NIPH, the Centre of Disease Burden is uniquely positioned to ensure direct impact on policy. We provide the overview needed by the health authorities to monitor progress towards the Norwegian public health targets, promote an evidence-based public health policy and adjust the capacity in the health system to meet current and future needs. Our research is made known for our stakeholders through both written reports, as well as direct contact and presentations in meetings and seminars with relevant ministries, directorates, and other stakeholders. Our knowledge has served as the evidence-base in a range of policy plans, strategies, programs and reforms aimed to meet current and future needs in the public health and health and welfare service arenas. In the following, we will give some examples of our policy impact.

Disease burden analyses, including socioeconomic differences in disease burden

In March 2015, the first **Public Health Plan** (source 1) from the Ministry of Health was released. Evidence from the GBD project, processed, detailed, and presented by the Centre, provided essential insights for this plan, and affected several of the stated targets. For instance, the results revealed a high disease burden due to mental health in Norway, but also identified a lack of necessary data to monitor mental disorders in the population. This served as a key argument by the Government for integrating mental health as an important and focused part of the public health work, as well as initiate data collection on mental disorders, piloted in the HUNT study (November 2018 to September 2020). The following Public Health Plans (**Public Health Plan of 2018-2019,** released in April 20219, source 2 and **Public Health Plan of 2022-2023**, released in April 2023, source 3), have underscored the significance of disease burden analyses as a vital source of information regarding the health status in Norway. In the latest Public Health Plan (source 3), great attention was also given to our evidence on social inequalities in disease burden, strengthening the knowledge-base for the current government's strategy to eliminate social inequalities in health. In addition, we provided knowledge on excess mortality during the COVID-19 pandemic and future health challenges, as identified by our forecasting analyses. Disease burden analyses were also part of the evidence-base for the **National Health and Hospital Plan (2020 – 2023)** of November 2019, demonstrating the increasing burden from neurological diseases, diabetes and mental disorders, and the related impact this have on current and future health service needs (source 4).

Based on data from GBD, we have generated rankings of the most important causes and risk factors for disease burden in Norway. This served as the basis for the Health Directorates **recommendations for interventions to reduce disease burden and improve public health** in September 2018 (source 5). These recommendations were also incorporated in the Governments

Public Health Plans. In addition, we contributed with assistance, analyses and input in the Health Directorate's recommendations on the introduction of fruit and free meals at schools, the societal and economic benefits of following the Directorates diet recommendations, and in calculation of societal costs of diseases and injuries. Work conducted at the Centre has also contributed to the evidence base of the revised **Nordic Nutrition Recommendations** (source 6).

Disease burden is frequently discussed as a relevant criterion for prioritization of health resources, and our research has been used to inform these discussions in **prioritization reports** from both the Norwegian Government in 2015-2016 (source 7) and the Finnish Government in 2022 (source 8).

Disease burden from air pollution and noise
In a **joint report** (source 9) from the Norwegian Environment Agency, the Norwegian Public Roads Administration, the Norwegian Meteorological Institute, and the NIPH, the Centre was responsible for developing methodology for assessment of the burden of disease due to particulate matter (PM) in Norway, including quality control, comparison with GBD estimates and sensitivity analyses. The change in BoD due to implementation of policies were monetized and included in a cost-benefit analysis. The Norwegian limit values for PM2.5 and PM10 were lowered as of January 1st 2022 as a result of this work.

Forecasting and future health scenarios
Forecasts of future health scenarios are highly warranted for planning and scaling of the health services, the welfare state and public health work. Our forecasting of future disease burden has been used in a range of policy documents, reports and reforms. One example of this is **the Perspective Plan (2020-2021)** (source 10), in which the Ministry of Finance presented key strategies to address future demographic, social, economic and climate challenges.

5. Sources to corroborate the impact (indicative maximum of ten references)

1) Meld. St. 19 (2014-2015). Folkehelsemeldingen. Mestring og muligheter
2) Meld. St. 19 (2018-2019). Folkehelsemeldinga. Gode liv i eit trygt samfunn
3) Meld. St.15 (2022-2023). Folkehelsemeldinga. Nasjonal strategi for utjamning av sosiale helseforskjellar.
4) Meld. St. 7 (2019-2020). Nasjonal helse- og sykehusplan 2020-2023.
5) Helsedirektoratet (2018). Ti tiltak for å redusere sykdomsbyrden og bedre folkehelsen.
6) Nordic Nutrition Recommendations 2023. Integrating Environmental Aspects.
7) Meld. St. 34 (2015-2016). Verdier i pasientens helsetjeneste. Melding om prioritering.
8) Terveydenhuollon palveluvalikoiman priorisointi. Valtioneuvoston selvitys- ja tutkimustoiminnan julkaisusarja 2022:53
9) Grenseverdier for svevestøv. Forslag til reviderte grenseverdier for PM10 og PM2,5.
10) Meld. St. 14 (2020-2021). Perspektivmeldingen 2021.

Impact case guidelines

Each case study should include sufficiently clear and detailed information to enable the evaluation committee to make judgements based on the information it contains, without making inferences, gathering additional material, following up references or relying on members' prior knowledge. References to other sources of information will be used for verification purposes only, not as a means for the evaluation committee to gather further information to inform judgements.

In this evaluation, impact is defined as an effect on, change or benefit to the economy, society, culture, public policy or services, health, the environment or quality of life, beyond academia.

Timeframes

- The impact must have occurred between 2012 and 2022
- Some of the underpinning research should have been published in 2012 or later
- The administrative units are encouraged to prioritise recent cases

Page limit

Each completed case study template will be limited to **five pages** in length. Within the annotated template below, indicative guidance is provided about the expected maximum length limit of each section, but institutions will have flexibility to exceed these so long as the case study as a whole remains no longer than **five pages** (font Calibri, font size 11). Please write the text into the framed template under the sections 1–5 below. The guiding text that stands there now, can be deleted.

Maximum number of cases permitted per administrative unit

For up to 10 researchers: one case; for 10 to 30 researchers: two cases; for 30-50 researchers: three cases; for 50-100 researchers: four cases, and up to five cases for units exceeding 100 researchers.

Naming and numbering of cases

Please use the standardised short name for the administrative unit, and the case number for the unit (1,2,3, etc) in the headline of the case. Each case should be stored as a separate PDF-document with the file name: [Name of the institution and name of the administrative unit] [case number]

Publication of cases

RCN plans to publish all impact cases in a separate evaluation report. By submitting the case the head of the administrative units consents to the publication of the case. Please indicate below if a case may not be made public for reasons of confidentiality.

If relevant, describe any reason to keep this case confidential:

Not relevant

Norwegian Institute of Public Health, Division of Mental and Physical Health, case number 2

Institution: Norwegian Institute of Public Health
Administrative unit: Division of Mental and Physical Health
Title of case study: CO-CREATE - Confronting Obesity: Co-creating policy with youth
Period when the underpinning research was undertaken: 2018-2023
Period when staff involved in the underpinning research were employed by the submitting institution: 2018-2023
Period when the impact occurred: 2018-2023

1. Summary of the impact (indicative maximum 100 words)

The H2020 funded "CO-CREATE - Confronting Obesity: Co-creating policy with youth" developed tools, methodologies and resources that have had an impact on youth involvement in policy decision making processes; a dialogue forum tool, methods for youth involvement in policy making, Youth-led Change toolkit developed by youth; and a Youth Task Force declaration written by youth. In addition, CO-CREATE had a role in the development of MOVING policy database complementing the NOURISHING database https://policydatabase.wcrf.org/ , which were benchmarked for their youth relevance.

2. Underpinning research (indicative maximum 500 words)

The CO-CREATE was coordinated by the NIPH and the Centre for Evaluation of Public Health Measures. The project has published more than 45 scientific papers, with several new papers in the pipeline. The project synthesized systematic reviews of interventions aimed at preventing overweight and obesity among adolescents. The findings revealed a scarcity of evidence supporting interventions' impact on adolescents' body mass index and physical activity levels, and little evidence of youth involvement in the research literature (Flodgren et al 2020).

The project conducted group building sessions with youth groups in five European countries (2019-2020) and delivered of a set of visual system maps of policy-dependent multi-level drivers of adolescent obesity across five countries: the Netherlands, Norway, Poland, Portugal, and the United Kingdom. These sessions provided new research evidence of European youth's perspectives on factors influencing their energy balance related behaviour. We found that youth's perspectives somehow the evidence from the research literature.

In each of the five countries, 15 Youth Alliances in five European and South Africa were established with the aim to engage and empower diverse youth and co-create policy proposals for overweight and obesity prevention. The project successfully engaged youth in participatory action towards system-directed obesity prevention. A total of 199 adolescents were engaged coming from diverse backgrounds in terms of urban/rural, economic, and ethnic backgrounds. Together with youth organizations and building on youth led participatory action, the alliances developed and implemented a set of participatory activities which were flexibly applied according to local conditions and the youth-led process in the Alliances. Through the Youth Alliances, over 100 ideas for overweight and obesity prevention policies were generated and 29 of those were further developed through participatory action. Adolescents were empowered, had new experiences, and were trained in policy planning and negotiations.

In CO-CREATE we developed both a digital and a physical Dialogue Forum tool which is an inclusive space for discussion and co-creation across generations and sectors. The free canvas and a five-step process are designed to allow participants to connect with others, discuss an idea or

intervention, and collaborate on action. The tool and process, developed for and with young people, promotes youth inclusion and leadership in policy decision making. The Dialogue Forum tool has been used both within the project but also in many occasions outside the project.

The key researchers at the administrative unit at the time of the research were: Knut-Inge Klepp (PI), Arnfinn Helleve (WP-leader), Anne-Siri Fismen (2019-2022, post doc), Jonas Rekdal Mathisen (2021-2022, researcher), Isabelle Budin Ljøsne (researcher), Gerd Flodgren (researcher)

3. References to the research (indicative maximum of six references)

Most recent, relevant research output:

Klepp K-I, Helleve A, Brinsden H, et al. Overweight and obesity prevention for and with adolescents: The "Confronting obesity: Co-creating policy with youth" (CO-CREATE) project. Obesity Reviews. 2023; 24(S1):e13540. doi:10.1111/obr.13540

Bröer C, Ayuandini S, Baillergeau E, Moerman G, Veltkamp G, Luszczynska A, Budin-Ljøsne I, Rito AI, Stensdal M, Lien N, Klepp KI. Recruiting and engaging adolescents in creating overweight and obesity prevention policies: The CO-CREATE project. Obes Rev. 2023 Feb;24 Suppl 1:e13546. doi: 10.1111/obr.13546. Epub 2023 Jan 9. PMID: 36623291

C. Bröer, G. Veltkamp, S. Ayuandini, E. Baillergeau, G. Moerman, R. de Sauvage, A. Banik, A. Luszczynska, A. Rito, S. Mendes, K.-I. Klepp, A. Helleve, S. Nesrallah, N. Lien, N. Kaur Grewal, Negotiating policy ideas: Participatory action research projects across five European countries, Ethics, Medicine and Public Health, 28, 2023, https://doi.org/10.1016/j.jemep.2023.100905.

Budin-Ljøsne I, Ayuandini S, Baillergeau E, et al. Ethical considerations in engaging young people in European obesity prevention research: The CO-CREATE experience. Obesity Reviews. 2023; 24(S1):e13518. doi:10.1111/obr.13518

Conway-Moore K, Knai C, Finegood D, et al. Co-creating obesity prevention policies with youth: Policy ideas generated through the CO-CREATE project. Obesity Reviews. 2023; 24(S2):e13623. doi:10.1111/obr.13623

Ulloa MA, Nesrallah S, Shafafi P, et al. Designing a youth-led Dialogue Forum tool: The CO-CREATE experience. Obesity Reviews. 2023; 24(S2):e13611. doi:10.1111/obr.13611

4. Details of the impact (indicative maximum 750 words)

The research activities in CO-CREATE on youth involvement were theoretically guided by models on youth involvement by the leading academic work on youth involvement (i.e. Hart (1992), Shier (2001) and OECD (2017)). These models describe the different degrees of involvement, where CO-CREATE aimed involving youth through collaboration (i.e. exploring youth perspectives through group model building, development of policy idea in youth alliances and dialogue with policy makers) and empowerment (i.e. the youth initiated CO-CREATE Youth Task Force). The Youth Alliances in the five European countries were implemented as participatory action research (PAR), guided by the four principles of benefitting from young people's direct experience, valuing knowledge in action, conducting research as a transformative process and through collaboration in dialogue (Cornish et al 2023). The impact of the CO-CREATE tools and resources was secured actively dissemination through the youth organisation involved in the project, presentations and

demonstrations at national (i.e. Norwegian Public Health conference, 2022) and international conferences (Health and Well-being Forum for Youth, 2023), a designated web-site (Healthy Voices: https://www.worldobesity.org/healthy-voices) and in other settings.

CO-CREATE was initiated and coordinated by Knut-Inge Klepp, and the administrative unit for the project was Centre for Evaluation of Public Health Measures. The project had 14 partners in total: 1 youth organisation, 3 policy organisations and 10 academic research institutions across Europe. It was organised into 10 work packages, but with integrated and interdependent research activities. As coordinator, the Centre was involved in all the WPs and activities in the project.

The beneficiaries of the projects outcomes are relevant for policy processes in any constituency or organisation, but particularly when children and youth are involved. The tools and resources developed by the project will secure the integrity of children and youth in policy processes where they are involved as stakeholders. The CO-CREATE tools and resources can furthermore be seen in relation to UN Convention on the Rights of the Child, particularly §15 stating children and youth have their rights to express their views freely in all matters affecting themselves and they shall be provided an opportunity to be heard.

CO-CREATE has provided several innovative, evidence-based and ready-to-use tools and strategies. The description of and experiences with youth involvement through group model building and alliances activities are innovative ways to bring young people's own perceptions and perspectives forward. The dialogue forum tool, both the digital and physical versions, is freely available and has already been used by other organizations and in other settings than those created by CO-CREATE. The experiences from using the dialogue forum in the variety of policy settings and have demonstrated the applicability and impact of the tools.

The tools develop by CO-CREATE have been used in relation to the EU School Fruit & Vegetable Scheme, in the process leading towards the WHO report "Youth engaged for mental health. A framework for youth participation under the WHO Pan-European Mental Health Coalition", it has been used as a tool for involvement applied by the Norwegian Police Directorate, it has been presented to 48 WHO national focal points and at Youth Health Conferences.

The impacts occurred throughout the project period (2018-2023), but with particular strength in the final years (2021-2023). Throughout the project period, CO-CREATE has been presented at more than 90 conferences, had two symposia at international conferences, produced 11 policy briefs, 38 practice abstracts and 11 webinars.

5. Sources to corroborate the impact (indicative maximum of ten references)

1. Commentary by a CO-CREATE Youth Task Force member: Burzyńska Z. Young people will shape the future. Obesity Reviews. 2023; 24(S1):e13551. doi:10.1111/obr.13551 (Commentary by one of the youth task force members)

2. Description of the content and availability of the Dialogue Forum developed by CO-CREATE: https://eatforum.org/initiatives/co-create/

3. Description of the Youth Advocacy Tool Kit developed by youth involved in CO-CREATE: https://www.worldobesity.org/healthy-voices/advocate/co-creates-youth-advocacy-toolkit

4. CO-CREATE's Youth Taskforce reflection from participation at Health and Well-being Forum for Youth #Youth4Health 25–27 October 2022, Tirana, Albania.

https://www.worldobesity.org/healthy-voices/discuss/blog/co-creates-youth-taskforce-send-a-postcard-from-the-youth4health-event-in-tirana

5. CO-CREATE final conference. At the conference, 48 WHO national focal points for nutrition from European countries attended. October 2023. https://www.fhi.no/en/li/studies/co-create/co-create-final-conference/

6. The Co-Create Dialogue Forum tool was used to support the co-creation of a methodology to develop a youth participation framework for the WHO Euro pan-European Mental Health Coalition. https://cdn.who.int/media/docs/librariesprovider2/euro-health-topics/child-and-adolescent-health/youth-engaged-for-mental-health-eng.pdf?sfvrsn=938e0658_3&download=true

7. The CO-CREATE dialogue Forum tool was used in collaboration with the Norwegian Police Directorate, to support their "Citizens' Voice" work. A follow-up presentation was given to the local Tøyen Police Department in Oslo in September 2023, with the goal of the police using the Dialogue Forum tool for future youth engagement activities.

8. CO-CREATE dialogue forum tool was used in relation to the EU School Fruit & Vegetable Scheme. https://www.fhi.no/contentassets/0a74196d35c64da89d337e25af982f5f/co-create-report-on-pupils-views-on-the-eu-food-schemes-using-the-dialogue-forum-tool.pdf

9. Pre-conference on youth involvement in public health at the Norwegian Conference of Public health, 17.10.2022: https://folkehelsekonferansen.no/program/forkonferanse-barn-unge-og-folkehelse

10. The tools and resources from CO-CREATE will be applied in the new, large Joint Action on prevention of NCDs and cancer, coordinated from Norway https://hadea.ec.europa.eu/system/files/2022-11/JA%20on%20Cancer%20and%20other%20NCDs%20prevention%20action%20on%20health%20determinants.pdf

Norwegian Institute of Public Health, Division of Mental and Physical Health
Case 3

Institution: Norwegian Institute of Public Health
Administrative unit: Division of Mental and Physical Health
Title of case study: Evaluation of Prompt Mental Health Care (PMHC)
Period when the underpinning research was undertaken: 2014-
Period when staff involved in the underpinning research were employed by the submitting institution: 2014-
Period when the impact occurred: 2016-

1. Summary of the impact

The results of the evaluations have contributed to continuation and further dissemination of the Prompt Mental Health Care (PMHC) program in Norway. As such our research has contributed to making evidence-based psychological treatments more available at the primary care level. Moreover, our initial studies have promoted new initiatives to further improve the fidelity and quality of the service, more specifically the implementation of internet-based guided self-help, the inclusion of job-specialists in the service (under development) and development of a national outcome registry for PMHC (under development). Finally, the evaluations have contributed facilitating further dissemination of IAPT in England and inspired similar initiatives in Lithuania.

2. Underpinning research

Prompt Mental Health Care (PMHC) is the Norwegian adaptation of the English "Improving Access to Psychological Therapies (IAPT)". It is a program that aims to reduce the treatment gap for people struggling with anxiety and depression by establishing teams of health care workers (psychologists, nurses, physiotherapists etc.) who can provide cognitive behavioral therapy (CBT) after completing a 1-year training program. More therapists and frequent use of low-intensity treatment forms (guided self-help, group-based psychoeducation) are considered key ingredients to be able to offer evidence-based treatment to more people in need. Important outcomes of the program are decreased symptom pressure, increased quality of life and improved work ability.

PMHC was initially piloted and evaluated in the period 2013-2016 in 12 municipalities. Results of the evaluation indicated that PMHC was associated with clinically significant decreases in symptoms of anxiety and depression and the recovery rates were on par with the initial evaluations of IAPT (50-60%). Quality of life and work participation did also improve. The evaluation also pointed to areas of improvement, most notably the need for increased use of guided self-help in order to optimize the use of available therapist resources, and the need for increased focus on return to work during therapy in order to further improve work outcomes (Smith et al., 2016; Knapstad et al., 2018).

Both IAPT evaluations and the initial PMHC evaluation have been evaluated using single-group pre-post designs and benchmark methodology, which are considered suboptimal research designs. To counter the uncertainty from existing evaluations, we conducted a randomized controlled trial (RCT) of PMHC in two of the pilot sites (Kristiansand and Sandnes) in which PMHC treatment was compared to treatment as usual at the municipality level (TAU). Results indicated moderate to large treatment effects in favour of PMHC on symptoms, (reliable) recovery rate, functioning, and health-related quality of life at 6 months follow-up (Knapstad et al., 2020). These intervention

effects were maintained at 12-month follow-up (Myrtveit Sæther et al., 2020) and among participants in the PMHC group at 24- and 36-months follow-up (Smith et al., 2022).

A process evaluation, conducted in relation to the RCT showed that several aspects of PMHC were implemented in line with the guidelines provided by Norwegian Directorate of Health (Lervik et al., 2020). Importantly, both services reached out to the intended target group, and could further be characterized as low-threshold with relatively short waiting times, no waiting lists, and frequent use of self-referral. From the client perspective, results indicated a high degree of treatment satisfaction, and this was true across demographic characteristics and symptom severity at baseline. Most notable challenges that came forward were again the low provision of guided self-help, the lack of focus on work participation, and the collaboration with other services.

Using registry data from the period 2018-2020, the PMHC group was more likely than TAU to be in regular work without receiving welfare benefits in 2019 and 2020, while no differences were found in 2018 (Smith et al, submitted). Some evidence was found that the PMHC group spent less on health care. The benefit-cost ratio was estimated to 3.73 when comparing overall economic gain in terms of occupational income levels against the overall costs of the intervention. Differences in public sector spendings were negligible. These results supported the societal economic benefit of investing in PMHC-like services.

The following key researchers were involved:

Robert Smith (Research Professor, 2014-)
Marit Knapstad (Research Professor, 2015-)
Leif Edvard Aarø (Research Professor, 2014-)
Linn Vathne Lervik (Phd student 2017-2021)
Solbjørg Makalani Myrtveit Sæther (Post doctor 2017-)

3. References to the research

Smith ORF, Alves DE, Knapstad M. Rask psykisk helsehjelp: Evaluering av de første 12 pilotene i Norge [Prompt Mental Health Care: Evaluation of the first 12 pilot municipalities in Norway]. Folkehelseinstituttet 2016. Rapport. Link: https://www.fhi.no/publ/2016/rask-psykisk-helsehjelp-evaluering-av-de-forste-12-pilotene-i-norge/

Knapstad M, Nordgreen T, Smith ORF: Prompt mental health care, the Norwegian version of IAPT: clinical outcomes and predictors of change in a multicenter cohort study. BMC Psychiatry 2018, 18(1):260. Link: https://doi.org/10.1186/s12888-018-1838-0

Knapstad M, Lervik LV, Sæther, SMM, Aarø LE Smith ORF. Effectiveness of Prompt Mental Health Care, the Norwegian version of Improving Access to Psychological Therapies: A randomized controlled trial. Psychotherapy and Psychosomatics 2020, 89, 90-105. Link: https://karger.com/pps/article/89/2/90/283211/Effectiveness-of-Prompt-Mental-Health-Care-the

Sæther, SMM; Knapstad, M; Grey, N; Rognerud, MA; Smith, ORF. Long-term outcomes of Prompt Mental Health Care: A randomized controlled trial. Behaviour Research and Therapy 2020; Volume 135:103758. s. 1-11. Link: https://doi.org/10.1016/j.brat.2020.103758.

Smith ORF, Sæther SMM, Haug E, Knapstad M. Long-term outcomes at 24- and 36-month follow-up in the intervention arm of the randomized controlled trial of Prompt Mental Health Care. BMC Psychiatry. 2022 Sep 9;22(1):598. Link: https://doi.org/10.1186/s12888-022-04227-0.

Lervik, LV, Knapstad, M, & Smith, ORF (2020). Process evaluation of Prompt Mental Health Care (PMHC): the Norwegian version of Improving Access to Psychological Therapies BMC Health Services Research, 20, 1-17. Link: https://doi.org/10.1186/s12913-020-05311-5.

Smith ORF, Clark DM, Hensing G, Layard R, Knapstad M (submitted). Cost-benefit of IAPT Norway and effects on work-related outcomes and health care utilization: Results from a randomized controlled trial using registry-based data (*available on request*).

4. Details of the impact

The results of our evaluations of PMHC have been important for the continuation and further dissemination of the Prompt Mental Health Care (PMHC) program in Norway. During the pilot period, municipalities received central funding from the Norwegian Directorate of Health for 3-4 years in order to establish the service. After this period, the teams were dependent on funding from the municipality. From 2021, the establishment of new teams became also almost fully dependent on local funding. For people working in the field to be able to show that the PMHC model is evidence-based, alleviates mental health problems, improves quality of life, and increases work participation has been and likely still is an important factor in convincing the leadership at the municipality level to continue with and/or to establish PMHC. The knowledge generated by our work has also contributed to convince the central government to continue the investment in PMHC at a national level by providing funding for training of new therapists, and by providing extensive implementation support. It's also interesting to note that there is broad support for PMHC across political parties. The assertions about the impact of our studies are supported by the fact that our research is widely referred to in documents at the national and local level, as well as by the media.

Our studies have also promoted new initiatives to further improve the fidelity and quality of the service, more specifically:

- The implementation of internet-based guided self-help: we argued in our evaluations that guide-self help should be used much more frequently to improve the efficiency of the service. At the same time, the central government was interested in piloting digital tools to aid psychological treatment at the municipality level. A new project was therefore launched in which a internet-based treatment program was piloted in 6 different PMHC teams across the country (Fosen, Karmøy, Modum, Notodden, Sandnes, Vestvågøy). Our team was asked to evaluate this project in 2020. First results are expected in 2024.
- The inclusion of employment advisers in PMHC (under development): we recommended in our evaluations to initiate measures to improve collaboration between services and to increase focus on work during therapy, amongst others by the inclusion of employment advisers. Late 2023, the government asked the Norwegian Directorate of Health and the Norwegian the Directorate of Labour and Welfare to initiate a pilot project to promote increased collaboration between PMHC teams and the Norwegian Labour and Welfare Administration. It is expected that employment advisers from the Norwegian Labour and Welfare Administration will be placed at PMHC teams on a part-time basis. A scientific evaluation of the pilot will also be conducted.
- The development of a national outcome registry for PMHC (under development): Already in our first report, we have argued for the development of a system that allows for continuous evaluation of the service, similar to the system that IAPT uses. This is both important to ensure model fidelity and for the further development of the service. Late 2022, the Norwegian Directorate of Health was given the assignment to develop such a system for PMHC in Norway.

Finally, the evaluations have contributed to the further expansion of IAPT in England (the results from our cost-effectiveness paper) and inspired similar initiatives in Lithuania (results of our work were presented to 3 different delegations from Lithuania).

5. Sources to corroborate the impact.

Examples of various sources that include descriptions and references to results of our evaluations of PMHC, such as governmental documents, political party programs, webpages and media pages:

Governmental White Paper: Investment plan for mental health 2023-2033 (Meld St. 23):
https://www.regjeringen.no/contentassets/0fb8e2f8f1ff4d40a522e3775a8b22bc/no/pdfs/stm202220230023000dddpdfs.pdf

Homepage National competence center for community-based mental health work (commissioned to facilitate implementation of PMHC):
https://napha.no/content/13931/rask-psykisk-helsehjelp

PMHC Handbook, incl. chapter summarizing results from our evaluations:
https://napha.no/multimedia/10878/rph-handboka.pdf

Homepage Norwegian Association for Cognitive Therapy:
https://www.kognitiv.no/utdanning/vare-videreutdanninger/opplaeringsprogram-i-kognitiv-terapi-for-rask-psykisk-helsehjelp/

National report of municipality-based mental health work 2019: FTEs, competence and content of the services (SINTEF, commissioned by the Norwegian Directorate of Health):
https://www.sintef.no/globalassets/sintef-digital/helse/endelig_rapport_2019_01307.pdf

Report on collaboration between the Norwegian Labour and Welfare Administration (NAV) and PMHC (Oslo Economics 07.11.2020):
https://osloeconomics.no/wp-content/uploads/2021/04/Samarbeid-NAV-og-RPH-17.11.2020.pdf

Kristiansund municipality – 10-year celebration of their PMHC service (took part in the evaluation of the first pilot sites):
https://www.kristiansund.kommune.no/aktuelt/rask-psykisk-helse-i-kristiansund-feirer-10-arsjubileum-med-stor-suksess.44854.aspx

Opinion article in Aftenposten 28.02.2020 (national newspaper) on the need for support to secure continuation and further implementation the PMCH in Norway:
https://www.aftenposten.no/meninger/debatt/i/wPL5M1/norge-trenger-rask-psykisk-helsehjelp-dyregrov-hovgaard-bjoernsund-berge-og-sandvik

National daily news program, case on the results of the first PMHC evaluation, 07.11.2016:
https://tv.nrk.no/serie/dagsrevyen/201611/NNFA19110716

Newspaper coverage (Stavanger Aftenblad) 28.06.2018, on the results of the RCT study:
https://www.aftenbladet.no/lokalt/i/9mdEX5/dette-lavterskeltilbudet-hjelper-folk-ut-av-depresjon

Political party “Høyre” mental health plan, published 2023:
https://hoyre.no/content/uploads/2023/05/Hoyres-plan-for-bedre-psykisk-helsehjelp.pdf

Opinion article in Dagens Medisin (03.05.2023) on the need to invest more in community-based mental health services, such as PMHC:
https://www.dagensmedisin.no/det-er-behov-for-a-styrke-psykiske-helsetjenester-i-kommunene/562713

Impact case guidelines

Each case study should include sufficiently clear and detailed information to enable the evaluation committee to make judgements based on the information it contains, without making inferences, gathering additional material, following up references or relying on members' prior knowledge. References to other sources of information will be used for verification purposes only, not as a means for the evaluation committee to gather further information to inform judgements.

In this evaluation, impact is defined as an effect on, change or benefit to the economy, society, culture, public policy or services, health, the environment or quality of life, beyond academia.

Timeframes

- The impact must have occurred between 2012 and 2022
- Some of the underpinning research should have been published in 2012 or later
- The administrative units are encouraged to prioritise recent cases

Page limit

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For up to 10 researchers: one case; for 10 to 30 researchers: two cases; for 30-50 researchers: three cases; for 50-100 researchers: four cases, and up to five cases for units exceeding 100 researchers.

Naming and numbering of cases

Please use the standardised short name for the administrative unit, and the case number for the unit (1,2,3, etc) in the headline of the case. Each case should be stored as a separate PDF-document with the file name: [Name of the institution and name of the administrative unit] [case number]

Publication of cases

RCN plans to publish all impact cases in a separate evaluation report. By submitting the case the head of the administrative units consents to the publication of the case. Please indicate below if a case may not be made public for reasons of confidentiality.

If relevant, describe any reason to keep this case confidential:

The case may be made public.

Norwegian Institute of Public Health, Division for Metal and Physical Health 4

Institution: Norwegian Institute of Public Health
Administrative unit: Division for Metal and Physical Health
Title of case study: Real-time surveillance of covid-19 immunization program in Norway
Period when the underpinning research was undertaken: 2012-2024
Period when staff involved in the underpinning research were employed by the submitting institution: 2004 - 2024
Period when the impact occurred: 2020-2024

1. Summary of the impact (indicative maximum 100 words)

The **covid-19 immunization** program has been the largest ever vaccination program in Norway. We developed an innovative surveillance system for adverse event monitoring using real time data from the Emergency Preparedness Register. The ability to rapidly establish Nordic collaboration studies to verify findings and increase study population size was crucial. This system was used for systematic monitoring and was especially important in signal evaluation. Our analyses underpinned governmental decision to exclude virus vector vaccines (AstraZeneca Vaxzevria) from the immunization program after acute severe events post-vaccination (VITT - Vaccine-induced Immune Thrombotic Thrombocytopenia). Our data later indicated an excess risk of heart inflammation (myocarditis) in young males after receiving mRNA-vaccines, leading to recommendations to preferentially use Comirnaty over Spikevax for young persons.

2. Underpinning research (indicative maximum 500 words)

The Norwegian Institute of Public Health (NIPH) is a central part of the Norwegian health authorities, delivering recommendations, reviews and research summaries to the Norwegian government. The Department of Chronic Diseases in Division for Mental and Physical Health engages in high-quality research on epidemiology and risk factors of somatic chronic diseases, and has had as a main responsibility surveillance of these. Earlier research has been on environmental factors (such as e.g infections and vaccines during the 2009 swine flu pandemic) and later development of immune-mediated diseases. The department has had a long-standing research focus on use, safety and effect of pharmaceuticals in the general population and among specific groups, such as those with chronic diseases or pregnant women. The department has expertise in epidemiology, statistics, data management and harmonization, and usage of health and administrative register data for research is a core part of the research activity. The department has longstanding collaboration with researchers in all Nordic countries and have extensive experience in combining Nordic register data in research studies. This prior expertise and experience in the department was perfectly suited to take responsibility of surveillance and research on vaccine safety when the SARS-CoV-2 pandemic hit, and to rapidly establish collaborative studies with other Nordic countries. This highlights the importance of establishing and investing in strong research groups to ensure high quality of evidence used in government decision-making processes during “normal” times to have organizational preparedness and expertise to handle health crises like a pandemic. The research underpinning the impact described in section 3 can be broadly grouped into three categories: **1. Supporting the government's efforts in handling the pandemic** through reports and commissioned tasks to the Ministry of Health and Care Services. For instance, our research contributed to estimating prevalence and geographic distribution of individuals at risk for severe COVID-19 outcomes. These figures were utilized in planning vaccination strategies and allocation of vaccines among municipalities. **2. Continuous surveillance of potential vaccine**

adverse events during the pandemic in close collaboration with the Norwegian Medicines Agency (NOMA), by performing repeated analyses in real-time register data as well as in-depth analyses of signals detected in adverse event reporting systems in Norway and the EU. **3. Performing scientific studies** on specific signals of serious vaccine adverse events including EMA- commissioned study on vaccine safety in children and adolescents and disseminating findings to relevant authorities in the Nordic countries and EMA, ECDC, FDA, WHO, and other authorities.

It is worth noting that most of the research results were used and shared during the pandemic prior to publication, which usually takes a long time, and that many results have yet to be published.

Key researchers: Hanne Løvdal Gulseth, Research director/MD, 2020–2024; German Tapia, senior researcher, 2020–2024; Jesper Dahl, researcher/MD 2021–2024; Paz Lopez-Doriga Ruiz, researcher/MD 2020–2023; Øystein Karlstad, senior researcher, 2021–2024; Nina Gunnes, senior researcher/statistician, 2020–2023; Randi Selmer, senior researcher/statistician, 2021–2022; Inger Johanne Bakken, researcher/statistician 2023; Lars Jøran Kjerpeseth, researcher/MD 2023–2024

3. References to the research (indicative maximum of six references)

1. Lopez-Doriga Ruiz P, Gunnes N, Michael Gran J, Karlstad Ø, Selmer R, Dahl J, Bøås H, Aubrey White R, Christine Hofman A, Hessevik Paulsen T, Viksmoen Watle S, Hylen Ranhoff A, Bukholm G, Løvdal Gulseth H, Tapia G. Short-term safety of COVID-19 mRNA vaccines with respect to all-cause mortality in the older population in Norway. *Vaccine*. 2023;41(2):323-332. doi:10.1016/j.vaccine.2022.10.085
2. Pottegård A, Lund LC, Karlstad Ø, Dahl J, Andersen M, Hallas J, Lidegaard Ø, Tapia G, Gulseth HL, Ruiz PLD, Watle SV, Mikkelsen AP, Pedersen L, Sørensen HT, Thomsen RW, Hviid A. Arterial events, venous thromboembolism, thrombocytopenia, and bleeding after vaccination with Oxford-AstraZeneca ChAdOx1-S in Denmark and Norway: population based cohort study. *BMJ*. 2021;373:n1114. doi:10.1136/bmj.n1114
3. Karlstad Ø, Hovi P, Husby A, Härkänen T, Selmer RM, Pihlström N, Hansen JV, Nohynek H, Gunnes N, Sundström A, Wohlfahrt J, Nieminen TA, Grünewald M, Gulseth HL, Hviid A, Ljung R. SARS-CoV-2 Vaccination and Myocarditis in a Nordic Cohort Study of 23 Million Residents. *JAMA Cardiology*. 2022;7(6):600-612. doi:10.1001/jamacardio.2022.0583
4. Husby A, Gulseth HL, Hovi P, Hansen JV, Pihlström N, Gunnes N, Härkänen T, Dahl J, Karlstad Ø, Heliö T, Køber L, Ljung R, Hviid A. Clinical outcomes of myocarditis after SARS-CoV-2 mRNA vaccination in four Nordic countries: population based cohort study. *BMJ Medicine*. 2023;2(1). doi:10.1136/bmjmed-2022-000373
5. *Report to EMA, Registration Number EUPAS48979: Association between COVID-19 Vaccines and Pediatric Safety Outcomes in Children and Adolescents Aged 5-19 in the Nordic Countries*.; 2023. Accessed April 27, 2023. https://www.encepp.eu/encepp/viewResource.htm?id=103722
6. Ihle-Hansen H, Bøås H, Tapia G, Hagberg G, Ihle-Hansen H, Berild JD, Selmer R, Karlstad Ø, Gulseth HL, Ariansen I. Stroke After SARS-CoV-2 mRNA Vaccine: A Nationwide Registry Study. *Stroke*. Published online 2023. doi:10.1161/STROKEAHA.122.040430

4. Details of the impact (indicative maximum 750 words)

During the pandemic, the NIPH gathered small teams of researchers to answer research questions deemed to be of urgent societal importance. By combining real-time data from several nationwide registries, developments during the pandemic could be followed and analysed. This was used to monitor infections, hospitalizations, deaths, and vaccination uptake in at-risk groups and the general population. A first milestone was defining which groups were at risk for severe SARS-CoV-2

disease, and these numbers were used to distribute the needed number of vaccine doses per health region/hospital/municipality, as at-risk groups were not uniformly distributed in Norway. This impacted the whole Norwegian society, by informing vaccination recommendations and guidelines, assess if any groups were lagging in their vaccination uptake, or needed higher prioritization due to high SARS-CoV-2 burden.

As vaccination unrolled, there were further impacts. During first-dose mRNA vaccine administration, there were concerns of vaccine-associated deaths in the elderly (January 2021), which gained media attention. Our analysis found no association between vaccination and mortality, which quelled fears and led to no vaccination pause or policy change. Later, ChadOx-1 vaccination was put on hold (March 2021) following reports of a novel adverse event with high mortality (VITT). Together with Danish researchers we reported an increased incidence of blood clots post-vaccination, as found in cases of VITT. Our results led to the NIPH recommending excluding vector vaccines from the vaccination program (April 2021), which directly informed policy as this became the official policy in Norway less than a month after the first results were presented (May 2021). Similarly, we reported increased incidence of myo- and pericarditis following mRNA vaccination, which was used by EMA for signal assessment and led to changes in recommendations in Nordic countries that younger individuals should choose Pfizer over Moderna mRNA vaccine in the Nordics (October 2021). The scientific article was published in Aprile 2022 and received the Paper of the Year award from the Norwegian Epidemiological Association for 2022. We have done commissioned studies by EMA (2022-2023), together with Scandinavian collaborators, on adverse events after vaccination in children and adolescents, which has informed policy for further vaccination of children and adolescents.

In addition to the examples listed above, we have also investigated several other suspected adverse events after vaccination (such as stroke, cardiac arrest, Guillain-barre syndrome, appendicitis, to name a few), with weekly monitoring of selected adverse events and at-need analysis of suspected adverse events. Most of these have been negative findings, and had less immediate impact, but these investigations have a crucial long-term impact in society at large as they develop trust and confidence in the vaccination programme by being open and responsive to the needs of the public. Also, each negative finding crucially adds to the knowledge of the safety of the covid/mRNA vaccines, which has a clear future impact. There have also been many requests where results have been sent directly to stakeholders, e.g requests from researchers, clinicians, interest groups, hospitals, journalists and the general population, with a high number of public information and transparency requests. Our results have been used extensively in the media and in debates, showing a clear impact in public discourse. Our published papers have generally attracted attention (e.g references 2, 3, 6 all have 99th percentile Altmetric attention scores compared to outputs of the same age). We have also advised and contributed to several governmental reports (such as reports on mortality, assessments on booster doses for at risk-groups, or assessments for vaccination of children), which have been used when planning future covid vaccinations and evaluate the handling of the pandemic. These have had a clear impact, such as vaccine recommendations in children and adolescents, although as part of a wider body of research.

Results were shared continuously with national and international authorities, such as ECDC, CDC, FDA, WHO and EMA, during the pandemic. This has clearly benefitted governing bodies and health authorities, the medical and academic community at large, and the general public in their charge. These impacts have all been quite substantial and immediate, with e.g the VITT study presenting combined results 14 days after the first reported death, and new recommendations <1 month after this, illustrating the impact on the Norwegian vaccination programme and policy.

5. Sources to corroborate the impact (indicative maximum of ten references)

- **NIPH changes in national vaccination recommendations**
  - Folkehelseinstituttet. Myokarditt hos gutter og unge menn kan forekomme oftere etter Spikevax-vaksinen fra Moderna. Published October 6, 2021. https://www.fhi.no/historisk-arkiv/covid-19/nyheter-2021/okt/myokarditt-spikevax/
  - Folkehelseinstituttet. Koronavaksinasjonsprogrammet: Anbefaling Om Videre Bruk Av AstraZeneca-Vaksinen. Folkehelseinstituttet; 2021. Published April 15, 2021. https://www.fhi.no/contentassets/3596efb4a1064c9f9c7c9e3f68ec481f/2021_04_14-anbefalingsnotat-oppdrag-21.pdf

- **EMA signal assessment report**
  - European Medicines Agency (EMA). Signal assessment report on myocarditis and pericarditis with Spikevax - COVID-19 mRNA vaccine (nucleosidemodified). Published December 2, 2021. https://www.ema.europa.eu/en/documents/prac-recommendation/signal-assessment-report-myocarditis-pericarditis-spikevax-previously-covid-19-vaccine-moderna-covid_en.pdf

- **EMA-commissioned study report on adverse events post-vaccination in children and adolescents**
  - Report to EMA, Registration Number EUPAS48979: Association between COVID-19 Vaccines and Pediatric Safety Outcomes in Children and Adolescents Aged 5-19 in the Nordic Countries.; 2023. https://www.encepp.eu/encepp/viewResource.htm?id=103722

- **National news prior to the stoppage of the AstraZeneca vaccine**
  - https://www.nrk.no/urix/na-begynner-selv-britene-a-tvile-pa-vaksinen-fra-astrazeneca-1.15487016

- **Presentation at award ceremony for Paper of the Year award from the Norwegian Epidemiological Association**
  - Award received for the paper *Karlstad Ø et al. SARS-CoV-2 Vaccination and Myocarditis in a Nordic Cohort Study of 23 Million Residents. JAMA Cardiology. 2022;7(6):600-612. doi:10.1001/jamacardio.2022.0583.* Presented at The 28th Norwegian Conference on Epidemiology, Tromsø 26 October 2022 https://nofe.no/arets-artikkel/.

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If relevant, describe any reason to keep this case confidential:

NA

[Norwegian Institute of Public Health and Division of Mental and Physical Health] [5]

Institution: Norwegian Institute of Public Health
Administrative unit: Division of Mental and Physical Health
Title of case study: The Dynamics of Family Conflict Study (FAM-C) [FamilieForSK]
Period when the underpinning research was undertaken: 2016-
Period when staff involved in the underpinning research were employed by the submitting institution: 2016-
Period when the impact occurred: 2017-

1. Summary of the impact (indicative maximum 100 words)

Dynamics of Family Conflict (FAM-C) findings have impact on different levels of society. Foremost, FAM-C provides evidence-based knowledge and validated measurements to the F**amily counselling service** through close collaboration with the service's expert teams and through regular presentations at regional gatherings. This has strengthened the service provision for families seeking help. FAM-C findings have further provided **authorities** with knowledge about the welfare of children and families in vulnerable situations, particularly during the Covid-19 pandemic. Finally, through popular science summaries and media engagement, FAM-C has engaged in public debate and information sharing benefitting **the lay public**.

2. Underpinning research (indicative maximum 500 words)

The Dynamics of Family Conflict study (FAM-C) is a Norwegian ongoing longitudinal multi-informant survey study with an established cohort that enables investigations of child and parent wellbeing, family dynamics, and conflicts. Families (N = ~2800) were recruited through family counselling centers (Dec 2017 to July 2019). The FAM-C data source is unique and extensive covering many domains and has register linkages to several registers. FAM-C is the umbrella project for new projects covering related research foci, including family life during and after Covid-19, children's agency when parent separate, custody arrangements, and interparental conflict and parenting experiencing across living arrangements, gender, and social class. Several projects are ongoing. FAM-C insights and findings are considerable and have potential for impacts at different levels.

Scale validation

Findings from the validation and short form development of the Conflict Strategy Scale from the Conflicts and Problem-Solving Scales showed that the short form had better psychometric properties compared to the original scale (Helland et al., 2021). The validation of the Children's Perception of the Interparental Conflict Scale and the Interparental Subsystem (both child-reported measures) showed comparable validity of the short forms to the original full scales (Holt et al, 2020). The utility in these short forms lie in their brevity, and parent and child perspectives.

The validation of a short survey that parents complete over the phone with the family welfare service prior to attending divorce mediation showed that compared to when parents completed the same questions anonymously, parents under-reported to the service regarding substance abuse and violence (Dittmann et al., 2021). This finding questions the validity of the screening practice implemented by the service today.

Interparental conflict

Compared to parents living apart, parents living together (with or without children from former relationships) reported more frequent conflicts, but better conflict resolution and less destructive conflict behaviours. Among parents living apart, those in less complex family systems (i.e., where

neither parent has a new partner) showed better conflict resolution and less destructive conflict behaviours compared to those in complex family systems (Helland et al., 2020). When investigating children's reactions to interparental conflict, parents tend to underestimate these compared to children's self-report (Holt et al., 2021a).

Covid-19
Focusing on children's reactions to the new everyday life under the pandemic compared to before, findings showed that children had fewer emotional but more somatic and cognitive reactions. The strongest predictor of children's reactions was family stress and instability, and this was particularly true for older children (Larsen et al., 2021).

Key researchers
Espen Røysamb (Professor 2015-)
Maren Sand Helland (Researcher 2015-)
Tonje Holt (Researcher 2016-)
Linda Larsen (Post doctor 2019-2022, Researcher, 2022-)
Silje Kvam Bårdstu (Researcher 2021-)
Dina Sunde (Researcher short-term contract 2021)
Solveig Dittmann (Researcher short-term contract 2021)
Maria Morbech (PhD candidate 2020-)
Olav Bertin Tveit (PhD candidate 2020-)

3. References to the research (indicative maximum of six references)

Scale validation
Helland, M. S., Holt, T., Gustavsson, K. & Røysamb, E. (2021) Validation and short-form development of Conflict and Problem-solving Strategy Scales. *Journal of Family Studies, 29*(2), 738-757. https://doi.org/10.1080/13229400.2021.1981977

Holt, T., Helland, M.S., Gustavson, K. *et al.* (2020). Assessing Children's Responses to Interparental Conflict: Validation and Short Scale Development of SIS and CPIC-Properties Scales. *Journal of Abnormal Child Psychology, 48*, 177–196. https://doi.org/10.1007/s10802-019-00586-7

Dittmann, S., Holt, T., & Larsen, L. (2021). Foreldre underrapporterer om konflikter og utfordringer I forkant av mekling. En evaluering av familievernets differensieringsverktøy [Parents underreport conflicts and difficulties before attending mediation]. *Tidsskrift for Norsk Psykologforening, 9*(58), 766-775. https://doi.org/10.52734/3WfR437s

Interparental conflict
Helland, M.S., Larsen, L., Lyngstad, T.H., Gähler, M. & Holt, T. (2020). Konflikt i familier: Mønstre innenfor og på tvers av familieform når familiesystemet utfordres [Interparental conflicts: Patterns across family constellations when the family system is under pressure]. *Norsk Sosiologisk Tidsskrift, 4*(3), 131-50. https://doi.org/10.18261/issn.2535-2512-2020-03-02

Holt, T., Helland, M. S., Morbech, M., Larsen, L., Gustavson, K., Ha, A., & Cummings, E. M. (2021a). Agreement between child and parent reports of children's reactions to interparental conflict. *Journal of Family Psychology*, 35(8), 1138–1148. https://doi.org/10.1037/fam0000861

Covid-19
Larsen, L., Helland, M. S., & Holt, T. The impact of school closure and social isolation on children in vulnerable families during COVID-19: a focus on children's reactions. *European Child & Adolescent Psychiatry, 31*, 1–11 (2022). https://doi.org/10.1007/s00787-021-01758-x

4. Details of the impact (indicative maximum 750 words)

The insights and findings from FAM-C provide an important knowledge base for policy discourse and development, supporting health and welfare authorities in ensuring safe upbringing conditions and supportive family environments for children. Impacts extend to clinical practice through close and mutual collaborations with the family counselling service. This collaboration is maintained through financial support from the Norwegian Directorate for Children, Youth and Family Affairs (Bufdir) generating new research projects particularly relevant for the service. FAM-C researchers serve as advisors for health and welfare services, as well as governmental directorates and ministries, fulfilling the Norwegian Institute of Public Health's (NIPH) mandate as a producer of knowledge.

*Impact on **service level** (see sources 1-3 below)*
The need for validated screening instruments covering family conflicts provided the background for Bufdir to initiate and fund research to translate and further develop commonly used international questionnaires and validate them in a Norwegian context and evaluate the Family counselling service's divorce mediation screening tool. The work was carried out between 2016-2021. The results were published in three peer-review articles (Helland et al., 2021; Holt et al., 2020; Dittmann et al., 2021) and shared with Bufdir in an internal report, and to the service through the service's resource and development teams. Providing the service with validated and free-of-charge screening instruments ensures a high standard practice crucial for offering tailored interventions to families and children. Validated short scales enable therapists to conduct time-efficient assessments capturing both initial challenges as well as treatment progress, without imposing excessive burden on families.

FAM-C has generated a substantial body of knowledge relevant for the Family counselling service. The underpinning research started in 2016 when FAM-C was initiated and is ongoing. Certain findings have had impact by providing new knowledge to therapists in their daily practice. One example is the distinction between destructive and less destructive parental conflicts. Understanding that destructive conflicts most often occur in families where parents live apart provides important insight, suggesting that efforts should particularly be directed towards parental conflicts in these families (Helland et al., 2020). Another example is that children experience family conflicts differently to their parents. This has implications for the service and for families, emphasizing the importance of striving to understand children's perspective (Holt et al., 2021a). Finally, a study by Sunde et al. (2021) points to aspects that children find important when parents separate. These include continuity (e.g., participate in the same activities irrespective if at mum's or dad's place) and openness (i.e., can express emotions to both parents). This knowledge may guide therapists when working with parents in establishing post-separation family life and shows the importance of children's own perspective.

To integrate the empirical knowledge generated by FAM-C into the Family counselling service, FAM-C has had close collaboration and regular meetings with the service. Dissemination efforts have been a strategic priority through engaging with the service's national resource and development teams (i.e., Family violence and high conflict and Children and youth in Family counselling services), presenting finding at the service's regional gatherings, and being represented in relevant reference groups for service development.

*Impact on **policy level** (see sources 4-6)*
FAM-C had an active role in informing policy and the health and welfare authorities in Norway during the Covid-19 pandemic. Concerns were raised that the pandemic would disproportionally impact the most vulnerable families, and it was important to identify and provide help to at-risk families to mitigate the negative consequences of the societal lockdown. An interdisciplinary working group representing relevant authorities and institutions including NIPH was appointed by the Government with this mission. FAM-C findings were used by the working group, and relevant results are mentioned in some of the working group's reports. The results from the FAM-C Covid-

19 project were also published in a report to Bufdir as well as in three separate peer-review articles (Helland et al., 2021; Holt et al., 2021b; Larsen et al., 2022). FAM-C and the research generated by FAM-C has also been mentioned in other governmental documents, for example in the Government's new escalation plan for mental health (2023-2033).

*Impact on **public level** (see sources 7-10)*
FAM-C researchers have taken an active role in public debate concerning interparental conflict, parental separation, and children's agency in matters that concern them. Research findings have been made available through popular science summaries, newsletters, and the project website. Since the study inception there has been more than 23 500 clicks on the project website. Results summaries have also been shared with the public through news channels including ones specifically aimed at children and youth (forskning.no, ung.forskning.no).

5. Sources to corroborate the impact (indicative maximum of ten references)
The FAM-C research on family dynamics is particularly relevant to the Family counselling service. This relevance is reflected in documents describing The Norwegian Directorate for Children, Youth and Family Affairs' (Bufdir) research strategy and research efforts:

1. Bufdirs arbeid med forskning 2020 [Bufdir Research Strategy 2020]. Pages 16, 17, 67, 69, 79, 132.
2. Bufdirs arbeid med forskning 2021 [Bufdir Research Strategy 2021]. Pages 22, 23, 24, 25, 59.

The FAM-C research is highlighted in governmental initiatives and efforts:

3. Meld.St. 23 (2022-2023). Opptrappingsplan for psykisk helse [Escalation Plan for Mental Health]. Page 25.

The FAM-C has provided insights and findings about the consequences of Covid-19 pandemic for vulnerable families that are relevant for health and welfare authorities:

4. Statusrapport 10: Utsatte barn og unges tjenestetilbud under Covid-19 pandemien [Status Report 10: Service offer to vulnerable children and youth during the Covid-19 Pandemic]. Bufdir. Pages 42-43, 46-47.
5. Statusrapport 11: Økt bekymring under Covid-19 pandemien [Status Report 11: Increased concern during the Covid-19 pandemic]. Bufdir. Page 41.

FAM-C regularly communicates findings to the lay public through popular science summaries and the media:

6. 23 557 clicks on the FAM-C website since 2016 (obtained from NIPH communications department).
7. Barn vil treffe vennene sine uansett om de bor hos mamma eller pappa [Children want to see their friends irrespective if they live with mum or dad]. Ung.forskning.no
8. Barn blir lei seg når foreldrene krangler, men det skjønner ikke alltid de voksne [Children get sad when parents argue, but adults don't always understand]. Ung.forskning.no
9. Få spør barna om hvordan skilsmissen oppleves for dem [Children are rarely asked how they experience parental separation]. NRK.no
10. Psykisk oppvekst. Barn og unges psykiske helse (2022) [Healthy upbringing conditions. Child mental health and wellbeing]. The Norwegian Council for Mental Health. Pages 215-222.

NORCE, Division of Health and Social Sciences case 1

Institution: Uni Research (now NORCE Norwegian Research Centre)
Administrative unit: Uni Research Health and Uni Research Rokkan Centre (now NORCE Division for Health and Social Sciences)
Title of case study: Effect evaluation of Individual Placement and Support (IPS)
Period when the underpinning research was undertaken: 2013-2019
Period when staff involved in the underpinning research were employed by the submitting institution: 2013-2019
Period when the impact occurred: 2016-ongoing
1. Summary of the impact Individual Placement and Support (IPS) is an approach to vocational rehabilitation among individuals with mental illness, developed in the USA in the 1990s. The method was piloted and evaluated in the Norwegian context in 2013-2016 in a randomized controlled study, conducted by a research team in NORCE (form. Uni Research), and follow-up analyses were conducted in 2019. The research documented that IPS was more effective than treatment as usual (TAU) for individuals with moderate to severe mental disorders, also in the Norwegian context. The follow-up study demonstrated long-term effect of IPS 3.5 years after inclusion to the study, in favor of the IPS group. This is the longest follow-up period that has been reported in IPS studies globally. As a result of the effect evaluation, the government at the time reallocated resources in the national budget to ensure that IPS was scaled-up across the country**.**
2. Underpinning research The IPS trial was commissioned by the Directorate of Health and the Directorate of Labour and Welfare in a rare cross-sectoral collaboration. The trial consisted of three parts: An effect study, a cost-effectiveness analysis, and a process evaluation. Six pilot IPS centres participated in the trial. The effect study was designed as a randomized controlled trial. A total of 410 participants were included in the study and randomly assigned to two groups: 229 were offered IPS through six pilot centers, while 181 were offered a high-quality version of regular follow-up in NAV aiming to increase work participation. Both groups also received ordinary psychiatric treatment. Effect analyses were conducted on 18 months´ follow-up data, using registry data on work participation. Results showed that a significantly higher proportion in the IPS group was employed (37%), compared to the TAU group (27%). Sub-group analyses showed no differences in effects between participants with moderate versus serious mental illness, demonstrating the effectiveness of IPS in a broader target group than serious mental illness (which is the original target group for the method). IPS participants also experienced more positive effects on health and quality of life compared to TAU, effects that have not been demonstrated across such a broad range of indicators in previous IPS studies. A follow-up study, using employment registry data spanning a period of 3.5 years from baseline, showed that the differences in work participation between the intervention arms were sustained, and that the effect was strongest among younger participants with low education. Cost-effectiveness analyses with data over this time span concluded that the intervention was cost-effective in the long term.

The process evaluation carried out alongside the trial documented aspects of the implementation process using mixed methods, including fidelity measures, dose given, dose received, participant satisfaction, and barriers and facilitators for implementation and participation. Process evaluations aim to increase the external validity of psychosocial intervention trials. All six pilot centers reached fair to good fidelity according to the IPS Fidelity Scale. Indications of implementation issues were related to employer contact, providing community-based services, and the required integration with health services. Survey data showed that less than half of the participants regarded their illness as a barrier for participating in IPS and that freedom of disclosure was important. Participant interviews gave further insight into the role of the IPS specialist, emphasizing their availability and consistent job focus.

Names of key researchers and the positions they held at the time of research:

- Silje E. Reme (PhD), senior researcher (left the institution in 2016)
- Tonje Fyhn (MSc), PhD candidate
- Karin Monstad (PhD), research professor
- Tor Helge Holmås, (PhD), research professor
- Kari Ludvigsen, (PhD), research professor (left the institution in 2016)
- Vigdis Sveinsdottir (MSc), researcher
- Camilla Løvvik (PhD), senior researcher

3. References to the research

Reme, S. E., Monstad, K., Fyhn, T., Sveinsdottir, V., Løvvik, C., Lie, S. A., & Øverland, S. (2019). A randomized controlled multicenter trial of individual placement and support for patients with moderate-to-severe mental illness. *Scandinavian journal of work, environment & health*, *45*(1), 33-41. DOI: 10.5271/sjweh.3753

Fyhn, T., Ludvigsen, K., Reme, S. E., & Schaafsma, F. (2020). A structured mixed method process evaluation of a randomized controlled trial of Individual Placement and Support (IPS). *Implementation science communications*, *1*(1), 1-11. DOI: 10.1186/s43058-020-00083-9.

Holmås, T. H., Monstad, K., & Reme, S. E. (2021). Regular employment for people with mental illness–An evaluation of the individual placement and support programme. *Social Science & Medicine*, *270*, 113691. DOI: 10.1016/j.socscimed.2021.113691

Fyhn, T., Øverland, S., & Reme, S. E. (2021). Predictors of employment in people with moderate to severe mental illness participating in a randomized controlled trial of Individual Placement and Support (IPS). *International Journal of Social Psychiatry*, *67*(2), 150-157. DOI: 10.1177/0020764020934845

Sveinsdottir, V., Bull, H. C., Evensen, S., Reme, S. E., Knutzen, T., & Lystad, J. U. (2020). A short history of individual placement and support in Norway. *Psychiatric Rehabilitation Journal, 43*(1), 9–17.DOI: 10.1037/prj0000366

4. Details of the impact

Although international studies have proven IPS to be more effective than traditional forms of vocational rehabilitation, the current trial was the first to investigate its effect in a Norwegian context. The context of the analysis is a generous welfare system, which has many advantages, but which may also create incentives to remain outside the workforce. It was therefore not given that IPS would be more effective than ordinary vocational services in this context. The process evaluation aimed to provide insights into aspects of the implementation in order to guide further implementation of the method at scale in Norway.

The final report was published in December 2016, and results were made known through presentations of numerous professional conferences and coverage in broad media outlets. The Solberg government continued to financially support both existing IPS services and the establishment of new services in 2017, and in the national budget for 2018, doubled the budget for IPS from 100MNOK to 200MNOK, by enabling NAV to transfer financial resources from other labour market programs with unknown effect, and channel them to sustain and expand IPS services.

In 2018, the Solberg government launched the "Inclusion effort", a nationwide mobilization of private and public sector actors to increase work participation. One of the three strategic investments was to expand IPS services for individuals with mental illness and/or substance abuse problems.

In 2021, follow-up analyses using individual register data of 3.5 years after inclusion, were published in a multi-disciplinary journal ranked at the highest level in The Norwegian Register for Scientific Journals, Series and Publishers. This analysis demonstrated the long-term effect of IPS on work participation, particularly for young people with low levels of education. It also assessed the effect on receipt of social insurance benefits and health care utilization and assessed the cost-effectiveness of the method.

While in 2013 there were six IPS pilot centers, by 2022 close to 100 IPS services had been established across the country. The method has been institutionalized and have gained accept across the political spectrum as an effective work rehabilitation program, as shown in national budgets and political priorities also after changes in government (i.e., National budgets after governmental change, Report to the Storting on Mental health/Opptrappingsplan for psykisk helse 2022-2023).

Since the IPS trial, NORCE has conducted several other IPS research projects: For employees on sick leave, at risk of sick leave, or on long-term health benefits; for young people on long-term health benefits; for refugees in the introduction program; and young people on permanent disability benefits. We consider the sum of this research to have contributed substantially to the large-scale implementation of IPS for a range of sub-groups at risk of marginalization from the labor market.

Beneficiaries of the research are first and foremost patients in psychiatric health care with a desire to participate in ordinary work. The IPS trial showed that not only did IPS increase work participation for this group, but the IPS approach also had a positive impact on health-related measures and measures of quality of life. Moreover, the effect was sustained over time particularly for those younger in age and with low levels of education. Published results from the IPS trial provided actionable knowledge for politicians across the political spectrum to improve vocational services for this under-served group.

Examples of mentions and prioritizations of IPS in government documents:

The Norwegian National budget 2018

The Norwegian National budget 2022

Report to the Storting, Meld.St.23 (2022-2023)

5. Sources to corroborate the impact

Kristin Vold Hjerpås (contact person Labour and Welfare Administration): kristin.vold.hjerpas@nav.no, tel. +47 414 36 271

Randi Røed Andersen (contact person Health Directorate): Randi.Roed.Andersen@helsedir.no, tel. +47 24 16 30 91

Kine Nan Lium (Labour and Welfare Administration, Work inclusion office): kine.nan.lium@nav.no, tel. +47 911 40 564

NORCE, Division of Health and Social Sciences case 2

Institution: Uni Research (now NORCE Norwegian Research Centre)
Administrative unit: Uni Research Health (now NORCE Health and Social Sciences)
Title of case study: Independent medical evaluation
Period when the underpinning research was undertaken: 2015-2018
Period when staff involved in the underpinning research were employed by the submitting institution: 2015-2018
Period when the impact occurred: 2018-2021

1. Summary of the impact

I 2014 the Norwegian government announced a policy change limiting the length of sick leave issued by one´s general practitioner (GP) to six months. The intention was that after this, a GP employed in the Norwegian Labour and Welfare Administration (NAV) would conduct an independent medical evaluation (IME) of the employee. Before the policy change was set in motion, NAV commissioned a trial in Hordaland County to test whether the change would have the intended effect. The results showed no effect on sick leave of the independent medical evaluation, and also provided insights into the explanatory factors for the lack of effect. The policy change had been stated in the government´s political platform, but nevertheless was cancelled due to the results of the trial.

2. Underpinning research

The trial made use of various data sources, including interviews, consultation data, and registry data. The mixed methods approach enabled the researchers to not only estimate the effect of the IME, but also to shed light on the mechanisms behind the effect – or lack of effect. The trial consisted of three parts: An effect study, an interview study, and a cost efficiency study.

The effect study was designed as a randomized controlled trial (RCT), comparing treatment as usual (TAU) with an independent medical evaluation by a doctor employed in NAV, on the outcome of return to work. All patients in the target group were randomized to TAU or IME, based on a change in a NAV directive, enabling NAV to summon sick-listed employees to IME. The outcome was measured using registry data on length of absence, use of graded sick leave, and probability of transitioning to long-term health benefits. The results showed no difference between intervention groups in any of the outcomes. No differences on outcomes were found between those who showed up and those who did not show up for the independent medical evaluation. No differences were found in subgroups based on gender, age, or diagnosis. The rigorous study design and use of several registry data sources strengthens the validity and reliability of the study results.

The interview study explored how patients and GPs experienced the piloting of IME. *Individual interviews* were conducted with nine patients. The patients were unsure what the purpose of the IME was but felt morally obliged to show up for the IME appointment. The second opinion of the IME was useful but did not help them return to work. *Three focus group interviews* were conducted with GPs (n=14) who had patients who had been randomized to an IME. The GPs were initially positive to having a second opinion from an experienced colleague but did not consider the reports from the IME consultation particularly useful or enlightening. They did not believe that implementing IME would have any effect on sick leave rates. The GPs had to spend time assuring the patients that the IME was a control of them as a GP, and not the patient. They

also highlighted the advantage of continuity in patient care, which was breached by IME. *Two focus group interviews* were conducted among IME GPs (n=8). The IME GPs felt they contributed with a valuable second opinion, but also described some challenges related to communication with the patient´s GP. They felt the organization of the IME needed adjustments before a large-scale implementation. The interview study gave enough richness in the data material to investigate the research questions. As is the case for most interview studies, self-selection is likely to have influenced the data material, however, the recruited informants all had relevant information to share. The structured method of analysis (systematic text condensation) ensures closeness to the empirical data and its presentation.

Cost/benefit analysis was not carried out as the intervention did not prove effective.

Names of key researchers and the positions they held at the time of research (all researchers were employed during the entire project period):

- Silje Mæland (PhD), senior researcher
- Irene Larsen Øyeflaten (PhD), senior researcher
- Karin Monstad (PhD), research professor
- Tor Helge Holmås (PhD), research professor
- Elisabeth Husabø (dr.psychol.), researcher
- Aase Aamland (PhD, dr. med), senior researcher, part-time position
- Erik Werner, (PhD, dr. med.), senior researcher, part-time position

3. References to the research

Final report:

Mæland, S., Monstad, K., Holmås, T. H., Øyeflaten, I. L., Husabø, E., & Aamland, A. (2018). Sluttrapport for forsøk med ny medisinsk vurdering (NMV) etter seks måneders sykmelding. Permanent link: https://hdl.handle.net/1956/20028

Scientific output:

Husabo, E., Monstad, K., Holmås, T. H., Oyeflaten, I., Werner, E. L., & Maeland, S. (2017). Protocol for the effect evaluation of independent medical evaluation after six months sick leave: a randomized controlled trial of independent medical evaluation versus treatment as usual in Norway. *BMC Public Health*, *17*(1), 1-6. DOI: 10.1186/s12889-017-4469-3

Aamland, A., Husabo, E., & Maeland, S. (2018). Independent medical evaluation for sick-listed patients: a focus group study of GPs expectations and experiences. *BMC health services research*, *18*(1), 1-7. DOI: 10.1186/s12913-018-3481-3

Aamland, A., & Maeland, S. (2018). Sick-listed workers' expectations about and experiences with independent medical evaluation: a qualitative interview study from Norway. *Scandinavian Journal of Primary Health Care*, *36*(2), 134-141. DOI: 10.1080/02813432.2018.1459168

Aamland, A., Øyeflaten, I. L., & Maeland, S. (2019). Independent medical evaluation for sick-listed workers in Norway: a focus group study of the experience of IME doctors. *Scandinavian Journal of Public Health*, *47*(1), 70-77. DOI: 10.1177/1403494817745001

Øyeflaten, I., Maeland, S., & Haukenes, I. (2020). Independent medical evaluation of general practitioners' follow-up of sick-listed patients: a cross-sectional study in Norway. *BMJ Open*, *10*(3). DOI: 10.1136/bmjopen-2019-032776

Mæland, S., Holmås, T. H., Øyeflaten, I., Husabø, E., Werner, E. L., & Monstad, K. (2022). What is the effect of independent medical evaluation on days on sickness benefits for long-term sick listed employees in Norway? A pragmatic randomised controlled trial, the NIME-trial. *BMC Public Health*, *22*(1), 400.DOI: 10.1186/s12889-022-12800-1

4. Details of the impact

Both nationally and internationally, the experiment was groundbreaking. Nationally, it was pioneering because a politically initiated NAV measure was evaluated through a randomized controlled study, including socio-economic analysis, and conducting qualitative methods before a decision on potential national implementation was made. Internationally, it is the first time the effect of this type of measure (internationally referred to as independent medical evaluation) was being investigated in an RCT.

In the final report, the researchers argued in favor of governmental policies that are based on the best available knowledge of the impact of interventions. As the research team used the gold standard to evaluate the effectiveness of IME, supplemented with qualitative studies, the authors concluded that the evaluation results provide strong arguments for Norwegian decision-makers not to implement IME at six months of sick leave in a Norwegian context.

The IME trial was a rare case of political will to pilot and test the effect of an intervention before implementation, that was politically initiated, rather than knowledge-based or based on expert-advice. The trial was based on an explicit intention in the governing parties´ political platform related to reducing long-term sick leave (Regjeringen, 2013a), and was outlined in a Parliamentary Proposition (1, 2014-2015).

Based on the evaluation and its conclusions, the government did not follow through with their intentions to implement IME nationally.

Considering beneficiaries of this impact, this first and foremost includes patients on long-term sick-leave, who do not have to see a new GP and possibly feel mistrusted by the welfare and health system. Moreover, it benefits regular GPs, who are already under heavy time pressure. Lastly, it benefits society, as the intervention would have been an investment with no return.

There is no specific date for the impact of the research, but as IME has not been a topic politically since the final report was submitted the impact can be considered to have started from then and is still ongoing.

Regjeringen. (2013a) Politisk plattform for en regjering utgått av Høyre og Fremskrittspartiet. Sundvollen, 7. oktober 2013. Hentet fra: https://www.regjeringen.no/no/dokumenter/politisk-plattform/id743014/

Prop. Nr. 1, (2014-2015) p. 15.: https://www.regjeringen.no/no/dokumenter/Prop-1-S-20142015-/id2005477/

5. Sources to corroborate the impact

Kristian Munthe (Department director, Labour and Welfare Administration):
Kristian.munthe@nav.no

Anne Bogstad Kverneland (former county director, NAV Hordaland):
anne.kverneland.bogsnes@nav.no

NORCE, Division of Health and Social Sciences case 3

Institution: NORCE Norwegian Research Centre
Administrative unit: National Centre for Emergency Primary Health Care (NKLM), NORCE Health & Social Sciences
Title of case study: Telephone triage and counselling in Norwegian local emergency medical communication centres
Period when the underpinning research was undertaken: 2016-2023
Period when staff involved in the underpinning research were employed by the submitting institution: All researchers involved have been employed by the National Centre for Emergency Primary Health Care during the whole period
Period when the impact occurred: 2017 and onwards

1. Summary of the impact

This project's impact is to show that the inhabitants' help-seeking behaviour can be altered by relatively small interventions, and that quality improvement measures initiated by the service itself, such as implementing a decision support tool or adding new services, can backfire on the accessibility and preparedness of the service. The operators at local emergency medical communication centres provide counselling for a wide range of medical problems, and changes in their decision-making impact the use of resources within emergency primary health care as well as in specialist pre-hospital emergency care. Implemented changes need monitoring to allow for amendment of undesirable effects.

2. Underpinning research

Since 2006, the Watchtower project has surveilled the activity in emergency primary care through a network of seven emergency primary care services, representative of Norwegian municipalities. The services record anonymous, administrative information on all contacts to their services. The longitudinal approach allows for discovering trends and exploring effects of changes. During the past years we have conducted several studies on telephone triage and counselling based on this data.

First, a cross-sectional study published in 2017 highlighted the operators' role in counselling patients. On average 23% of total telephone contacts were handled solely by nurse telephone advice, with fever, abdominal pain, cough, ear pain, and general symptoms as the most frequent reasons for advice. Advice was given for altogether 447 different reasons, showing the diversity in contacts.

During the project period, three major changes occurred that allowed us to explore their impact on the services:

1. One of the participating services changed their preferred mode of contact from direct attendance to telephone triage.
2. Two of the participating services changed their use of decision support tools.
3. The COVID-19 pandemic resulted in the services being given new tasks.

In 2022 we published a study on the effect of changing preferred mode of contact from direct attendance to telephone triage. In 2007, the service in question had a high rate of direct attendance (73%) compared with the other services (12%). In 2013 an information campaign was aimed at the public, encouraging people to call before attending. The proportion of direct attendance decreased from 69% to 23%. The effect occurred quickly and persisted. Concurrently, share of medical consultations by a GP decreased from 78.3% to 57.0% of all patient contacts. Furthermore, proportion of advice given increased from 11.7% to 29.2% of all contacts.

In 2023 we published a study on the effect of change of decision support tool. The two services in question implemented the same decision support tool. Both services saw an increase in proportion of acute and urgent contacts. Proportion of acute contacts increased from 4% to 9% and from 3% to 11%, respectively. Urgent contacts increased from 30% to 40% and from 22% to 31%, respectively. The change increased the general risk of concurrency conflicts within acute and urgent cases. No similar changes were seen in the other services.

In 2023 we also published a study on how the COVID-19 pandemic affected the activity in the services. All the services were similarly affected by national measures. However, their activity level was also affected by the local municipal pandemic response. The initial national lock down decreased the level of direct attendance, an effect that persisted after the pandemic.

Our findings show that the inhabitants' help-seeking behaviour can be altered in persisting ways. Changes to the services can have unforeseen effects on their accessibility and preparedness. The operators provide counselling for a wide range of medical problems, and their decision-making impacts the use of resources within pre-hospital emergency care. Implemented changes need monitoring to allow for amendment of undesirable effects.

Over the last decades, local emergency medical communication centres (LEMCs) have gained a more professionalised role within emergency primary care. This role has been underpinned by changes in legal regulations specifying minimum obligatory service level in the municipalities. As part of NKLM's mandate given by the Norwegian Directorate of Health, NKLM has several research, quality improvement, and service innovation initiatives which include LEMCs.
Key researchers are consultants and PhD-students Vivian Midtbø and Siri-Linn Schmidt Fotland, and the senior researchers Steinar Hunskår, Ingrid H. Johansen, and Guttorm Raknes.

3. References to the research

All papers have been published in open access peer reviewed scientific journals:

1. Midtbø V, Raknes G, Hunskaar S. Telephone counselling by nurses in Norwegian primary care out-of-hours services: a cross-sectional study. BMC Fam Pract. 2017;18(1):84. DOI: 10.1186/s12875-017-0651-z

2. Midtbø V, Fotland SS, Johansen IH, Hunskaar S. From direct attendance to telephone triage in an emergency primary healthcare service: an observational study. BMJ Open 2022;12:e054046. DOI: 10.1136/bmjopen-2021-054046

3. Midtbø V, Johansen IH, Hunskaar S. The association between municipal pandemic response and COVID-19 contacts to emergency primary health care services. An observational study. BMC Health Serv Res 2023; 23: 479.
DOI: 10.1186/s12913-023-09489-2.

4. Johansen IH, Midtbø V, Fotland SS, Hunskår S. Endret beslutningsstøtte i legevaktsentralen: effekter på hastegradsvurdering og ressursbruk (Effects on triage and use of resources of changed decision support tools in local emergency medical communication centers). Tidsskr Omsorgsforsk. 2023;9(2):53-66. DOI: 10.18261/tfo.9.2.5

4. Details of the impact

High demand for emergency medical services, including emergency primary care services, is a well-known phenomenon worldwide. Reasons for this development are complex and several factors may contribute. Examples include an increased number of older people in the population, limited access to daytime primary care services, and an increasing tendency of people with non-urgent

symptoms contacting emergency medical services due to factors such as patients' worry or anxiety, and convenience for the patient.

A well-known and much used strategy to handle overcrowding is the use of telephone triage. Telephone triage is well established in several European countries, including Norway, and the free European non-emergency medical assistance number 116117 has been introduced in Norway and several other countries. The driving force for implementation of telephone triage has been a notion that it is possible to direct patients to the right level of care and help patients to self-manage non-urgent symptoms. Our study published in 2022 is the first study which actually shows the effect of converting from direct attendance to telephone triage. Furthermore, it shows that it is possible to change help-seeking behaviours with relatively small interventions. It also shows that the effect of the intervention persists.

All over the world decision support tools are used by operators during the triage process, to support them in the assessment of the patient, to decide urgency level and to guide the patient to the most appropriate level of care. Our study published in 2023 is the first study to show the potentially detrimental effect of applying decision support tools which are not appropriately fitted to the clinical context. Decision support tools are meant to increase equity and patient safety but might inhibit the services' ability to prioritise between less and more urgent cases. To our knowledge, our study is the first international study to show the impact of decision support tools on workflow and use of resources in emergency primary care.

Our finding that the use of different decision support tools contributes to differences in urgency levels and in the use of resources, points to the need of a national decision support tool to ensure equal services to all the inhabitants. Furthermore, it underscores the need to develop the tools in a manner that is adapted to the level of over- and undertriage that is considered acceptable in the Norwegian health care system.

The findings from our studies are essential in understanding, planning, and improving emergency primary care. Telephone triage and counselling allow for more appropriate use of resources. The share of telephone advice differs between countries and between the different services within a country. In some services that provide a high share of telephone advice, the potential of telephone triage might be near to fully exploited, while other services might have a huge potential in improving their use of resources.

The knowledge from these studies has been incorporated in guidelines and normative documents and has inspired further research and innovations. It has allowed NKLM to give evidence-based advice and guidance to leaders of the services and governmental bodies, and to improve decision support tools. The findings also set the agenda for further research within NKLM, for example, studies that investigate and quality assure the patient pathway from the first triage in the local emergency medical communication centre, to triage upon eventual arrival at the emergency primary care clinic or the outcome of telephone advice.

Findings have been presented at the yearly conferences for leaders of emergency primary care and for health personnel within emergency primary care in 2015, 2017, 2022 and 2023. Preliminary results were presented in a dialog meeting with the Directorate of Health in 2015, and stakeholders in the Directorate of Health have been informed of new results throughout the project. Furthermore, results were presented at a national conference for collaboration between primary and secondary care in 2023, and internationally at the EurOOHnet conference in 2022 and 2023 (the yearly conference for the European network for emergency primary care services), and at the Nordic Congress for General Practice in 2022. The findings have also been disseminated through teaching at educational programmes for personnel in the emergency medical services.

5. Sources to corroborate the impact

Citations of the studies

The first study has been cited by 8 scientific papers, published in international journals, se a list of selected citations below:

- Registered nurses´ views on telephone nursing for patients with respiratory tract infections in primary healthcare - a qualitative interview study. Kaminsky E, Aurin IE, Hedin K, Andersson L, André M. BMC Nurs. 2020 Jul 14;19:65. DOI: 10.1186/s12912-020-00459-1.
- Preschool children in Danish out-of-hours primary care: a one-year descriptive study of face-to-face consultations. Lous J, Moth G, Huibers L, Vedsted P, Christensen MB. BMC Fam Pract. 2019 Feb 26;20(1):36. DOI: 10.1186/s12875-019-0922-y.
- Effect of an educational intervention for telephone triage nurses on out-of-hours attendance: a pragmatic randomized controlled study. Lindberg BH, Rebnord IK, Høye S. BMC Health Serv Res. 2023 Jan 3;23(1):4. DOI: 10.1186/s12913-022-08994-0.
- How often do nurses suspect violence and domestic violence in local emergency medical communication centre? A cross-sectional study. Steen K, Alsaker K, Raknes G. Scand J Prim Health Care. 2022 Jun;40(2):281-288. DOI: 10.1080/02813432.2022.2097615.
- Phone triage nurses' assessment of respiratory tract infections - the tightrope walk between gatekeeping and service providing. A qualitative study. Lindberg BH, Rebnord IK, Høye S. Scand J Prim Health Care. 2021 Jun;39(2):139-147. DOI: 10.1080/02813432.2021.1908715. Epub 2021 Apr 1

The second study, published in 2022 has the following citation:

- The Triage Capability of Laypersons: Retrospective Exploratory Analysis. Kopka M, Feufel MA, Balzer F, Schmieding ML. JMIR Form Res. 2022 Oct 12;6(10):e38977. DOI: 10.2196/38977.

The two most recent studies were published less than a year ago and have not yet been cited by other authors.

Presentations on selected conferences

- Collaborative conference for the emergency medical services, November 2023. Title of presentation: “What role should decision support tools have?”.
- EurOOHnet conference, May 2023. Title of presentation: “Effects on triage and use of resources of changed use of decision support tools in the local emergency medical communication centre”.
- EurOOHnet conference, May 2022. Title of presentation: “From direct attendance to initial telephone contact in an emergency primary health care service: an observational study”.
- Nordic Congress for General Practice, June 2022. Title of presentation: “Emergency primary health care contacts in Norway during the COVID-19 pandemic”.

NORCE, Division of Health and Social Sciences case 4

Institution: NORCE Norwegian Research Centre
Administrative unit: RKBU Vest
Title of case study: Bergen Child Study
Period when the underpinning research was undertaken: 2007-2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2012-2022
Period when the impact occurred: 2012-2022

1. Summary of the impact

The impact of the knowledge generated from the Bergen Child Study is evident across a range of indicators and settings. Updated prevalence rates of psychiatric disorders have contributed towards service planning. By evaluating psychometric properties of a wide range of key assessment instruments we have contributed to valid assessments of child and adolescents' mental health, in health services. Further, our research is included as references and knowledge base for key governmental white papers and professional guidelines. In addition, we have directly impacted service delivery by including our research findings in basic and further education and directly towards parents and children/adolescents through media reports.

2. Underpinning research

The Bergen Child Study (BCS) was launched in Norway in 2002 to study children's mental health in response to a national strategic plan to improve mental health services. The BCS (including the study in adolescence, youth@hordaland) constitute four cross-sectional waves of data collection at ages 7-9 (2002), 11-13 (2006), 14-16 (2009), and 17-19 (2012) years in the municipality of Bergen (Waves 1-3) and Hordaland County which also comprises Bergen municipality (Wave 4), Norway. The data-collection is multi-informant with both teacher-, parent-, and self-report. The main component of the project is the multi-informant questionnaire covering mental health, service delivery, and a range of risk and protective factors. For the three first waves, a detailed psychiatric screening was conducted, and for the first and second wave a psychiatric interview was conducted on a subset of participants. In wave one a, neuropsychological evaluation was also carried out on smaller subsets of participants. To date, we have linked the study data from the youth@hordaland study to administrative data on grades and school attendance in the National Education Database (NUBD), to mental health services information in the National Patient Registry (NPR), and to information on adoptions in the National Adoption Registry. We have also served as a population control group for several clinical studies.

The formal end of the study was December 2023. We have contacted participants who have previously consented to participation as adults to extend the project period until 2033.

The Bergen Child Study has resulted in 12 PhDs and 151 publications. The publication rate has been steady and is still strong with ten international peer-reviewed publications in 2023 and more ongoing projects. Thus, there is a wide range of research findings that together form the knowledge base and thus the basis of its impact. To exemplify, we have estimated prevalence rates for psychiatric disorders, which was the first large scale prevalence estimates in children in Norway (1). We have also investigated how a range of factors influence mental health problems and psychiatric problems (2,6,3). For instance, we have confirmed the hypothesis that there is a social gradient in mental health in Norwegian children and adolescents, and key mechanism for this gradient, including parental well-being, parenting practices, sleep problems, and more (3). We

have indicated high risk groups for mental health problems, including children with chronic illnesses, youth with separated parents, adolescents who have experienced trauma or been in contact with welfare services, investigating nuanced associations and mechanism (5). We have also focused on outcomes for children and adolescents, and especially how risk and protective factors influence school performance and school completion, as one of the key functional outcomes in these developmental periods (4). We have also focused on service delivery by linkage between questionnaire data and registry information from Child and Adolescent Mental Health Services (CAMHS). We have found that access to and treatment in CAMHS seems to be largely dependent on symptoms of mental health problems and not on socioeconomic variables like parental education level. Further, while very few had received a formal sleep diagnosis in CAMHS, we found a very high prevalence of sleep problems across diagnoses, warranting specific treatments for sleep problems in this setting (6).

Kjell Morten Stormark, Professor, former PI of the Bergen Child Study (2006-2009, 2011-2013).
Astri Lundervold, Professor, former PI of the Bergen Child Study (2009-2011)
Mari Hysing, Professor, current PI of the Bergen Child Study (2013-). Former PhD candidate and post-doctoral fellow in the study.
Tormod Bøe, Professor. Former PhD candidate and post-doctoral fellow in the study.
Kristin Gärtner Askeland, Senior researcher (2013-), former PhD candidate and post-doctoral fellow in the study.
Sondre Aasen Nilsen, Senior researcher (2020-), former PhD candidate in the study.

3. References to the research

1.Heiervang, E., Stormark, K. M., Lundervold, A. J., Heimann, M., Goodman, R., Posserud, M. B., Ullebø AK, Plessen, KJ, Bjelland I, Lie SA & Gillberg, C. (2007). Psychiatric disorders in Norwegian 8- to 10-year-olds: an epidemiological survey of prevalence, risk factors, and service use. Journal of the American Academy of Child & Adolescent Psychiatry. DOI: 10.1097/chi.0b013e31803062bf (citations: 542)

2.Hysing, M., Pallesen, S., Stormark, K. M., Jakobsen, R., Lundervold, A. J., & Sivertsen, B. (2015). Sleep and use of electronic devices in adolescence: results from a large population-based study. BMJ open, 5(1), e006748. DOI: 10.1136/bmjopen-2014-006748 (citations: 770)

3.Bøe, T., Sivertsen, B., Heiervang, E., Goodman, R., Lundervold, A. J., & Hysing, M. (2014). Socioeconomic status and child mental health: The role of parental emotional well-being and parenting practices. Journal of abnormal child psychology, 42, 705-715. DOI: 10.1007/s10802-013-9818-9 (citations: 313)

4.Askeland, K. G., Bøe, T., Sivertsen, B., Linton, S. J., Heradstveit, O., Nilsen, S. A., & Hysing, M. (2022). Association of depressive symptoms in late adolescence and school dropout. School mental health, 14(4), 1044-1056. DOI: 10.1007/s12310-022-09522-5 (citations: 8)

5.Heradstveit, O., Gjertsen, N., Iversen, A. C., Nilsen, S. A., Askeland, K. G., Christiansen, Ø., & Hysing, M. (2020). Substance-related problems among adolescents in child welfare services: A comparison between individuals receiving in-home services and those in foster care. Children and Youth Services Review, 118, 105344. DOI: 10.1016/j.childyouth.2020.105344 (citations: 12)

6.Hysing, M., Heradstveit, O., Harvey, A. G., Nilsen, S. A., Bøe, T., & Sivertsen, B. (2022). Sleep problems among adolescents within child and adolescent mental health services. An epidemiological study with registry linkage. *European Child & Adolescent Psychiatry.* DOI: 10.1007/s00787-020-01676-4
(citations: 19)

4. Details of the impact

One of the main mechanisms for impact from our research is through its inclusion in governmental white papers, strategy plans, and national guidelines that again impact service delivery. We included issues relevant for national planning of child and adolescent mental health services (CAMHS) in the study design as this was one of the main aims of the study. For instance, the prevalence rates have been widely cited as a basis for scaling of services on specific diagnoses, both directly and through inclusion in other official reports. More specifically, we found that anxiety disorders were prevalent, and that a majority of those with these disorders were not in contact with mental health services. This spurred a change in the CAMHS services for this group, and large- scale intervention projects to improve the evidence base for anxiety treatment for children.

We are also included in a range of governmental papers on major public health problems that we have documented and addressed; the social gradient in health, the short sleep duration among adolescents, and predictors of dropout from school, are examples of results that have been included as references and backgrounds for national guidelines (a). In the national official guidelines for the health center services, the Bergen Child Study is cited as underpinning research for their guidelines on sleep with three of the sleep papers from the Bergen Child Study (b). Our work on school absenteeism and health service use is also included as underpinning research for interventions to prevent school dropout, and our results on socioeconomic status and mental health was reference as a background for follow-up for parents' mental health.

Folkehelserapporten (Public health report) (c) is an example of key governmental white papers that form an important basis for policy development and includes our research for the prevalence of psychiatric disorders in different age groups and sleep problems in the chapter on mental health. We are also referenced in the sleep disorders chapter on prevalence, risk factors, and outcomes. The Governments plan for “Coping throughout life” (d) also referenced our work, for instance on social gradients of mental health and the association between bullying and mental health. We are also a key knowledge provider in *local* service plans and guidelines, for instance plan for service use in Bergen Municipality, in which they have referred to our research regarding socioeconomic status, mental health, and school absenteeism as basis for their plans (e).

In addition to the impact through reports, we are also invited into trusted positions to share our knowledge based on the research in the project. As an example, two of the key researchers are on two expert panels for the government to advise policy development, one concerning childhood poverty and one on screen use in children and adolescents.

While many of our publications have high citation rates mirroring its interest in the research community, we have also aimed at reaching service providers and the public which we know have an interest in our findings. All our publications have short Norwegian popularized summaries, that are included in our online booklet (j) and is the basis for new stories on information channels for service delivery and as teasers for media. We get media coverage on many publications in newspapers and radio, but also TV reports (f). As an example, one of the papers on the association between screen use and sleep had hundreds of reports in international and national newspapers, tv, and radio interviews worldwide and in Norway.

We have also published on psychometric properties of commonly used assessment instruments in services for children and adolescents. Assuring psychometric properties of key instrument is important to assure valid and reliable assessments. This information may be directly found in our publications, but most often it is conveyed through systems such as PsykTestBarn, that provides information on assessment instruments to professionals (g).

The knowledge base we have developed has also been included in educational resources, from inclusion in high school syllabus, to university and college education courses, and further education. Some of these courses are part of the RKBUs role as a course provider and education for health personnel (i) and we are often represented at key seminars and conferences for health personnel. We are also in close collaboration with clinical studies that focus on high-risk groups such as children born premature, children with chronic illness and children who have been maltreated, and we serve as a population-based control (h)

Research from the project has also formed the basis for research projects and collaborations with the municipalities. As an example, our research on school attendance and school dropout is part of the background of the Back2School pilot project where an intervention for school attendance problems is evaluated, for participation in a public health project in Bjørnafjorden municipality, and collaboration with the newly appointed school attendance team in Bergen municipality.

5. Sources to corroborate the impact

a. A childhood for life: Increased belonging, coping and learning for children in poor families (Norwegian: En barndom for livet: Økt tilhørighet, mestring og læring for barn i fattige familier)
https://www.regjeringen.no/no/dokumenter/en-ny-barndom-for-livet/id3000835/

b. "Helsestasjon, skolehelsetjeneste og helsestasjon for ungdom"
https://www.helsedirektoratet.no/retningslinjer/helsestasjons-og-skolehelsetjenesten

c. Folkehelserapporten/Public health report
https://www.fhi.no/he/folkehelserapporten/?term=

d. Mestre hele livet, Regjeringens strategi for god psykisk helse (Coping throughout life. The Government strategy for good mental health)
https://www.regjeringen.no/contentassets/f53f98fa3d3e476b84b6e36438f5f7af/strategi_for_god_psykisk-helse_250817.pdf

e. Local plans for service providers for children and adolescents, Bergen Municipality
https://www.bergen.kommune.no/politikere-utvalg/api/fil/bksak/2016464436-6382215/Bergens-barn-byens-fremtid-Plan-for-helsestasjons-og-skolehelsetjenesten-psykisk-helsearbeid-barn-og-unge-og-barnevernet-i-Bergen-2016-2026

f. Example of media coverage:
https://www.huffpost.com/entry/teens-sleep-day-screen-time_n_6604706

g. Psyktestbarn
https://psyktestbarn.r-bup.no/no/artikler/sdq-p-strengths-and-difficulties-questionnaire-foreldrerapport

h. Control group for clinical studies
Fevang, S. K. E., Hysing, M., Markestad, T., & Sommerfelt, K. (2016). Mental health in children born extremely preterm without severe neurodevelopmental disabilities. Pediatrics, 137(4). DOI: 10.1542/peds.2015-3002

i. E-learning
https://rise.articulate.com/share/D6LqCF6RV_5fncwcldHjSxCre4ujhvhp#/

j. Popularized summary of the Bergen Child Study
https://relayto.com/s-c1/barn-i-bergen-2023-yjveiks1xz4o6

NORCE, Division of Health and Social Sciences case 5

Institution: NORCE Norwegian Research Centre
Administrative unit: RKBU Vest
Title of case study: Pathways to Independence
Period when the underpinning research was undertaken: 2018
Period when staff involved in the underpinning research were employed by the submitting institution: 2012-2022
Period when the impact occurred: 2018-2022

1. Summary of the impact

The impact of the Pathways to Independence study (PTI) is both on a scientific and societal level. The study has led to increased knowledge about unaccompanied refugee minors (URM) under settlement through publications in national and international peer reviewed journals. On a societal level, the study was initiated in close collaboration with Child Welfare Services (CWS) in Bergen during a large wave of URMs arriving in European countries. Increasing knowledge on successful settlement was critical at this time and the aim of the study was to improve the quality of services, with transfer value to other Norwegian municipalities.

2. Underpinning research

The PTI-study was developed in close collaboration with the CWS in Bergen municipality in 2015 with an overall aim to gain knowledge on how to facilitate healthy development for URMs after settling in Norwegian municipalities.

A comprehensive survey was developed in collaboration between researchers and the CWS consisting of more than 200 questions related to background information (age, gender, country of origin, current housing), experiences with the CWS and schooling, and social support and participation in activities after settlement. We also included standardized and validated questionnaires measuring exposure to potential traumatic events, symptoms of mental health problems and somatic complaints, sleep, protective factors, quality of life, and acculturation strategies. Many of these questionnaires have previously been used in two Norwegian epidemiological studies, *the Bergen Child study and The Young in Fostercare*, facilitating comparison with other youth populations in Norway.

Although a relatively small sample size of 81 URMs, the response rate of the study was 80%, and sample characteristics such as country of origin and sex is representative of URMs on a national level. Hence, the sample is representative for URMs settled in Norway in this period and findings generalizable beyond URMs settled in Bergen municipality.

An important asset of the PTI-study is the close collaboration between the researchers, service providers, and users that has been essential and present in all parts of the project. Researchers, service providers, and users were involved in the selection and piloting of questionnaires, designing the study procedures, administering the survey, interpretation and dissemination of results, and implementation of changes to the services informed from the knowledge gained. The difference in expertise and knowledge of the collaborators has been important for the success of this study.

The PTI-study has resulted in two publications in Norwegian; one report available online and in printed versions summarizing results from the survey and one publication in a Norwegian peer-reviewed journal describing the strong user-involvement advocated in the study arguing that this increased both the quality of the research and led to quality improvements in the CWS. Moreover, there are three publications published and one accepted for publication in international peer-reviewed journals. Data has also resulted in one master thesis. Finally, as part of a project funded by the Norwegian Research Council (The Pathway to Active Citizenship (PACT)-study, 2021-2026), work with data from the PTI-study is still ongoing.

A unique part of the current project is how the results from the survey were disseminated directly to the participants and to the CWS caseworkers, including the management team, team of case workers, social workers. The dissemination process has facilitated quality improvements within the services that are close to the needs of the users. Moreover, this process has informed the clinical implications of findings in scientific publications. In the PACT-study the dissemination process has been taken further to include three settlement municipalities in Norway, in which results from both the PTI and PACT-study have been disseminated to CWS in all municipalities.

Names of key researchers:
Ingrid Kvestad, Researcher, 2017-2024
Tormod Bøe, Researcher, 2017-2024
Sondre Nilsen, Researcher, 2021-2022
Kristin Gartner Askeland, Researcher, 2022-2024

3. References to the research

Kvestad, I., & Bøe, T. (2019). Veien til selvstendighet. Et prosjekt i Barneverntjenesten for enslige mindreårige flyktninger i Bergen kommune. http://hdl.handle.net/11250/2625986

Kvestad, I., Randal, S. B., Sayyad, N., Lehmann, S., & Bøe, T. (2021). Study design: Pathways to Independence–A study of unaccompanied minor refugees settled in a Norwegian city municipality. *Scandinavian journal of public health*, *51*(3), 323-329. DOI: 10.1177/14034948211025446

Kvestad, I., Bøe, T., Sayyad, N., Skogen, J. C., Randal, S., & Lehmann, S. (2021). Potential traumatic events and symptoms of post-traumatic stress in unaccompanied refugee minors—a comparison with youth in foster care. *European child & adolescent psychiatry*, 1-11. DOI: 10.1007/s00787-021-01876-6

Sayyad, N., Randal, S. B., Bøe, T., & Kvestad, I. (2021). «Det var godt å si det jeg hadde på hjertet» Når stemmen til enslige mindreårige flyktninger bidrar til tjenesteutvikling og ny kunnskap. *Tidsskriftet Norges Barnevern*, *98*(2), 122-135. DOI: 10.18261/ISSN1891-1838-2021-02-04

Vedvik, A. I. (2022). Enslige mindreårige flyktningers akkulturasjonsprosess. Nettverk, psykisk helse og livskvalitet etter bosetting i Norge. Masteroppgave. Master i interkulturelt arbeid. VID vitenskapelig høyskole. Stavanger

Nilsen, S. A., Kvestad, I., Randal, S. B., Hysing, M., Sayyad, N., & Bøe, T. (2023). Mental health among unaccompanied refugee minors after settling in Norway: A matched cross-sectional study. *Scandinavian journal of public health*, *51*(3), 430-441. DOI: 10.1177/14034948221100103

Heimlie, O.M., Kvestad, I., Bøe, T., Sayyad, N., Nilsen, S.A., Randal, S., & Askeland, K. (In press). Protective factors associated with resilience among unaccompanied refugee minors after settling in Norway: A matched cross-sectional study. *European child & adolescent psychiatry*

4. Details of the impact

The large number of URMs seeking asylum in Norway in 2015 led to a mobilization of the Norwegian municipalities to increase the rate of settlements. Many Norwegian municipalities had no previous experience with settlements of URMs, and there was a lack of knowledge on factors critical for successful settlement of URMs. URMs is a vulnerable group with a high burden of mental health problems and improving URMs settlement process may contribute to healthy development of these minors. The PTI-study provides a comprehensive data source of the needs and recourses of URMs after settlement in Norway. The inclusion of standardized and validated instruments used in previous Norwegian epidemiological studies allows for a comparative perspective on the situation of URMs. Hence, results from the study have been valuable in the process of reaching empirically based recommendations on how to succeed with URMs after settlement in Norway with the potential to fill in important knowledge gaps and with transfer value to other European countries.

Findings from the study were initially summarized in a report made available online and in written format. This report shows a high burden of mental health problems and low levels of perceived protective factors and health related quality of life among URMs. At the same time, although the URMs communicate the importance of CWS and school in their daily life, they report a lack of perceived social support and network outside of these arenas. These initial findings were disseminated to the CWS and relevant policy makers/stake holders in Bergen municipality focusing on how findings could lead to improved services for URMs. The dissemination process (described in Sayyad et al 2021) also included meetings with the URMs themselves, where their reflections upon the findings resulted in immediate changes to services such as tasks groups directly targeting mental health work and social network for URMs within the CWS and Sunday dinners organized by the CWS where all URMs were invited.

The opportunity to compare URMs responses to that of other groups of Norwegian adolescence has also increased the impact of the PTI-study. In Kvestad et al (2021), we compare the number of potential traumatic events (PTE) and post-traumatic symptoms between URMs and youth in foster care, both high-risk groups under the care of CWS in Norway. Findings demonstrate that the frequency and types of PTEs and the post-traumatic symptom load and profile differed between the groups, underscoring the importance of qualified and targeted care for URMs differing from that of other high-risk groups in the CWS. In Nilsen et al (2023), findings suggest that URMs appear to have moderately more emotional problems than Norwegian young people. They are more likely to report being alone, getting along better with adults than with their peers and being bullied, but also report being more helpful and sharing with others. At the same time, we demonstrate poor psychometric properties of a widely used questionnaire for mental health problems (Strength and Difficulties Questionnaire) when used among URMs, suggesting other instruments would be better assessing mental health in this group. As for the general report, results from these peer-reviewed publications have been communicated to the CWS leading to knowledge-based adjustments to the services.

The content and quality of services are important determinants for a successful transition for URMs to an independent life in Norwegian society. As shown, an important impact of the results from the PTI-study was more targeted services to URMs settled in a Norwegian municipality, contributing to a healthy transition for URMs to the Norwegian society.

Ultimately the PTI-study has contributed indirectly and directly to new, large research projects. Professor Ravi Kohli from Bedfordshire University was engaged in the PTI-study as a lecturer and moderator and initiated contact with researchers at NORCE resulting in the “Relational well-being" project across three countries funded by NordForsk. In the PACT-study funded by the Norwegian Research Council, data from the PTI-study is part of one work package examining pathways from a life within the CWS to an independent life for URMs.

The project’s aim will be reached through qualitative and register-based data in addition to data from the PTI-study. In this project, three municipalities are involved and attend regular meetings to discuss planned papers and analyses, and to discuss and help investigators understand the findings. The project group has also presented results to all employees in the CWS in the municipalities and facilitated debates and suggestions for service adjustments following the findings. Such workshops will also be held at the end of the project period in 2025.

5. Sources to corroborate the impact

a. Report summarizing results:
Kvestad, I., & Bøe, T. (2019). Veien til selvstendighet. Et prosjekt i Barneverntjenesten for enslige mindreårige flyktninger i Bergen kommune. http://hdl.handle.net/11250/2625986

b. Collaborators:

- Sølve Randal – head of Child Welfare Services for Unaccompanied minors in Bergen municipality
- Alette Hilton Knudsen, head of Child Welfare Services in Bergen municipality
- Ravi Kohli, Professor at Bedforshire University

c. New projects:

Relational well-being: https://www.norceresearch.no/en/projects/relational-wellbeing-in-the-lives-of-young-refugees-in-finland-norway-and-the-uk

Pathways to Active Citizenship (PACT): https://www.norceresearch.no/en/projects/pact-pathways-to-active-citizenship

d. Online publications:

Pathways to Independence. Improved services for unaccompanied minor refugees after settlement in a Bergen municipality. - Norce (norceresearch.no)

https://rkbu.norceresearch.no/aktuelt/enslige-mindrearige-flyktninger-klarer-seg-forbausende-bra-til-tross-for-traumer

https://kunnskapombarn.no/aktuelt/psykisk-helse-hos-einslege-mindreårige-flyktningar

e. Media:

https://www.nrk.no/vestland/behrouz-kom-til-norge-som-17-aring_-_-barnevernet-var-like-viktige-som-familien-min-1.14727048

Nord University, Faculty of Nursing and Health Sciences, case number 1

Institution: Nord University
Administrative unit: Faculty of Nursing and Health Sciences (FSH)
Title of case study: Venous air embolism—Research impact on clinical training, practice and guidelines
Period when the underpinning research was undertaken: 2017–2022
Period when staff involved in the underpinning research were employed by the submitting institution: Benjamin Storm: 1 August 2019–present, Erik W. Nielsen: 1 October 2009–present, Tonje Braaten: 5 October 2019–present, Bent Aksel Nielsen: 1 January 2021–present, Knut Dybwik: 1 September 2012–31 July 2021.
Period when the impact occurred: 2017–2022

Summary of the impact (indicative; maximum 100 words)
Educational initiatives targeting hysteroscopy-related venous air embolism significantly enhanced global awareness and prompted revisions in clinical practices, thereby influencing national guidelines. Enhanced understanding of thromboinflammatory pathophysiological mechanisms associated with air embolism led to advancements in *in vitro* methodologies, and established a theoretical foundation for medical interventions in clinical air embolism cases. These insights were incorporated into a comprehensive international air embolism review. The recognition of an open thorax as a pivotal risk factor emphasized the increased likelihood of venous air emboli arterialization during thoracic surgery, highlighting specific complications associated with this context.

Underpinning research

Air embolism may complicate most surgical and many medical procedures. Most air emboli are asymptomatic. However, occasionally, symptomatic air embolism with devastating effects may occur. This has been known and studied since the beginning of the 20th century. Nonetheless, worldwide awareness and recognition of air embolism as a severe medical condition that should be prevented and diagnosed, vary considerably among countries. Air embolism triggers inflammation, but thus far, the exact pathophysiological mechanism has not been ascertained. Therefore, no specific treatment recommendations exist. Three catastrophic clinical events of fatal and near-fatal air embolism at the Nordland Hospital Trust sparked this project. The aim of our project was to clarify the mechanisms of air embolism, disseminate this knowledge to avoid and prevent future cases, and examine the pathophysiological mechanisms to suggest a medical intervention for air embolism. The project was divided into three working packages:

a. The initial component of our project focused on investigating the mechanisms leading to severe injuries, including one fatality, during routine hysteroscopies. Our goal was to identify pathophysiological mechanisms, symptoms, and effective preventive and therapeutic interventions. Through thorough analysis of the clinical cases including examination of the involved equipment, multidisciplinary discussions, rigorous literature review, and *in vivo* animal model studies, we identified iatrogenic air embolism introduced during hysteroscopy as the most likely cause for the acute deterioration of the three patients. Furthermore, we identified the specific signs and symptoms of perioperative air embolism, including a sudden drop in expired end tidal CO_2, and we identified potential risk-reducing actions, including the altered positioning of the patient, reduced insufflation pressure, and modified hysteroscopic technique. To disseminate these critical insights, we employed national channels, such as the Norwegian Directorate of Health bulletin, and

international platforms through the publication of case reports and presentations at international conferences.

b. Second, we elaborated upon the immunological mechanisms driving air embolism-induced inflammation *in vitro* in a human whole blood model. Our objective was to discern the impact of specific immunomodulating drugs on air-induced thromboinflammation. This component of the research aimed at enhancing our understanding of the intricate interplay between immunology and thromboinflammatory responses in the context of air embolism. These studies showed how air embolism trigged activation of the thromboinflammatory system, including complement, leucocytes, cytokines, thrombocytes, and coagulation. We ascertained the mechanism whereby air emboli trigger the complement system (an integrated part of the immune system), and demonstrated how inhibition of complement C3 with commercially available complement inhibitors effectively attenuated the thromboinflammatory response. Additionally, we showed how air activated platelets through a complement-independent pathway—however, we could not fully elucidate the underlying mechanism of this activation. Finally, we showed how avoiding ambient air in test tubes during *in vitro* experiments significantly decreased 'background activation' of the biological cascades, increasing the signal-to-noise ratio.

c. The third facet involved an *in vivo* examination of the pathophysiological mechanisms of venous air embolism in pigs. This comprehensive investigation encompassed both hemodynamic effects, including the influence of an open thorax, and thromboinflammatory effects. By employing an animal model, we sought to closely mimic the physiological conditions relevant to hysteroscopy procedures, providing valuable insights into the complexities of venous air embolism. These animal studies showed how air embolism triggered the thromboinflammation *in vivo* through the same mechanisms as in our *in vitro* study, supporting the theoretical foundation for targeted complement inhibition in patients with air embolism. However, as no effective porcine C3 inhibitor exists, we could not demonstrate the effect of complement inhibition in this model. Our animal studies also showed how open thorax—for example, during thoracic surgery—significantly decreased the lung filtering capacity towards air emboli, and thus, increased the lethal effect of even small amounts of venous air emboli.

This research was conducted from 2015 through 2021 at the Animal Research Laboratory (ANILAB), Faculty of Nursing and Health Sciences (FSH), Nord University. The primary FSH researchers leading these efforts were PhD student (now associate professor) Benjamin Stage Storm, professor and supervisor Erik Waage Nielsen, and nurse anesthesiologist and laboratory technician Bent Aksel Nielsen. Adjunct professor and biostatistician Tonje Braaten[15] joined the team in 2019. Professor Erik W. Nielsen (until recently 50%) [236], associate professor Benjamin Storm (50%) [1234], and Bent A. Nielsen (25%)[13] are part-time FSH employees; they are affiliated to other institutions, as indicated. Since 1 January 2022, Erik W. Nielsen has been employed in a 10% part-time position as adjunct professor.

However, the above-mentioned body of work represents a collective effort over several years, combining the expertise of interdisciplinary researchers from many research institutions. Professor and supervisor Tom Erik Mollnes [467 89] is a pivotal member of the research group.

The outcomes of this research endeavor promoted many awareness initiatives and laid the theoretical foundation for medical intervention in patients with air embolism. Further details and references to specific research outputs supporting these findings are provided in the subsequent sections.

[1]Faculty of Nursing and Health Sciences, Nord University, Bodø, Norway

[2]Department of Clinical Medicine, Faculty of Health Sciences, UiT The Arctic University of Norway, Tromsø, Norway

[3] Department of Anesthesia and Intensive Care Medicine, Nordland Hospital, Bodø, Norway

[4]Research Laboratory, Nordland Hospital Trust, Bodø, Norway

[5]Department of Community Medicine, Faculty of Health Sciences, UiT The Arctic University of Norway, Tromsø, Norway

[6] Faculty of Medicine, Institute of Clinical Medicine, University of Oslo, Oslo, Norway

[7]Faculty of Health Sciences, KG. Jebsen TREC, UiT The Arctic University of Norway, Tromsø, Norway

[8]Department of Immunology, Oslo University Hospital, The University of Oslo, Oslo, Norway

[9]Centre of Molecular Inflammation Research, Norwegian University of Science and Technology, Trondheim, Norway

3. References to the research (indicative; maximum of six references)

1. Marsh P. L., Moore E. E., [….] **Nielsen E. W., Storm B. S.**, Walsh, M. M. et al. Iatrogenic air embolism: Pathoanatomy, thromboinflammation, endotheliopathy, and therapies. *Frontiers Immunol*., 2023(Aug), 14(1230049). doi: 10.3389/fimmu.2023.1230049

2. **Storm B. S.**, Ludviksen J. K., Christiansen D., [….] **Nilsen B. A.**, **Dybwik K.**, **Braaten T.**, **Nielsen E. W.**, Mollnes T. E. Venous air emboli activate complement C3, and trigger inflammation and coagulation in vivo in a porcine model. *Frontiers in Immunology*., 2022, 13(839632), 1–13. doi:10.3389/fimmu.2022.839632

3. **Storm B. S.**, Christiansen D., Fure H., [….] **Braaten T.**, **Nielsen E. W.**, Mollnes T. E. Air bubbles activate complement and trigger C3-dependent hemostasis and cytokine release ex vivo in human whole blood. *J Immunol*., 2021, 207 (11), 2828–2840. doi:10.4049/jimmunol.2100308

4. **Storm B. S.**, Halvorsen P. S., Skulstad H., **Dybwik K.**, [….] **Braaten T.**, **Nielsen E. W.**, Mollnes T. E. Open chest and pericardium facilitate transpulmonary passage of venous air emboli. *Acta Anaesthesiol Scand*., 2021, 65, 648–655. doi:10.1111/aas.13796

5. **Storm B. S.**, Christiansen D., Mollnes T. E., **Nielsen E. W**. Avoiding ambient air in test tubes during incubations of human whole-blood minimizes complement background activation. *Journal of Immunological Methods,* 2020, 487, 112876. doi:10.1016/j.jim.2020.112876

6. **Storm B. S.**, Andreasen S., Hovland A., **Nielsen E.W.** Gas embolism during hysteroscopic surgery?: Three cases and a literature review. *A&A Case Reports,* 2017, 9(5), 140–143. doi:10.1213/XAA.0000000000000549

4. Details of the impact (indicative; maximum 750 words)

The research project made distinct contributions to clarifying the pathophysiological mechanisms driving air-induced thromboinflammation. This led to the development of an air-free *in vitro* whole

blood model with a superior signal-to-noise ratio compared to existing models. Additionally, the project identified C3 inhibition using, for example, pegcetacoplan, possibly combined with platelet inhibition as a potential target for medical intervention to mitigate air-induced thromboinflammation. The suggested drugs are already commercially available, establishing the theoretical foundation for targeted medical intervention in patients with air embolism. Our study highlighted the significance of patient positioning during hysteroscopy, insufflation pressure of the distention media, the hysteroscopic technique, and the meticulous focus on sudden reductions in end-expired CO_2 as an early warning sign of possible air embolism. Moreover, the project highlighted open thorax as a significant risk factor for severe arterial air embolism, emphasising the need to meticulously avoid venous air emboli during and after thoracic surgery. The in-depth knowledge in the clinical case report was disseminated at multiple conferences and shared via a national bulletin of the Directorate of Health. Furthermore, the findings, which have been published in an international review article, are being incorporated into the ongoing revision of the national obstetric anesthesia guideline.

The increased awareness of air embolism as a potential severe medical condition during various surgical procedures, including hysteroscopy, has prompted procedural changes nationwide, including at the Nordland Hospital Trust (NLSH). Since implementing these changes, no new case of air embolism has occurred during hysteroscopy at the NLSH. Thus, our findings have potentially benefited numerous surgical patients.

Moreover, the *in vitro* findings promise a better signal-to-noise ratio in whole blood experiments, potentially benefiting researchers worldwide. Finally, the identification of the mechanism behind air-induced thromboinflammation and the therapeutic possibilities may extend to other air-driven diseases, such as decompression disease, laying the theoretical foundation for treating such patients.

5. Sources to corroborate the impact

Gassemboli ved hysteroskopisk kirurgi. Læringsnotat fra meldeordningen IS-0586. Published online April 4, 2016. Accessed April 10, 2016. https://ehandboken.ous-hf.no/document/131233

Nordland Hospital Trust: Report on Research and Innovation 2021, p. 6–7 (in Norw.):

https://www.nordlandssykehuset.no/49a379/siteassets/documents/fag-og-forskning/forskningsrapport/k4_nlsh_forskningsrapport2021.pdf

Nord University, Faculty of Nursing and Health Sciences, case number 2

Institution: Nord University
Administrative unit: Faculty of Nursing and health Sciences (FSH)
Title of case study: Ethics studies and impact on the Code of Ethics for Nurses
Period when the underpinning research was undertaken: 2012–2017
Period when staff involved in the underpinning research were employed by the submitting institution: Brinchmann BS employed 50%: 2003–present; Bentzen G: 2013–present; Solvoll BA: 2018–2019; Ursin G: 2011–present; Moe CF, employed 20–100%: 2013–present
Period when the impact occurred: 2018–present

1. Summary of the impact

Professor Berit Brinchmann was nominated by the Norwegian Nurses Organisation and subsequently appointed by the International Council of Nurses (ICN), to become one in 13 to serve in the international expert group mandated to revise the ICN Code of Ethics for Nurses. The code defines and provides guidance on how to conduct ethical nursing in the various roles that nurses undertake. In this collaborative effort, Brinchmann proposed a new element to the code: 'Nurses and Global Health'—a particularly crucial issue at a time marked by pandemics, climate crises, and wars.

Underpinning research

Empirically based studies in nursing ethics—lead by professor Berit Brinchmann—in the research group, 'Ethics, Relationships and Actions in Nursing and Health Sciences', Faculty of Nursing and Health Sciences, Nord University

Studies b, c, d, and e address ethical challenges in the work situation of nurses. Studies c, d, and e present results from ethical reflection groups in various contexts. Studies a and f focus on ethical challenges within two different patient groups—that is, patients undergoing home ventilator treatment and multifamily therapy for eating disorders. The empirical findings are analysed based on the ethical theory. Results indicate that nurses encounter ethical challenges as part of their daily work in various contexts, in different patient situations, and in their role as nurses.

a. Ethical challenges in home mechanical ventilation: A secondary analysis (2012). The study explores ethical challenges in home mechanical ventilation (HMV). The data include perceptions of healthcare professionals in hospitals and community health services and family members of patients. A number of ethical challenges arise: deciding who should be offered HMV, respect for patient's and family's wishes, quality of life, dignity, and equal access to HMV. HMV has a significant impact on patients, families, healthcare services, and allocation of resources.

b. "Values That Vanish into Thin Air'': Nurses' Experience of Ethical Values in Their Daily Work (2013). This study examines how nurses experience ethical values as they are expressed in daily practice in a hospital. Data were collected via focus group interviews. Values and reflection are significant for the work of nurses. Nurses believe that ethical values are

crucial for the quality of nursing; however, ethical values are often repressed in daily practice because of time pressure and staff shortage.

c. Ethical challenges in everyday work with adults with learning disabilities (2014). This study, conducted in a community institution for adults with learning disabilities, explored the ethical challenges discussed among healthcare providers working with adults with learning disabilities. Participants included healthcare providers. The findings were: feeling squeezed between conflicting actions, being the client's spokesperson, seeking shared responsibility, and expecting immediate and definite solutions. Frequent conversations regarding ethical challenges do not resolve ethical problems; nonetheless, they help visualise them and the staff's requirement for support.

d. Ethical challenges related to next of kin—nursing staffs' perspective (2016). This study, based on data derived from group discussions among nursing staff in a nursing home, elucidated the ethical challenges of nursing staff in their encounter with patients' next of kin, and discussed the impact of these challenges on clinical practice. Ethical challenges related to patients' next of kin were frequently discussed. The findings were categorised as 'the professionals' and 'the shadows'. The study suggested the need to enhance nursing staff's communication and ethical skills, and to establish routines in clinical settings for informing and following up with the next of kin in a systematic and structured manner.

e. Care-managers' professional choices: Ethical dilemmas and conflicting expectations (2017). Care-managers are responsible for public administration of individual healthcare decisions and decide the volume and content of community healthcare services. This study investigated—and discussed the clinical implications of—the conflicting expectations and ethical dilemmas of these professionals in their daily work. Data were collected in reflection group meetings at a purchaser unit. The findings included: professional autonomy and loyalty, with subthemes: loyalty to whom/what, overruling of decisions, trust in and obligation to report, and boundaries of involvement and subthemes: private or professional, care-manager or provider and accessibility. When allocating services, healthcare professionals have to strike a balance between responsibility and accountability in their role as care-managers.

f. An Aristotelian view of therapists' practice in multifamily therapy for young adults with severe eating disorders (2017). Eating disorders are serious conditions that also impact the families of adult patients. This study explored therapists' practice in multifamily therapy. Data were collected based on participant observation in multifamily therapy groups and interviews with the therapists. The findings included: 'having many strings to one's bow', 'planning and readjusting', 'developing as therapist and team', and 'regulating the temperature of the group'. The findings were discussed within the framework of Aristotelian virtue ethics.

Several other studies in nursing ethics have been published since 2017 by professor Brinchmann and her team. Numerous studies are underway.

3. References to the research

a. Dybwik, Knut; Nielsen, Erik Waage; Brinchmann, Berit Støre (2012). Ethical challenges in home

mechanical ventilation: A secondary analysis, *Nursing Ethics*, Volum 19 s. 233-244. https://doi.org/10.1177/0969733011414967

b. Bentzen, Gro; Harsvik, Anita; Brinchmann, Berit Støre (2013). ''Values That Vanish into Thin Air'': Nurses' experience of ethical values in their daily work, *Nursing Research and Practice*, Volum 2013; Article ID 939153. https://doi.org/10.1155/2013/939153

c. Solvoll, Betty-Ann; Hall, E.; Brinchmann, Berit (2015). Ethical challenges in everyday work with adults with learning disabilities. *Nursing Ethics,* Volum 22 s. 417-427. https://doi.org/10.1177/0969733014538887

d. Tønnessen, Siri; Solvoll, Betty-Ann; Brinchmann, Berit Støre (2016). Ethical challenges related to next of kin—nursing staffs' perspective. *Nursing Ethics,* Volum 23 s. 804-814. https://doi.org/10.1177/0969733015584965

e. Tønnessen, Siri; Ursin, Gøril; Brinchmann, Berit Støre (2017): Care-managers' professional choices: Ethical dilemmas and conflicting expectations. *BMC Health Services Research*: Volum 17:630 s. 1–10. https://doi.org/10.1186/s12913-017-2578-4

f. Brinchmann, Berit Støre; Moe, Cathrine Fredriksen; Valvik, Mildrid; Balmbra, Steven; Lyngmo, Siri; Skarbø, Tove (2017). An Aristotelian view of therapists' practice in multifamily therapy for young adults with severe eating disorders, *Nursing Ethics*: Volum 26 s. 1149–1159. https://doi.org/10.1177/0969733017739780

4. Details of the impact (indicative maximum 750 words)

Based on her and her team's extensive publication track-record within nursing ethics, professor Berit Brinchmann was nominated by the Norwegian Nurses Organisation and subsequently appointed by the International Council of Nurses (ICN) to become one in 13 to serve in the international expert group mandated to revise the ICN Code of Ethics for Nurses.

On October 20, 2021, the ICN published the revised ethical code. It outlines the ethical values, responsibilities, and professional commitments of nurses. The code provides guidance on how to conduct ethical nursing in the various roles that nurses undertake. It is not a code of conduct but can serve as a framework for decision-making and practice to meet professional standards set by regulatory bodies (ICN 2021: Code of Ethics for Nurses). The ICN Code of Ethics has served as the standard for nurses worldwide since it was first adopted in 1953.

During the revision, professor Brinchmann proposed a new element to the code: 'Nurses and Global Health'—a particularly crucial issue at a time marked by pandemics, climate crises, and wars. This point has also been included in the newly revised professional ethics guidelines for nurses in Norway: https://www.nsf.no/etikk-0/yrkesetiske-retningslinjer-sykepleiere. According to the ICN President Annette Kennedy, the guidelines—launched on the Global Ethics Day—served to, 'Highlight the changes we see in the nursing work environment, the challenges they face, and the ethical dilemmas brought to light by COVID-19'.

The ICN is a federation comprising more than 130 national nurses' associations (NNAs), collectively representing more than 28 million nurses worldwide. The ICN engages directly with its member associations to address critical issues within the nursing profession. Hence, the potential impact of Brinchmann's contribution—especially regarding the new element, 'Nurses and Global Health'—is literally global, and thus, has the potential to impact nurse's practice and patients worldwide.

5. Sources to corroborate the impact (indicative maximum of 10 references)

The ICN code:

- https://www.icn.ch/resources/publications-and-reports/icn-code-ethics-nurses

The code is also translated into French and Spanish:

- https://www.icn.ch/sites/default/files/2023-04/ICN_Code-of-Ethics_FR_WEB.pdf
- https://www.icn.ch/sites/default/files/2023-04/ICN_Code-of-Ethics_SP_WEB.pdf

The national nurses' associations of Sweden and Denmark have translated the code and made adjustments to meet national conditions and standards.

- https://swenurse.se/publikationer/icns-etiska-kod-for-sjukskoterskor
- https://dsr.dk/media/bkskaqfo/icn_code-of-ethics_dansk_2023.pdf

Lindberg C, Brinchmann BS (2023). Nurses and global health responsibility: In light of the COVID-19 pandemic and the war in Ukraine. *International Nursing Review, Opinion piece of international interest*, 70, 141–144. https://doi.org/10.1111/inr.12844

Brinchmann BS (2022). Sykepleierens globale ansvar – hva nå? Dagens Medisin, mars 2022 (in Norwegian): https://www.dagensmedisin.no/debatt-og-kronikk/sykepleieres-globale-ansvar-hva-na/204621

Brinchmann BS, Lindberg C (2023). Sykepleieprat: Sykepleieren og global helse on Apple Podcasts (in Norwegian)

Brinchmann, BS (red.) (2024). Etikk i sykepleien. Oslo: Gyldendal akademisk, 6. utg. (in Norwegian)

Nord University, Faculty of Nursing and Health Sciences, case number 3

Institution: Nord University

Administrative unit: Faculty of Nursing and Health Sciences (FSH)

Title of case study: Working hours and working time organisation (staffing) for nursing staff

Period when the underpinning research was undertaken: 2014–2022.

Period when staff involved in the underpinning research were employed by the submitting institution: Kari Ingstad: 2013–present, Marianne Hedlund: 2017–2021, Bodil Brenne: 2018–present, May Norum: 2014–2016, Aud Moe: 2014–2016, Betty Ann Solvoll: 2019–2021.

Period when the impact occurred: 2015–2022

1. Summary of the impact (indicative; maximum 100 words)

Since 2015, there has been an increase in the proportion of full-time nursing staff in Norway. Various working time arrangements, such as long shifts, and nurse float pool are becoming more common in both hospitals and the municipal health service.

There has been a change in the legislation that makes it easier for local parties (unions and employers) to agree on shifts of up to 12.5 hours without having to apply to the central trade unions.

2. Underpinning research (indicative; maximum 500 words)

Although Norway is considered one of the most gender-equal countries in the world, it is characterised by a gender-divided labour market. Although many women participate in working life, most work part-time—nursing staff, in particular, work part time. A significant proportion of women work part-time involuntarily or are socialised into part-time positions because that is what they are offered at the onset of their careers. This research contributes to ascertaining how various working time practices emerge and evolve. Additionally, it illustrates how different methods of organising working time for nursing staff can have consequences for employees, patients, and employers. Research in this field has been ongoing for several years, with various projects building upon one other. The following provides a chronological description of the different projects that have contributed to their impact.

A. The first project (2013) was a qualitative study of 'float pool nursing staff' working in two different municipalities. Float pool nurses move around among different units and departments to meet staffing requirements. This study discussed the increase in the number of float pool nursing staff, highlighting more insecure working conditions because of assignments in multiple departments and increase in responsibilities due to dealing with more staff and patients. Nonetheless, despite limited inclusion in the work environment, the staff learnt to adapt.
B. The second project (2014–2015) investigated the experiences of nursing staff working extended shifts. Long shifts have long been a subject of controversy in Norway, and this project explored the firsthand experiences of those who worked these extended hours. Results suggest that long shifts actually reduce stress and improve both work continuity and accountability. However, these positive impacts of long shifts occur primarily when all departmental staff work long shifts. Furthermore, fewer shift changes imply more time spent with patients and better communication.
C. In 2017 and 2018, additional interviews were conducted with several nursing staff members working long shifts. The objective was to explore how the extended work hours impact the work–life balance. The results shows that extended shifts lead to a separation of work and leisure. During the work period, professional tasks assume primacy and social

life is limited. During periods of free time, staff have the flexibility to cultivate their interests and be with their family. The study concludes that for a few healthcare workers, extended shifts can lead to better work–life balance.

D. In 2018 and 2019, two PhD students initiated their projects, building on this research to explore, among other things, how various working time practices impact professional practice. One of them defended their thesis in 2023.

The research was conducted from 2013 to the present. This research area remains highly relevant, with a growing demand for greater knowledge from both politicians and practitioners.

The primary Faculty of Nursing and Health Sciences researcher leading these efforts was Professor Kari Ingstad. The team has otherwise varied over the years. Associate Professor Aud Moe and Lecturer May Norum joined the first part of the project (2013–2016). Professor Marianne Hedlund was part of the team from 2017 to 2021. Associate Professor Betty Ann Solvoll joined the project from 2019 until her retirement in 2021. The two PhD students: Bodil Brenne and Siw Watz, joined the project from 2018 and 2019, respectively, and are still part of the team.

Marianne Hedlund reduced her position from 100% to 20% in 2019. Otherwise, all the team members worked at 100% capacity at the Nord University.

3. References to the research (indicative; maximum of six references)

Anthologies:

Anthology 1:
Ingstad, K. (red) (2016). Turnus som fremmer heltidskultur. (Working time arrangements that promote a full-time culture). Oslo: Gyldendal. ISBN/EAN: 9788205490345 Turnus som fremmer heltidskultur | Gyldendal

The anthology comprises 15 chapters, of which 10 are written by academics from the Nord University. Of these 10 chapters, five are co-written with researchers from other institutions, and five are written exclusively by Nord University academics.

Chapters in anthology 2:
Ingstad, K. & Solvoll, B.A. (2021) Bedre arbeid-familie-balanse med tolvtimersvakter i helsesektoren? (Bedre arbeid-familie-balanse med tolvtimersvakter i helsesektoren?) I: Hedlund, M., Moe, A. & Ingstad, K. (eds) God helse: kunnskap for framtidens kommunehelsetjeneste. (Good health: knowledge for the municipal health service of the future). Universitetsforlaget: s. 168–183. http://dx.doi.org/10.18261/9788215042985-2021-08

Solvoll, B.A. & Ingstad, K. (2021). Helse- og omsorgspersonells erfaringer med travelhet. I M. Hedlund, K. Ingstad & A. Moe (Red.), God helse: Kunnskap for framtidens kommunehelsetjeneste. (Good health: knowledge for the municipal health service of the future). (s. 184-204). Universitetsforlaget. https://doi.org/10.18261/9788215042985-2021-09

Articles:

Ingstad, K. & Hedlund, M. (2017). Part-time or full-time employment: Choices and constraints, *Nordic Journal of Working Life Studies*, Volum 7, s. 73–89.
https://doi.org/10.18291/njwls.v7i4.102358

Ingstad, K., & Amble, N. (2015). En ny ro med langturnus: Less job stress with 12-hour shifts, *Nordic Journal of Nursing Research*, *35*(3), 152–157. https://doi.org/10.1177/0107408315584705

Peer-reviewed report:
Ingstad, K. (2014). *Innovasjon i turnus. Vikarpool – ikke optimalt, men bedre enn en 18 prosents stilling.* (Innovation in staffing rotation. Temporary pool—not ideal, but better than an 18% position). HiNT-rapport 98. http://hdl.handle.net/11250/194693

4. Details of the impact (indicative; maximum 750 words)

During the 2000s, it was common to organise work within the healthcare services in Norway with a six-week schedule, regular shifts lasting 7–8 hours, and work every third weekend. This is a schedule that does not add up to full-time, and numerous employees worked part-time. Our research has contributed to the fact that currently there are far more different rotas used in the healthcare sector, which has also led to more people working full-time positions. Just since 2018, the traditional scheduling system has declined by 20%—from 55 to 35%. There has been a particularly significant growth in the number of establishments where employees work long shifts, either during the weekends or throughout the week.

Our research has contributed to disseminating knowledge about different ways to organise work in the healthcare sector and how various solutions function in practice. The research has been disseminated via scientific articles; a scientific anthology and scientific report; professional articles; opinion pieces; and several lectures for employee representatives, politicians, hospital managers, and municipal leaders (approximately 10–20 lectures each year since 2013). Specifically, leaders, union representatives, and labour unions negotiating work schedule organisation have benefited from this research. Additionally, policymakers responsible for determining laws and regulations for work schedule organisation have found significant value in this research. Additionally, the then prime minister of Norway referred to our research in a news article in 2016.

Particularly, the research related to long shifts has had an impact. Long shifts have been controversial in Norway, and few nursing staff work long shifts. Our research shows that well-organised long shifts can produce a more efficient work experience for employees, an increased number of full-time positions, and improved service quality for patients. Our study has contributed to the fact that many more people are now working long shifts, which has also led to more people working in full-time positions.

Academics at the Nord University collaborated with their peers at other institutions in Norway to conducted this research during the period 2013–2022. Much of the research was published in Norwegian because the working-life contexts are different across countries and it was crucial to disseminate this research to the Norwegian and Nordic health sector.

5. Sources to corroborate the impact (indicative; maximum of 10 references)

National bulletin:

a. **White paper:** Meld. St. 15 (2017–2018) (regjeringen.no)
b. **Helsedirektoratet (health directorate):** Kompetanseløft 2020 - Årsrapport 2019.pdf (helsedirektoratet.no)

c. The then prime minister, Erna Solberg, highlights the research in an article in a national newspaper (Dagens næringsliv): https://www.dn.no/meninger/debatt/2016/05/06/2149/Med-egne-ord/strre-valgfrihet-mer-trivsel?_l

Social partners:

a. **Trade unions**
rapport_-samak-heltid-180122.pdf (lo.no)
Fagbladet 2016 10
Tilby hele stillinger! (sykepleien.no)

b. Employer organisation
Bemanningsutfordringene i helse- og omsorgssektoren – utfordringsbildet og løsningsdimensjoner (ks.no)
Rapport KS Organisering, kompetanse, heltidskultur i kommunale helse- og omsorgstjenester. En kunnskapsoppsummering (agendakaupang.no)
Heltidsforskeren - KS

National TV and radio:

1. **TV2 2023:** Norske kommuner bruker milliarder på vikarer i helsetjenestene på grunn av stor mangel på sykepleiere. (tv2.no)
2. **NRK 2020:** Arbeidsrettsadvokat mener Sykehuset Østfold sparker nedover i stedet for å kreve oppover – NRK Østfold – Lokale nyheter, TV og radio
3. **NRK 2019:** Kommunen lyste kun ut deltidsstillinger: – Det er en skam – NRK Nordland
4. NRK 2018: Derfor jobber så mange kvinner ufrivillig deltid – NRK Nordland
5. NRK 2018: Advarer mot farlige 12-timersvakter i sykepleien – NRK Nordland

Faculty of Medicine and Health Sciences [Impact case 1]

Institution: NTNU
Administrative unit: Faculty of Medicine and Health Sciences
Title of case study: Nucleic acid extraction – Covid diagnostics for a nation
Period when the underpinning research was undertaken: 2012-2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2012-2022
Period when the impact occurred: 2020-

1. Summary of the impact

2. When NTNU developed a corona test in a few weeks in the spring of 2020, there were many years of basic research behind it. Professor Magnar Bjørås at IKOM was initiating and leading the project for establishing and implementing a diagnostic test for COVID19 involving a cross disciplinary collaboration at NTNU, producing millions of tests for distribution to hospitals in Norway and internationally during the pandemic. This test was the most used extraction test for PCR based corona diagnostics in Norway, backing up for the urgent lack of delivery from international companies during the pandemic.

3. Underpinning research

4. There are two main reasons why the knowledge from Bjørås years-long research career in genome dynamics turned into a successful innovation in record time.

The first reason is the broad technology bases established through continuous funding mainly from the Research Council of Norway, Norwegian Cancer Society and Health Authorities of Norway on projects investigating fundamental mechanisms of DNA repair and genome integrity in viruses, prokaryotes and eukaryotes. Bjørås was Head of research section at Dep of Medicial Microbiology at Oslo University Hospital for 10 years (2005 – 2014), working with the diagnostic sections for virology and bacteriology on method development. The expertise and technology bases in the Bjørås group on nucleic acid extraction and detection, and implementation on advanced liquid handling systems combined with his experience with microbial and viral diagnostics was essential for this innovation. Bjørås has 245 peer-review articles, many of them in high impact journals (e.g., PNAS, EMBO, Nature, Nat Comm, NSMB, NAR, Mol Cell, Cell Rep Med).

The second reason is the proximity to other competent research environments at NTNU and the proximity to St Olavs University Hospital in Trondheim. The collaboration with Dr Sulalit Bandyopadhyay at Dep of chemical engineering was important for development and production of the magnetic nanoparticles used in the corona test. It was also critical that the IKOM and the entire university pulled out all the stops when it was most urgent and gave the researchers full support and funds to develop the test.

This impact case is based on projects studying genome integrity and DNA repair over the last 20 years establishing a broad technology portfolio for extraction, detection, and downstream analysis of nucleic acids from viruses, bacteria, mammalian cells and body fluids. Years of continuous funding of fundamental research of the Bjørås group has created a strong and robust multidisciplinary research environment with a technology bases enabling NTNU to establish in-house production and implementation of the corona test in a few weeks backing up for the lack of delivery in Norway. These are important assets for readjustments and urgent innovation during a crisis (e.g., COVID19 pandemic) and for preparedness. It is not possible attributing this impact case to a few scientific articles in the Bjørås group but rather his long-term efforts building up

competence and technology with strong potential for innovation in gene-technology and diagnostics. His 240 peer-reviewed scientific articles published in medium and high impact journals has provided extensive expertise in nucleic acid extraction (e.g., column technology, magnetic nanoparticles) and downstream analysis (e.g., PCR based methods; genome wide sequencing of DNA mutations, epigenetic DNA methylation and histone/chromatin modifications; mass spectrometry (MS) based detection of aberrant DNA bases and RNA base modifications) from viruses (e.g., HIV, corona virus, cytomegalovirus), organs (e.g., brain, liver, heart, lungs, aorta) and body fluids (e.g., blood, spinal fluid) using nucleic acid extraction. The referenced manuscripts from Bjørås below exemplify technology and competence of importance for the NTNU corona test innovation; informatics tools, DNA and RNA based extraction technologies, next generation sequencing for genome wide profiling of mutations and epigenetic modifications, and MS based quantification of aberrant base modifications in DNA and RNA in viruses, prokaryotes and eukaryotes.

3. References to the research

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2. Miaomiao Li, Xu Zhao1,2, Wei Wang3, Hailing Shi, Qingfei Pan6, Zhike Lu, Sonia Peña Perez, Rajikala Suganthan, Chuan He, **Magnar Bjørås#**, Arne Klungland#. Ythdf2-mediated m6A mRNA clearance modulates neural development in mice. **Genome Biology**. 2018 May 31;19 (1):69 # **Corresponding authors**

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5. Sejersted Y, Hildrestrand GA, Kunke D, Rolseth V, Krokeide SZ, Neurauter CG, Suganthan R, Atneosen-Åsegg M, Fleming AM, Saugstad OD, Burrows CJ, Luna L, **Bjørås M**. Endonuclease VIII-like 3 (Neil3) DNA glycosylase promotes neurogenesis induced by hypoxia-ischemia. **Proc Natl Acad Sci U S A**. 2011 Nov 15;108(46):18802-7.

6. Aukrust P, Luna L, Ueland T, Johansen RF, Müller F, Frøland SS, Seeberg EC, **Bjørås M**. Impaired base excision repair and accumulation of oxidative base lesions in CD4+ T cells of HIV-infected patients. **Blood.** 2005 Jun 15;105(12):4730-5.

4. Details of the impact

The NTNU corona test had an enormous impact on the test capacity, monitoring and controlling infection spread in the Norwegian society during the pandemic.

In the spring of 2020, Norwegian hospitals had to limit the testing of covid-19 because they did not have enough access to corona tests and the test reagents needed to diagnose corona virus had become an international shortage. In order to keep control of the infection, it was important to carry out widespread testing in the population. Bjørås and his team took on the challenge of developing a test method that did not depend on the limiting reagents. In collaboration with another research environment at NTNU, they developed a sensitive and rapid test in a very short time. Production of the test was quickly scaled up, and this test was one of Norway's most important cards for controlling the virus. The test was also exported to several other countries, including Denmark, India, Brasil and Nepal.

The NTNU corona test shows how basic research environments, which are academically far apart, can together create new opportunities and solve a particularly difficult challenge in a short time. This impact case clearly demonstrates how strong and robust basic research teams have a unique potential for innovation which is of particular importance for preparedness.

5. Sources to corroborate the impact

The NTNU test was the most used extraction method for PCR testing of corona virus in Norway during COVID19 pandemic. Norwegian hospitals saved hundreds of millions in corona testing reagents during pandemic. By example Oslo University Hospital saved 190 million NOK by using the NTNU test in costs for reagents as compared to commercial provider. In addition, the unlimited access to test reagents increased capacity of virus testing, strengthening the control of virus spread in Norway saving the society for large costs.

The NTNU corona test has been awarded several prestigious prizes in Norway, including Winner of Research Council of Norway Innovation Award (), Gold medal of The Norwegian Society of Graduate Technical and Scientific Professionals.
https://www.forskningsradet.no/nyheter/2021/ntnu-koronatest-mottar-forskningsradets-innovasjonspris/
https://www.tekna.no/magasinet/faar-teknas-gullmedalje-for-covid-19-test/

In February 2021, this technology was commercialized establishing a spin-off company, Lybe Scientific.
https://www.ntnutto.no/prosjekter-items/lybe-scientific/
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Faculty of Medicine and Health Sciences [Impact case 2]

Institution: NTNU
Administrative unit: Faculty of Medicine and Health Science
Title of case study: High-dose, twice-daily thoracic radiotherapy prolongs survival in limited stage small cell lung cancer
Period when the underpinning research was undertaken: 2014-2020
Period when staff involved in the underpinning research were employed by the submitting institution: 2007-
Period when the impact occurred: 2020-

1. Summary of the impact (indicative maximum 100 words)

SCLC is the most aggressive lung cancer and causes 4% of cancer deaths. Treatment for limited stage SCLC is concurrent chemo- and radiotherapy. Twice-daily (BID) thoracic radiotherapy (TRT) is recommended, but poorly implemented due to concerns about toxicity. We were the first to show that BID TRT is more effective than hypofractionated TRT and does not cause more toxicity. Subsequent implementation of BID TRT in Norway led to improved survival. We then showed that high-dose BID TRT almost doubles survival time and 40% more patients are cured. This is the first positive randomized trial in this setting for >25 years.

2. Underpinning research (indicative maximum 500 words)

Concurrent chemo- and radiotherapy has been standard treatment for limited stage (LS) SCLC since the early 1990's. A trial published in 1999 showed that BID TRT of 45 Gy in 30 fractions was superior to QD TRT of 45 Gy in 25 fractions. However, the BID schedule caused more toxicity and logistical challenges, and although BID TRT has been recommended in international guidelines, population-based studies show that only a minority actually receive such TRT.

Once-daily (QD) hypofractionated TRT was still standard schedule in Norway and other countries (especially UK and Canada). Survival for LS SCLC was much lower in Norway in the 1990's than in international trials (median overall survival 14.5 months, 5-year survival 10%). We performed the first randomized trial comparing hypofractionated QD with BID TRT (HAST-trial, enrolled patients from 2005-11, published in 2015). Numerically, BID TRT prolonged median overall survival (25.1 vs. 18.8 months) and did not cause more toxicity. These data supported the assumed superiority of BID TRT and we implemented the BID schedule as the new standard in Norway in 2012 when the first results were presented.

Using data from the Norwegian Cancer Registry, we evaluated the impact of implementing BID TRT on a population level (published in 2021). We found that the proportion who received BID TRT increased from 1.8% to >90% during the study period, and a clinically relevant improvement in median survival time similar to in our trial (26.2 vs. 19.6 months) and a doubling in 5-year survival (33% vs. 16%). The implementation rate of BID TRT (>90%) was the highest ever seen in a population based study (typically 15-35%).

Still, there was a need for better treatment. It had been hypothesized that higher TRT doses might improve local control and thus survival. However, large phase III trials have failed to show a survival benefit of high-dose QD TRT. We performed a randomized phase II trial comparing high-dose BID TRT of 60 Gy in 40 fractions with the 45 Gy in 30 fractions (patients enrolled 2014-18, first results presented 2020, first publication 2021). Median overall survival in the high-dose group was almost twice as long as in the control arm (43.6 vs. 22.6 months)

and 5-year survival increased with 40% (40.4% vs. 28.4%). Notably, the higher dose did not cause more toxicity. This is the first positive randomized trial in this setting for more than 25 years.

We have implemented 60 Gy as our standard schedule and will evaluate the impact using data from the Norwegian Cancer Registry (similar to our evaluation of the 45 Gy schedule). We were also the first to report patient-reported outcomes in this setting. These data show that severe radiotherapy esophagitis, considered to be the most dose-limiting toxicity, is transient and that almost all patients recover within a few weeks after completing TRT. Thus, the clinical impact is less and more transient than previously believed.

Population based studies show that older patients and those with comorbidity are less likely to receive standard chemoradiotherapy. Thus, we investigated whether outcomes differ among patients with severe comorbidity or old age compared with younger and more fit, and conclude that also these patients should receive standard chemoradiotherapy. This is important since a majority of LS SCLC patients are >70 years and have a history of heavy tobacco smoking which causes significant comorbidity.

- Names of the key researchers and what positions they held at the administrative unit at the time of the research (where researchers joined or left the administrative unit during this time, these dates must also be stated).
- Any relevant key contextual information about this area of research.

3. References to the research (indicative maximum of six references)

Grønberg, B. H. et al. Randomized phase II trial comparing twice daily hyperfractionated with once daily hypofractionated thoracic radiotherapy in limited disease small cell lung cancer. Acta oncologica (Stockholm, Sweden) 55, 591–597 (2016)

Halvorsen, T. O. et al. Comorbidity and outcomes of concurrent chemo- and radiotherapy in limited disease small cell lung cancer. Acta oncologica (Stockholm, Sweden) 1–9 (2016) doi:10.1080/0284186x.2016.1201216.

Graabak, G., Grønberg, B. H., Sandvei, M. S., Nilssen, Y. & Halvorsen, T. O. Thoracic Radiotherapy in Limited-Stage Small-Cell Lung Cancer – a Population-Based Study of Patterns of Care in Norway from 2000 until 2018. JTO Clin Res Reports 100270 (2021) doi:10.1016/j.jtocrr.2021.100270

Grønberg, B. H. et al. High-dose versus standard-dose twice-daily thoracic radiotherapy for patients with limited stage small-cell lung cancer: an open-label, randomised, phase 2 trial. Lancet Oncol 22, 321–331 (2021)

Killingberg, K. T. et al. Patient-reported health-related quality of life from a randomized phase II trial comparing standard-dose with high-dose twice daily thoracic radiotherapy in limited stage small-cell lung cancer. Lung Cancer 166, 49–57 (2022).

Killingberg, K. T., Grønberg, B. H., Slaaen, M., Kirkevold, Ø. & Halvorsen, T. O. Treatment outcomes of older participants in a randomized trial comparing two schedules of twice-daily thoracic radiotherapy in limited stage small-cell lung cancer. J Thorac Oncol (2023) doi:10.1016/j.jtho.2023.01.012.

4. Details of the impact (indicative maximum 750 words)

Even if guidelines have recommended BID TRT since the publication of the results of the Intergroup 0096 trial in 1999, a minority of patients actually receive such TRT. Most patients

receive QD schedules that have never been compared with the recommended schedules, and it appears that clinical practice to a large extent is opinion driven rather than evidence based.

This was also the case for the former Norwegian standard, hypofractionated QD schedule. According to calculations of biological effective dose, it should actually be slightly more effective than the BID 45 Gy schedule, and older colleagues were convinced that it was better tolerated, illustrating the need to perform comparisons through randomized controlled trials.

However, we know that patients eligible for clinical trials on average have less comorbidity, are younger and more fit than the average patient. Consequently, it is of essential to evalute the effect of new interventions on a population level. Supported by our subgroup analyses of patients with comorbidity, we have documented an implementation level that by far exceeds any other international population based study. More importantly, the implementation of BID TRT led to a survival improvement which mirrors the data from our trial.

Our trial demonstrating that BID TRT of 60 Gy prolongs survival represent the largest improvement in this setting for more than 25 years. Most notably, the higher dose did not cause more toxicity, and subgroup analyses show that also older patients tolerate this treatment, supported by patient reported health related quality of life data.

Since the presentation of the primary results of this trial in 2020, the 60 Gy schedule has been standard in Norway, and implementation has been easy. The exact implementation rate and impact on survival will be evaluated in 2025 using the same methods as when we evaluated implementation of the 45 Gy schedule. The Norwegian Cancer Registry has excellent data to identify LS SCLC patients and full overview over all radiotherapy administered to each individual patient.

Results have been presented at the largest cancer conferences in the world (oral presentations at ASCO and ESMO, invited speaker at WCLCs and ESMO) and published in the highest ranking oncology journal (Lancet Oncology, IF 51 in 2023). They have been cited in review articles and recommended by key opinion leaders, and we know from personal communication that it is standard in Scandinavian hospitals and implemented also internationally.

All trials have been designed, organized, and performed by our study group. The group leader is also the chairman of the Norwegian Lung Cancer Study Group which developed and updates Norwegian guidelines for diagnosis and treatment lung cancer and thus, he has been essential in the implementation of our research results. The trials have been conducted in collaboration with colleagues in Norway and abroad through a network that he has established for this purpose.

Lung cancer is one of the areas in oncology in which most progress has been seen the last decades, but unfortunately, not much improvement has been seen for SCLC and the prognosis for these patients have been unchanged. Thus, the research activity addresses large unmet needs, and has resulted in a most welcome treatment improvement for a largely neglected subgroup of patients with cancer.

5. Sources to corroborate the impact (indicative maximum of ten references)

The most important is the already mentioned article reporting the improvement in survival in Norway due to the implementation of BID TRT:

Graabak, G., Grønberg, B. H., Sandvei, M. S., Nilssen, Y. & Halvorsen, T. O. Thoracic Radiotherapy in Limited-Stage Small-Cell Lung Cancer – a Population-Based Study of Patterns of Care in Norway from 2000 until 2018. JTO Clin Res Reports 100270 (2021) doi:10.1016/j.jtocrr.2021.100270

The article reporting the results of the high-dose BID TRT is currently cited 80 times. The final survival analyses will be published Q1 2024, and since these numbers are even better (median was not reached in the primary analysis), we expect even more citations.

Some examples of citations of our results:

https://dailynews.ascopubs.org/do/podcast-asco23-novel-therapies-lung-cancer?cid=DM13647&bid=273135954

https://register.gotowebinar.com/register/6062998916380287066

Bogart JA, Waqar SN, Mix MD. Radiation and Systemic Therapy for Limited-Stage Small-Cell Lung Cancer. J Clin Oncol. 2022 Feb 20;40(6):661-670. doi: 10.1200/JCO.21.01639. Epub 2022 Jan 5. PMID: 34985935; PMCID: PMC10476774.

Dumoulin DW, Bironzo P, Passiglia F, Scagliotti GV, Aerts JGJV; ERN-LUNG Core Network Mesothelioma. Rare thoracic cancers: a comprehensive overview of diagnosis and management of small cell lung cancer, malignant pleural mesothelioma and thymic epithelial tumours. Eur Respir Rev. 2023 Feb 7;32(167):220174. doi: 10.1183/16000617.0174-2022. PMID: 36754434; PMCID: PMC9910338.

Faculty of Medicine and Health Sciences [Impact case 3]

Institution: NTNU
Administrative unit: Faculty of Medicine and Health Science
Title of case study: SelfBack
Period when the underpinning research was undertaken: January 2016 – March 2021
Period when staff involved in the underpinning research were employed by the submitting institution: 2016-2021
Period when the impact occurred: December 2020 and onwards (ongoing)

1. Summary of the impact

SELFBACK is an artificial intelligence (AI)-based decision support system that provide evidence-based and individually tailored self-management recommendations for people with low back pain. The recommendations for self-management are delivered via a smartphone app.

The SELFBACK system was in 2021 licenced to a Danish company – SelfBack Aps – with the purpose of commercialising the SELFBACK system. The company was founded in 2020 and has since 2021 had commercial activities in several European and overseas countries. The SelfBack app is currently available in nine languages (Norwegian, Danish, Swedish, English, German, Dutch, French, Spanish and Arabic). Approval for implementing the app in clinical practice in the National Health Service (NHS) in England has been obtained from the National Institute for Health and Care Excellence (NICE), i.e., general practitioners can prescribe the SelfBack app to patients with low back pain. Similar approvals are under way in several European countries.

2. Underpinning research

The SELFBACK project, carried out between January 2016 and March 2021, was funded by the European Union Horizon 2020 Research & Innovation Action programme (approximate budget EUR 5 mill.). The project was an interdisciplinary effort, bringing together seven partners from Norway, Denmark, Scotland and the Netherlands, with expertise in medicine, computer science, app development, psychology, exercise physiology, and innovation management.

The project succeeded in developing an AI-based decision support system - SELFBACK - that can be used by the patient him/herself to facilitate, improve and reinforce self-management of low back pain. Specifically, SELFBACK was designed to assist the patient in deciding and reinforcing the appropriate and evidence-based actions to manage own low back pain after consulting a health care professional in primary care. The evidence-based self-management recommendations are conveyed to the patient via the SELFBACK app and updated on a weekly basis. All self-management recommendations are individually tailored based on the patient's goal-setting, symptom state, symptom progression, and a range of patient characteristics including information from a physical activity-detecting wristband. The individual tailoring of the self-management recommendations is achieved by using case-based reasoning (i.e., a branch of knowledge-driven AI). The core of case-based reasoning is to reuse knowledge of previous successful patient cases along with data about the current case, which enables the system to provide patient-centred and tailored recommendations based on current needs and past interventions that proved effective.

The development of the evidence-based content as well as the design, architecture, functions, implementation, and evaluation of the SELFBACK system was informed and guided by applying an intervention mapping approach (*references 1-3, section 3*). The implementation of the SELFBACK

system was carried out in several iterative steps guided by the intervention mapping process, involvement of clinicians, and extensive and iterative user testing (*references 3 and 4, section 3*). The fully functional prototype of the SELFBACK system (technology readiness level 4/5) was tested in a randomised clinical trial in a primary care setting in Norway and Denmark. Patients who received the SELFBACK intervention as an adjunct to usual care had less low back pain-related disability at 3 months compared with patients who received usual care alone. This difference was sustained at 6 and 9 months (*references 5 and 11, section 3*). To explore whether the SELFBACK intervention is more or less effective for certain subgroups, and to generate new hypotheses, we performed a range of secondary analyses (*references 6-9, section 3*). Overall, the results from the secondary analyses indicate that the effect of the SELFBACK intervention is not modified by demographics (age, gender, education), low back pain duration, low back pain intensity, multimorbidity, co-occurring musculoskeletal pain, or mental symptoms (depression, stress).

The SELFBACK system was expanded to target patients with neck and/or low back pain in a secondary care setting. Specifically, the expansion involved the educational content and videos/ explanations of exercises. The expanded version of the SELFBACK system was tested in a randomised clinical trial in Norway. The results indicated that the SELFBACK app, as adjunct to usual care, was not more effective in improving musculoskeletal health than usual care alone or web- based non-tailored self-management support in patients with neck and/or low back pain in a secondary care setting (*reference 10 in section 3 below*). The work on expanding the SELFBACK system and the conduct of the randomised clinical trial was funded via the Horizon 2020 Research & Innovation Action project Back-UP, carried out between January 2018 and April 2021 (approximate budget EUR 6 mill.).

Process evaluations were carried in parallel to the randomised clinical trials and several publications are under way. These results will inform further development of the SELFBACK system to increase its effectiveness.

The SELFBACK project was led by Paul Jarle Mork (coordinator/project leader) and Kerstin Bach (project manager). Likewise, Mork and Bach were the lead research partners at NTNU in the Back-UP project. Mork held a position as professor at ISM at the time of the research and is currently holding the same position. At the time of the research, Bach was an associated professor at Department of Computer Science (IDI), NTNU. Bach has been affiliated with the musculoskeletal research group at ISM since 2016. She was promoted to professor in 2021.

Several researchers, PhD candidates, and post-docs at ISM were involved in the project. In total, 18 unique authors affiliated with NTNU have contributed to the publications coming from the SELFBACK project (12 of these having a position at ISM and/or being affiliated with the musculoskeletal research group at ISM during the time of the research; author names indicated in bold in section 3).

The nature of the research underpinning the development and implementation of SELFBACK was interdisciplinary, requiring collaboration between researchers in many different fields; most notable between health sciences/medicine and computer science. As a direct consequence of the impact and quality of this research, the musculoskeletal research group at ISM were in 2022 awarded an Onsager fellowship for further investments into this research area. The fellowship includes funding of a full-time position for 7 years (associate professor), running costs (NOK 200 000,- per year), and a PhD position. The high-ranked Onsager fellowships are awarded to a few research areas at NTNU with large potential.

3. References to the research

Authors affiliated with the musculoskeletal research group at ISM (i.e., the administrative unit) are indicated in bold.

1. **Mork PJ, Bach K**; SELFBACK Consortium. A decision support system to enhance self-management of low back pain: Protocol for the SELFBACK Project. *Journal of Medical Internet Research, Research Protocols*. 2018;7(7):e167.
   Type: Journal paper (doi: 10.2196/resprot.9379)
2. Nicholl BI, Sandal LF, Stochkendahl MJ, McCallum M, Suresh N, **Vasseljen O**, Hartvigsen J, **Mork PJ**, Kjaer P, Søgaard K, Mair FS. Digital support interventions for the self-management of low back pain: A systematic review. *Journal of Medical Internet Research*. 2017;19(5):e179.
   Type: Journal paper (doi: 10.2196/jmir.7290)
3. Svendsen MJ, Sandal LF, Kjær P, Nicholl BI, Cooper K, Mair F, Hartvigsen J, Stochkendahl MJ, Søgaard K, **Mork PJ**, Rasmussen C. Using intervention mapping to develop a decision support system-based smartphone app (SELFBACK) to support self-management of nonspecific low back pain: development and usability study. *Journal of Medical Internet Research*. 2022;24(1):e26555.
   Type: Journal paper (doi: 10.2196/26555)
4. **Bach K**, Szczepanski T, Aamodt A, Gundersen OE, **Mork PJ**. (2016). Case representation and similarity assessment in the SELFBACK decision support system. In: Goel, A., Díaz-Agudo, M., Roth-Berghofer, T. (eds) Case-Based Reasoning Research and Development. ICCBR 2016. *Lecture Notes in Computer Science*, vol. 9969. Springer, Cham.
   Type: Full conference paper (doi.org/10.1007/978-3-319-47096-2_3)
5. Sandal LF, **Bach K, Øverås CK**, Svendsen MJ, Dalager T, Stejnicher Drongstrup Jensen J, **Kongsvold A, Nordstoga AL, Bardal EM, Ashikhmin I**, Wood K, Rasmussen CDN, Stochkendahl MJ, Nicholl BI, Wiratunga N, Cooper K, Hartvigsen J, Kjær P, Sjøgaard G, **Nilsen TIL**, Mair FS, Søgaard K, **Mork PJ**. Effectiveness of app-delivered, tailored self-management support for adults with lower back pain-related disability: A SELFBACK randomized clinical trial. *JAMA Internal Medicine*. 2021;181(10):1288-1296.
   Type: Journal paper (doi: 10.1001/jamainternmed.2021.4097)
6. **Øverås CK, Nilsen TIL**, Nicholl BI, Rughani G, Wood K, Søgaard K, Mair FS, Hartvigsen J. Multimorbidity and co-occurring musculoskeletal pain do not modify the effect of the SELFBACK app on low back pain-related disability. *BMC Medicine*. 2022;20(1):53.
   Type: Journal paper (doi: 10.1186/s12916-022-02237-z)
7. Rughani G, **Nilsen TIL**, Wood K, Mair FS, Hartvigsen J, **Mork PJ**, Nicholl BI. The selfBACK artificial intelligence-based smartphone app can improve low back pain outcome even in patients with high levels of depression or stress. *European Journal of Pain*. 2023;27(5):568-579.
   Type: Journal paper (doi: 10.1002/ejp.2080)
8. **Nordstoga AL, Aasdahl L**, Sandal LF, Dalager T, **Kongsvold A, Mork PJ, Nilsen TIL**. The role of pain duration and pain intensity on the effectiveness of app- delivered self-management for low back pain (SELFBACK): Secondary analysis of a randomized controlled trial. *Journal of Medical Internet Research - Mhealth Uhealth*. 2023;11:e40422.
   Type: Journal paper (doi:10.2196/40422)
9. **Bardal EM**, Sandal LF, **Nilsen TIL**, Nicholl BI, **Mork PJ**, Søgaard K. Do age, gender, and education modify the effectiveness of app-delivered and tailored self-management support among adults with low back pain? Secondary analysis of the SELFBACK randomised controlled trial. *PLOS Digital Health*. 2023;2(9):e0000302.
   Type: Journal paper (doi: 10.1371/journal.pdig.0000302)
10. **Marcuzzi A, Nordstoga AL, Bach K, Aasdahl L, Nilsen TIL, Bardal EM**, Boldermo NØ, Falkener Bertheussen G, Marchand GH, **Gismervik S, Mork PJ**. Effect of an artificial intelligence-based

self-management app on musculoskeletal health in patients with neck and/or low back pain referred to specialist care: A randomized clinical trial. *JAMA Network Open*. 2023;6(6):e2320400.
Type: Journal paper (doi: 10.1001/jamanetworkopen.2023.20400)

11. Video of the core SELFBACK concepts (English and Norwegian)

4. Details of the impact

All parts of the original SELFBACK system were developed in the SELFBACK project and the intellectual property (IP) belongs to members of the SELFBACK consortium. In addition to developing all parts of the system, the consortium tested its clinical effectiveness in a randomised clinical trial in primary care in Denmark and Norway. To indicate the contribution of the musculoskeletal research group at ISM to the research in the SELFBACK project, about 39% of the total budget in the project was allocated to NTNU and the remaining distributed to the other six partners in the project. Moreover, the key innovators of SELFBACK are NTNU and SelfBack Aps (*source 1, section 5*).

A second randomised clinical trial targeting patients with neck and/or low back pain in a secondary care setting was carried out in Norway. The research underpinning the expansion to neck pain and the conduct of the randomised clinical trial was funded via the Back-UP project, where the musculoskeletal research group at ISM were partner. The additional IP developed (i.e., exercise videos/explanations and educational content) belongs to members of the musculoskeletal research group at ISM.

Via the NTNU Technology Transfer Office (TTO), the SELFBACK system was licenced to SelfBack Aps, a Danish company that has commercialised the SELFBACK system (*source 2, section 5*). The SelfBack Aps company was founded in December 2021 and the licence agreement between NTNU TTO and the company was signed in August 2021. Via the license agreement, SelfBack Aps has the rights to commercialize SelfBack worldwide.

The SELFBACK system was registered as a Medical Device Class 1 under the Medical Device Directive (MDD) in the European Database on Medical Devices (EUDAMED) in May 2021.

In January 2022, SelfBack Aps received a grant from the Danish Innovation Fonden (DKK 1 mill.) to support the company in bringing SelfBack to the market. After winning an innovation grant in England, an agreement was signed with NHS ICS Stoke-on-Trent for testing the implementation of the SelfBack app in primary care in England during 2022. Following the early value assessment by National Institute for Health and Clinical Excellence (*source 8, section 5*), this collaboration has been extended. In parallel to the activity in England, SelfBack Aps signed a contract with the first Danish municipality (Høje Taastrup Kommune) to offer SelfBack to their citizens. Currently, SelfBack can be offered to citizens in all Danish municipalities via 'KL og KOMBITs videncenter' (*source 3, section 5)*. In June 2022, SelfBack was nominated to two international prizes. First, SelfBack was one of the four finalists for EU's Innovation Radar Prize for the best HealthTech innovation in 2021 (*source 4, section 5)*. Second, SelfBack was nominated for the final round in TechArenan in Sweden (*source 5, section 5)*. In August 2022, SelfBack Aps signed a contract with King Saud University to develop and test an Arabic version of SelfBack. In September the same year, representatives from SelfBack Aps were selected to join the governmental working group for "Apps on prescription". The mandate of this group is to detail possible solutions for how apps on prescription can be implemented in the Danish healthcare system.

In January 2023, SelfBack Aps signed an agreement with Danish Chiropractors to offer SelfBack to patients referred via the insurance company "Pension Denmark" (*source 6, section 5)*. A major

achievement was made in August when SelfBack Aps was selected to join Ramsay Santé Accelerator Program (*source 7, section 5)*. Another major achievement was made in October 2023, when SelfBack Aps was recommended by the National Institute for Health and Care Excellence (NICE) for clinical use by the National Health Service (NHS) in England (*sources 8 and 9, section 5)*. During 2023, two subsidiaries of SelfBack Aps were established: one in France (SelfBack SAS) and one in England (SelfBack Ltd.). In December the same year, the company signed a contract with German Optimedics to test SelfBack in Germany together with Bbraun Betriebskrankenkasse during spring 2024.

In the beginning of 2024, SelfBack Aps made another major achievement when receiving approval for Level 1 registration in the Belgium mHealth register (*source 10, section 5)*. In the same month, agreements were signed with Sales Agents in England and France. Moreover, an agreement for a paid pilot was signed with a Danish Health Insurance company (Dansk Sundhedssikring).

As of January 2024, the SelfBack app is available in Norwegian, Danish, Swedish, English, German, Dutch, French Spanish and Arabic.

5. Sources to corroborate the impact

1. Key innovators of SELFBACK (note: SelfBack Aps is a subsidiary of Kleberg & Kuttemann Innovation Aps)
2. SelfBack Aps company website.
3. SelfBack offered as a tool to citizens in Danish municipalities via 'KL og KOMBITs videncenter'
4. SelfBack nominated as one of four finalists for the 2021 Innovation Radar Prize in Health Tech
5. SelfBack nominated as finalists for the 2022 Swedish TechArenan prize
6. SelfBack offered to patients referred from "Pension Denmark" to Danish Chiropractors
7. SelfBack Aps selected to join Ramsay Santé Accelerator Program in August 2023 (this is a lengthy pdf file; please see page 202 for details about the selection of SelfBack Aps)
8. National Institute for Health and Clinical Excellence. Digital technologies for managing non-specific low back pain: early value assessment. 13 October 2023.
9. Torjesen I. GPs can refer patients with low back pain to apps, says NICE. *BMJ*. 202313;383:2380. doi: 10.1136/bmj.p2380.
10. The SelfBack app approved at level 1 of the mHealth Belgium validation pyramid.

Faculty of Medicine and Health Sciences [Impact case 4]

Institution: NTNU
Administrative unit: Faculty of Medicine and Health Science
Title of case study: Obstructive lung diseases
Period when the underpinning research was undertaken: 2000 - 2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2000 -2023
Period when the impact occurred: 2012-2022

1. Summary of the impact (indicative maximum 100 words)

Lung function measurement as spirometry is pivotal for diagnosis and follow-up of obstructive lung diseases like chronic obstructive pulmonary disease (COPD) and asthma. Different reference values for spirometry and cut-offs for normality have been used for different regions, age groups and levels of health care. We have shown international reference values to fit Norwegians and questioned cut-offs for normality and severity grading for COPD. International clinical guidelines are very conservative. In line with international recommendations for interpretation of spirometry, we have contributed to development and implementation of modern Norwegian guidelines and thereby simplified and improved interpretation of spirometry and diagnosis of obstructive lung diseases.

2. Underpinning research (indicative maximum 500 words)

The Lung Study in the Trøndelag Health Study (HUNT) has collected extensive data on respiratory symptoms, use of medication, health status, lung function and bone mineral density for about 20% of participants in HUNT2 (1995-97), HUNT3 (2006-08) and HUNT4 (2017-19). We included random samples of participants (5 % in HUNT2, 10% in HUNT3 and 4) and those reporting respiratory symptoms, diagnoses or use of medication for obstruktive lung disease. In total, 11,000, 12,000 and 15,000 persons were included in the Lung Study in the three surveys, respectively.

Spirometry is pivotal for diagnoses of obstructive lung disease. There is lack of skills and knowledge in performing the spirometry manoeuvre and interpretation of the results, partly due to unnecessary complicated and contradictory recommendations. For individual interpretation results should be compared to reference values developed based on representative samples of the population. More than 300 different prediction equations have been developed and different sets have been used in countries, regions, and health care levels. One set was developed including data from the European Coal and Steel Community in 1993. Even if many studies showed how these data underestimated normal lung function and only were appropriate for age 20-70 years, most hospitals and general practices in Norway have used these. In 2001 national reference values were developed based on the Hordaland Study (Gulsvik et al) and HUNT-data (Langhammer et al), but these were restricted to age 20-80 years. In 2012 an international set of reference values for 5 ethnic groups including age span 3-95 years were developed (GLI-2012). The PI of HUNT Lung Study was asked to lead a committee in the Norwegian Association for Pulmonologists to suggest which reference values to be used in Norway. We combined spirometry data from the Hordaland Study, the Tromsø Study and HUNT, and analysed the fitness of GLI-2012 or alternative new Norwegian reference values for age 12-90 years. Even if there was not a perfect fit, the GLI-2012 was found to be acceptable with improved prediction independent of age and giving the possibility to use only one set for all age groups avoiding gaps between previous age limited reference sets. GLI-2012 has been endorsed for many countries but is not recommended in Sweden and Finland.

Cut-offs for obstruction have been heavily discussed the last 20 years. Even if lung physiologists and some clinicians advocate classification based on distribution and variance in healthy populations, international clinical guidelines (GOLD, NICE, GINA) still recommend less than 80% of predicted as pathological levels for the parameters FEV1 and FVC and < 0.70 for FEV1/FVC. The latter ratio after bronchodilator medications therefore is used as diagnostic cut-off for COPD. This cut-off for COPD overestimate and underestimate the prevalence among elderly and middle-aged, respectively. By use of the lower 5th percentile as cut-offs the prevalence of COPD in Norway is reduced from 350.000 to 170-180.000.

The GOLD guidelines have changed their recommended classification of COPD severity as guidelines for treatment including pharmaceutical treatment many times during the last 10 years. Partly due to a HUNT-study, GOLD made a major revision of the classification in 2017, but GOLD continues suggesting new classifications, the latest in 2023. The evidence behind these is low, and we have therefore in Norway agreed not to adhere to these. Repeated changes in the recommendations contribute to confusion among clinicians all over the world and unfortunately, use of inappropriate diagnostic criteria and classifications still are used in studies on medical treatment.

Researchers at ISM, NTNU.

Arnulf Langhammer, MD, PhD, Professor, HUNT Research Centre, ISM, NTNU. Head of HUNT databank, member of HUNT management group and PI of the HUNT Lung study and HUNT Osteoporosis Study 1994-2024.
Part time general practitioner, 2-3 days a week 1983-2024.

Linda Leivseth, MS, PhD, ISM, NTNU, 2009-2013

Ben Brumpton, MS, PhD, Associate Professor, ISM and Jebsen Center of Genetic Epidemiology 2011 -2024

Laxmi Bhatta, MS, PhD, Postdoc, ISM and Jebsen Center of Genetic Epidemiology, 2016-2024

Sigrid Anna Aalberg Vikjord, MD, PhD, Researcher HUNT Research Centre, ISM, NTNU and soon specialist in Respiratory Medicine St. Olavs Hospital, Trondheim

Tom Ivar Lund-Nilsen, MS, PhD, Professor, ISM, NTNU, 2011-2024

Turid Lingaas Holmen, MD, PhD, Professor, Pediatrician, HUNT Research Centre, ISM, NTNU 1994-2017

Collaboration:

The Tromsø Study: Professor emeritus Hasse Melbye

The Norwegian Institute of Public Health: Previous director of the department of chronic diseases

The Hordaland Study: Professor emeritus Amund Gulsvik, Professor Ane Johannesen

The Norwegian Health Directorate: Senior researcher Svein Høegh-Henricksen

National primary care respiratory group (LIP): Anders Østrem, MD, Kristian Jong Høines, MD

International groups: Nordic Epilung Study, CADSET, ERS-GLI ++

Context: The PI has been general practitioner for more than 40 years and have aimed to simplify and improve knowledge in the field of obstructive lung diseases in primary as well as secondary health care. GPs are responsible for diagnoses and treatment of most patients with mild to moderate asthma and COPD. Pulmonologists, therefore, to a limited extent, have shown interest in diagnostic criteria and reference values. In general practice we should avoid both under- and overdiagnosis of patients. We should identify persons having diseases in need of examinations and follow-up. In this perspective the HUNT Lung Study has contributed.

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3. References to the research (indicative maximum of six references)

Langhammer A, Jones R Usefulness of the COPD assessment test (CAT) in primary care. Prim Care Respir J. 2013 Mar;22(1):8-9. doi: 10.4104/pcrj.2013.00022.

Leivseth L, Brumpton BM, Nilsen TI, Mai XM, Johnsen R, Langhammer A. GOLD classifications and mortality in chronic obstr. pulmonary disease: the HUNT Study, Norway. Thorax. 2013;68(10):914-21.

Langhammer A, Johannessen A, Holmen TL, Melbye H, Stanojevic S, Lund MB, Melson MN, Bakke P, Quanjer P. GLI-2012 reference equations for spirometry in a Northern Europe population Eur Respir J April 2016

Quanjer PH, Ruppel GL, Langhammer A, Krishna A, Mertens F, Johannessen A, et al. Bronchodilator Response in FVC Is Larger and More Relevant Than in FEV1 in Severe Airflow Obstruction. Chest. 2017;151(5):1088-98.

Bhatta L, Leivseth L, Mai XM, Henriksen AH, Carslake D, Chen Y, Martinez-Camblor P, Langhammer A, Brumpton BM, Spirometric Classifications of COPD Severity as Predictive Markers for Clinical Outcomes: The HUNT Study. Am J Respir Crit Care Med. 2020.

Langhammer A. Contributions to simplifying the global interpretation of spirometry: high quality spirometry data from Asia. Eur Respir J. 2022;60(6).

4. Details of the impact (indicative maximum 750 words)

The HUNT Study is a population-based study focusing on common chronic diseases. PIs of the sub-studies naturally are involved in regional, national, and international collaborations. The influence on handling of relevant diseases is greater than specifically based on evidence from own research. AL was first author of the national guidelines for handling of asthma in children and adolescents published in 1991, have for decades been member of the national (LIP) and International Primary Care Respiratory Group (IPCRG), has been member of the group publishing the national guidelines for COPD Diagnosis and Treatment by the Norwegian Health Directorate (2012 and 2022), is a member of the Norwegian Association for Pulmonologists and has been involved in publishing of report on chronic diseases by The National Public Health Institute.

Partly based on own research as well as national and international collaboration the PI has influenced national guidelines. These are not revolutionary but are the first national guidelines to accept and implement strategies for interpretation of spirometry recommended by international lung physiologists and clinicians (the American Thoracic Society and the European Respiratory Society https://doi.org/10.1183/13993003.01499-2021). For COPD, diagnostic criteria and severity grades have been changed, as well as cut-offs for normal values for forced lung volume (FVC), forced lung volume in the first second (FEV1) and definitions of bronchodilator response test. Other countries still adhere to the international guidelines for COPD (GOLD) and asthma (GINA), the argument for this is that most of previous research are based on older cut-offs and criteria.

Based on own research, we recommend the use of GLI-2012 as reference values for spirometry in Norway. Sweden and Finland still use local and age-specific reference values due to studies indicating underestimation of FVC in these countries. Further we recommend use of lower limit of normal (LLN) as the 5th percentile of healthy persons as cut-offs for FEV1/FVC for the diagnosis of COPD and abnormal FEV1 and FVC in contrast to FEV1/FVC < 0,70 (age independent) and 80% of predicted (not taking the variance by age into account). Additionally, we have decided to recommend updated and improved definition of positive bronchodilator response; the change in

FEV1 should be related to predicted FEV1 instead of pretest FEV1 and corresponding cut of 10% independent of age.

We have succeeded including these changes in
A)the National Guidelines for COPD 2022 by the Norwegian Health Directorate,
B)the report from the National Public Health 2022,
C) relevant chapters in the new Norwegian Textbook for General Practice (published 2023),
D) relevant chapters in the Norwegian Electronic Handbook for Medical doctors, this is used by 90% of GPs in Norway and is translated into Swedish and Danish. Subscription needed.
E) published in the Journal of the Norwegian Medical Association, consensus of reference values and cut-offs between Association of Pulmonologists, Association of Pediatricians and General Practitioners
F) Published in Utposten, a journal for general practice, consensus between General practitioners, The Norwegian Organization for Quality Improvement of Laboratory Examinations (Noklus) and Suppliers of spirometers in Norway (Welch Allyn and Diagnostica) regarding spirometry performance, included indices, cut-offs and presentation of results on screen and printout. This really helps to reduce confusion among MDs and staff in interpretation of spirometry.

G) Further these recommendations have been included in lectures at yearly courses for doctors specializing in respiratory medicine last 5 years as well as lectures at courses for general practitioners with about 200 participants every year.

H)National guidelines for GPs on asthma and COPD developed by LIP

H) published two pages guidelines for GPs for asthma, COPD, spirometry, and allergy.

Norway is, so far, the only country having agreed on common recommendations for cut-offs and reference values for obstructive lung disease. Involvement in the above-mentioned topics has given the opportunity to influence development and distribution of updated guidelines through most available channels.

4. Sources to corroborate the impact (indicative maximum of ten references)

A. Norwegian Health Directorate:
https://www.helsedirektoratet.no/retningslinjer/kols

B. National Institute of Public Health: COPD in Norway
https://www.fhi.no/he/folkehelserapporten/ikke-smittsomme/kols/?term=

C. Textbook in General Practice, chapter on asthma, COPD, allergy, and spirometry
https://www.gyldendal.no/faglitteratur/medisin/laereboeker/allmennmedisin/p-10034039-no/

D. The Norwegian Electronic Handbook for Medical doctors. This is used by 90% of Norwegian general practitioners and is also translated into Swedish and Danish. Subscription is needed.
https://legehandboka.no/

E. Langhammer A, Crowley S, Humerfelt S, Melbye H, Nag T, Svanes O. Time for new reference values and cut-offs for spirometry Tidsskr Nor Laegeforen. 2018;138(13).

F. Langhammer A, Hoines, KJ, Sjaastad, GE, Tollanes MC, Ostrem A. Collaboration to improve

skills and interpretation of spirometry in Primary Health Care. Utposten 2021,7,
https://www.utposten.no/journal/2021/7/m66/Dugnad_for_%C3%B8kt_kvalitet_p%C3%A5_bruk_og_tolkning_av_spirometri_i_prim%C3%A6rhelsetjenesten

G. National primary care respiratory group (Lunger i Prakis**)**
Courses : https://www.lungeripraksis.no/

H. Clinical guidelines :

COPD for general practice, updated 2022
https://www.lungeripraksis.no/_files/ugd/2072ae_9eced8b60eaf4a828b565ba994ffa1da.pdf

Asthma for general practice, updated 2022

https://www.lungeripraksis.no/_files/ugd/2072ae_1e0dbfa85c1c4c3fa968f1ebdc8c479a.pdf

I. Short 2 pages guidelines
Spirometry
https://www.lungeripraksis.no/_files/ugd/2072ae_1000093909264c748d0ddc5553c57994.pdf

COPD
https://www.lungeripraksis.no/_files/ugd/2072ae_a92d87d51f1946c5a8e6c40c97d0adc8.pdf

Asthma **:**
https://www.lungeripraksis.no/_files/ugd/2072ae_38805b7fe47046e593805c0324b29827.pdf

Faculty of Medicine and Health Sciences [Impact case 5]

Institution: Norwegian University of Science and Technology (NTNU**)**
Administrative unit: Department of Circulation and Medical Imaging (ISB)
Title of case study: Adapt – Patient Adaptive Imaging in Echocardiography
Period when the underpinning research was undertaken: 2017-2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2017-2022
Period when the impact occurred: 2022

1. Summary of the impact (indicative maximum 100 words)

Cardiovascular disease is the leading cause of morbidity and mortality in the industrialized world, accounting for more than one-third of total deaths, and with increasing prevalence. Ultrasound imaging (echocardiography) is the leading and most cost-effective diagnostic and clinical assessment tool for heart disease and extensively used globally for diagnostic workup and patient management. However, image quality varies considerably from patient-to-patient and ultrasound image quality is still a challenge in many patients.

In a collaboration project between NTNU, St. Olavs hospital and GE Vingmed Ultrasound, a new technology, **Adapt**, has been developed capable of adapting the image processing of ultrasound images to the individual anatomy of the patient. Significant improvement in image quality have been demonstrated and the technology is now commercialized globally (launched in 2022) on the GE Vingmed Ultrasound (Norwegian subsidiary of GE HealthCare) echocardiography system Vivid E95. GE Vingmed systems are used to scan more than 300.000 patients per day on a global basis, indicating the potential impact of the innovation.

2. Underpinning research (indicative maximum 500 words)

One of the most important causes of image quality variation in echocardiograms is that different tissue types have a varying speed of sound, a critical parameter for ultrasound image quality. All ultrasound systems on the market today assume that body tissue has the same speed of sound everywhere, representing an average value over several tissue types. Research has shown that this assumption is not correct, and that especially sound speed variations in the human body wall (consisting of the skin, subcutaneous fat, connective tissue, and muscle layers) can cause significant patient dependent image degradation.

This phenomenon, which is called *aberration*, may be compared to smearing a thick layer of Vaseline on a camera lens. This will reduce the focusing capabilities of the camera and yield very poor and blurred images. The challenge is that the camera is not “aware” of the layer of Vaseline, and even though it has a focusing lens it cannot compensate for the effect of the Vaseline. In medical ultrasound, aberration is linked to subcutaneous fat (but also muscle layers, connective tissue, and ribs), and image quality degrades with increased thickness of the fat layer.

Aberration has been well known for decades and still represents a major limitation for image quality despite substantial amount of research trying to solve the reduced image quality based on aberration, often referred to as *aberration correction*.

Adapt has been developed by key researchers at NTNU and GE Vingmed Ultrasound, and GE HealthCare under the aegis of the SFI Center for Innovative Ultrasound Solutions (CIUS). The core of the technology is an algorithm that is capable of estimating and compensate for the effect of

aberration. This allows the ultrasound system to adapt its image processing to each individual patient.

In a pilot clinical trial encompassing 22 patients recruited from the Clinic of Cardiology at St. Olavs hospital, Trondheim, image quality was demonstrated to be significantly improved in standard echocardiography using Adapt. Data from the pilot showed that 4 independent cardiologists preferred Adapt in **98%** of the cases. The clinicians also reported that cardiac structures such as the endocardial border, leaflets, chordae, atrium septum appear slimmer, more clearly defined, and less "smeared" using Adapt. Improvements with the potential to improve sensitivity and reproducibility of clinically relevant echocardiographic parameters.

The core of the research was carried out from 2017 – 2023, but this has been an ongoing research question at both GE and NTNU for more than 30 years.

Key researchers:

Svein-Erik Måsøy, Researcher, ISB, NTNU

Tore Bjåstad, Researcher, ISB, NTNU and GE Vingmed Ultrasound AS

Bastien Dénarié, GE Vingmed Ultrasound AS

Andres Sørnes, GE Vingmed Ultrasound AS

Kjell Kristoffersen, GE Vingmed Ultrasound AS

Wayne Rigby, GE HealthCare

Torvald Espeland, ISB, NTNU, St. Olavs hospital

Erik Andreas Rye Berg, ISB, NTNU, St. Olavs hospital

Bjørnar Grenne, ISB, NTNU, St. Olavs hospital

Espen Holte, ISB, NTNU, St. Olavs hospital

3. References to the research (indicative maximum of six references)

Svein-Erik Måsøy, Bastien Dénarié, Anders Sørnes, Espen Holte, Bjørnar Grenne, Torvald Espeland, Erik Andreas Rye Berg, Ole Marius Hoel Rindal, Wayne Rigby, and Tore Bjåstad
Aberration correction in 2D echocardiography
2022

Bastien Dénarié, Kjell Kristoffersen, Wayne Rigby, Svein-Erik Måsøy
cSound ADAPT: Continuous beamforming optimization, adapting to patient anatomy and probe position
2023

cSound Adapt: Commercial launch video from GE Healthcare

Sølvi W. Normannsen
Forskere kan takke gamere for bedre ultralydbilder av hjertet
2022.

Kari Williamson
In sharper focus, CIUS blog.
2022

4. Details of the impact (indicative maximum 750 words)

GE HealthCare is a global market leader (40% of the market) of cardiovascular ultrasound and estimates that more than 250 million echocardiographic exams are carried out world-wide every year. With Adapt now released on the Vivid E95 system from GE with their global reach, this technology will enable improved image quality for millions of patients in the years to come. More than 300.000 patients are scanned every day with ultrasound systems from GE Vingmed Ultrasound in Horten, Norway.

"Adapt sharpens images, increasing contrast resolution and improving diagnostic confidence," says Echo technician Lill Merete Skretteberg Lindøe at Oslo University Hospital. "The imaging enhancements reduce non-diagnostic images and improve productivity and workload by reducing scan time and improving ergonomics." (Statement provided in collaboration with GE HealthCare).

A key to solving the challenge of aberration correction was a close collaboration between technical and clinical researchers at NTNU, St. Olavs hospital and GE Healthcare. Only in such a multidisciplinary team could this issue be resolved.

Modern ultrasound systems have moved ultrasound image reconstruction from dedicated hardware chips to software using GPUs, allowing for storage of so-called raw-unprocessed ultrasound data. This data can be used to recreate images by testing variations of algorithms over and over again on realistic, clinical data. This was simply not possible before, and therefore represented a game-changer in the possibilities for making Adapt work. The Vivid E95 is the first clinical echocardiographic system with such capabilities and having access to such a system through the collaboration with GE and their team was essential for this work. The research team collected and studied more than 40 000 ultrasound images of the heart. This was to understand the fundamental mechanisms needed to make the algorithm work – regardless of the great variations in patients' body walls.

Adapt was commercial launched at the European Society of Cardiology conference in Barcelona, August 2022.

NTNU has a commercial license agreement with GE HealthCare about the use of Adapt.

5. Sources to corroborate the impact (indicative maximum of ten references)

Dagfinn Sætre, CEO, GE Vingmed Ultrasound AS
(Dagfinn.Saetre@gehealthcare.com)

Kjell Kristoffersen, Chief Engineer, GE Vingmed Ultrasound AS
(kjell.kristoffersen@gehealthcare.com)

Impact case guidelines

Each case study should include sufficiently clear and detailed information to enable the evaluation committee to make judgements based on the information it contains, without making inferences, gathering additional material, following up references or relying on members' prior knowledge. References to other sources of information will be used for verification purposes only, not as a means for the evaluation committee to gather further information to inform judgements.

In this evaluation, impact is defined as an effect on, change or benefit to the economy, society, culture, public policy or services, health, the environment or quality of life, beyond academia.

Timeframes

- The impact must have occurred between 2012 and 2022
- Some of the underpinning research should have been published in 2012 or later
- The administrative units are encouraged to prioritise recent cases

Page limit

Each completed case study template will be limited to **five pages** in length. Within the annotated template below, indicative guidance is provided about the expected maximum length limit of each section, but institutions will have flexibility to exceed these so long as the case study as a whole remains no longer than **five pages** (font Calibri, font size 11). Please write the text into the framed template under the sections 1–5 below. The guiding text that stands there now, can be deleted.

Maximum number of cases permitted per administrative unit

For up to 10 researchers: one case; for 10 to 30 researchers: two cases; for 30-50 researchers: three cases; for 50-100 researchers: four cases, and up to five cases for units exceeding 100 researchers.

Naming and numbering of cases

Please use the standardised short name for the administrative unit, and the case number for the unit (1,2,3, etc) in the headline of the case. Each case should be stored as a separate PDF-document with the file name: [Name of the institution and name of the administrative unit] [case number]

Publication of cases

RCN plans to publish all impact cases in a separate evaluation report. By submitting the case the head of the administrative units consents to the publication of the case. Please indicate below if a case may not be made public for reasons of confidentiality.

If relevant, describe any reason to keep this case confidential:

Please write the text here

Norwegian University of Science and Technology, Department of Psychology
Case 1

Institution: NTNU
Administrative unit: Department of Psychology
Title of case study: The Pollution Pods
Period when the underpinning research was undertaken: 2012-2018
Period when staff involved in the underpinning research were employed by the submitting institution: 2012-2018
Period when the impact occurred: 2016-2022

1. Summary of the impact

Out of a mutual interest in their work, NTNU professor in environmental psychology Christian Klöckner and visual artist Sam Jury (UK) developed a series of projects studying the impact of climate change inspired artwork on their audience. A major outcome of this collaboration was the commissioned artwork Pollution Pods by Michael Pinsky in the research project CLIMART, which since its first show in Trondheim in 2017 attracted tens of thousands of visitors all over the world, including world leaders and activists like Greta Thunberg. The Pollution Pods – based on psychological research at NTNU have become one of the most important artworks that defined the last decade (according to Artnet, see below).

2. Underpinning research

A number of research activities have been undertaken in the research program that eventually led to the Pollution Pods: As outlined below, the initial idea originated from the stimulating conversations visual artist Sam Jury (University of Heartfordshire, UK) and Prof. Christian Klöckner (NTNU) had from 2012. Jury contacted Klöckner and wanted some psychological input for her artistic practice, but soon this conversation evolved also into a research program. Initially, Klöckner and Jury started a pilot project which received funding from the Norwegian Research Council. In this project, Klöckner and Jury created artwork together with students of NTNU which was then exhibited at the Kosmorama Film Festival in Trondheim. Klöckner surveyed visitors of the festival and found some initial indication for that climate change inspired artwork might be reaching people in a different, more emotionally engaging way than more scientific climate change communication, especially people not being environmentalists. Following up on these findings, Klöckner and Jury applied for a four year research project (CLIMART), funded by RCN, which was a collaboration between the coordinators Klöckner at NTNU and Jury, as well as the climate art organization Cape Farewell (lead by artist David Buckland), journalist Courtney St. John from the US, high ranking environmental psychologists Paul Stern (National Research Council, US) and Janet Swim (Penn State University, US), climate scientist Peter Huybers (Havard University, US), environmental scientist Edgar Hertwich (NTNU), Martina Zienert and Joachim Borner (KMGNE, Germany). In this ground-breaking project, two PhDs were educated (Laura Sommer & Liselotte Roosen).

A number of research activities in the were undertaken in the project, which culminated in the creation of the Pollution Pods and the subsequent evaluation of their impacts during the first two shows in Trondheim and London. (a) A substantial literature review was conducted and published in Roosen et al. (2018). The review concluded with that art typically uses novel metaphors, analogies or narratives, which climate communication generally lacks. In addition, art can provide people with visualizations of the problem and give them a personal experience with the subject-matter, which is especially important regarding climate change as many people still see it as an abstract issue that poses no direct threat. Art may also help to establish a group identity and to give people a sense of being supported in their efforts to help combat climate change. (b) Research was conducted at an exhibition in Brighton where an experiment was conducted comparing the effects of art-based communication to a documentary (see Roosen & Klöckner,

2020). Results show that art as well as documentaries have the potential to be an effective medium to convey climate change to audiences. Art may speak to the audience on a different (i.e. emotional rather than cognitive) level than documentaries, and therefore could be a helpful way to introduce the subject to an audience that may not yet be overly familiar with climate change. To further encourage behaviour change, a solution should be presented that is novel, relatively easy to implement and impactful. (c) We surveyed the audience of 37 artworks presented during the ArtCOP21 at the COP21 in Paris in 2015 (see Klöckner & Sommer, 2021; Sommer & Klöckner, 2021). We found support for a model based on findings from art perception and environmental psychology, which indicate that the response of the viewer to the artwork is (1) first an emotional reaction, which can be positive and/or negative. The emotional activation leads to (2) evaluation of the perceived quality of the artwork. This forms the first impression of the artwork the viewer gets, which then triggers (3) reflections on the artwork that are finally related to support for climate policies. Furthermore, we found that artworks that caused a feeling of awe were perceived as most successful by the audience in triggering the intention to act against climate change.
Based on these findings, we commissioned an artwork in a large international competition curated by members of the CLIMART team (both scientific and artists). The commissioned artist was Michael Pinsky, who frequently visited the CLIMART team over the course of a year during which the idea for the Pollution Pods was born. The Pollution Pods are five interconnected geodesic domes which contain carefully mixed recipes emulating the relative presence of ozone, particulate matter, nitrogen dioxide, sulphur dioxide and carbon monoxide which pollute London, New Delhi, San Paolo and Beijing. Starting from a coastal location in Norway, the visitor passes through increasingly polluted cells, from dry and cold locations to hot and humid (see https://www.youtube.com/watch?v=I7nMME-3aC8&t=1s for a video of the pods). In Sommer et al. (2019) the results of the evaluation are summarized, showing that intentions to act against climate change were generally strong and slightly increased after visiting the art installation. Individual changes in intentions were positively associated with self-reported emotions of sadness, helplessness, and anger and self-reported awareness of the environmental consequences of people's action, their willingness to take responsibility for their consequences, and belief in the relevance of environmental problems for daily life.
In recent years, a follow-up project was funded by the RCN (Nature in Your Face, www.niyf.no), which explores the potential of such disruptive and unusual communication tools further. A book about the concept of disruptive communication has been edited as a result of that project (Klöckner & Löfström, 2022).

The research in this case originated from a collaboration between NTNU **Prof. Christian A. Klöckner** and the UK-based visual artist Samantha Jury. She contacted Klöckner in 2012 because she wanted input from an environmental psychologist for her creative practice. They immediately found a common understanding and mutual interest in their work and started planning out a collaboration. As a result, first a pilot project was funded by the Norwegian Research Council (NRC) which explored possibilities to communicate climate change via artwork, where Jury and Klöckner coordinated an Experts in Teamwork village at NTNU creating climate change inspired artwork with students (mostly video art), exhibiting it at the local film festival. After a successful pilot, the full-size research project CLIMART (www.climart.info) was funded by NRC. In this project, two PhDs (**Laura Sommer** and **Liselotte Roosen**) were hired for three years each during the lifetime of the CLIMART project (2015-2018). Both of them graduated in the evaluation period. Within the CLIMART project, an embedded artist was commissioned (UK-based Michael Pinsky – https://www.michaelpinsky.com/), who created the artwork Pollution Pods in close collaboration with the project researchers. The project further resulted in a follow-up project (Nature In Your Face – http://www.niyf.no), which is currently ongoing, which is lead by NTNU researcher **Erica Löfström** and **Klöckner**.

3. References to the research

Klöckner, C. A. & Löfström, E. (2022). Disruptive Environmental Communication. Series: Psychology and our planet. Cham: Springer Nature. https://doi.org/10.1007/978-3-031-17165-9

Sommer, L. K., & Klöckner, C. A. (2021). Does activist art have the capacity to raise awareness in audiences?—A study on climate change art at the ArtCOP21 event in Paris. Psychology of Aesthetics, Creativity, and the Arts, 15(1), 60-75. https://doi.org/10.1037/aca0000247

Klöckner, C. A., & Sommer, L. K. (2021). Visual art inspired by climate change—An analysis of audience reactions to 37 artworks presented during 21st UN climate summit in Paris. PloS one, 16(2), e0247331. https://doi.org/10.1371/journal.pone.0247331

Roosen, L. J., & Klöckner, C. A. (2020). Art and documentaries in climate communication: Experiencing the reality of climate change and leading the way to change. Art | Research International: A Transdisciplinary Journal, 5 (2), 524-552. https://doi.org/10.18432/ari29520

Sommer, L. K., Swim, J. K., Keller. A., & Klöckner, C. A. (2019). "Pollution Pods": The merging of art and psychology to engage the public in climate change. Global Environmental Change, 59, 101992. https://doi.org/10.1016/j.gloenvcha.2019.101992

Roosen, L. J., Klöckner, C. A., & Swim, J. K. (2018). Visual art as a way to communicate climate change: a psychological perspective on climate change–related art. World Art, 8 (1), 85-110. https://doi.org/10.1080/21500894.2017.1375002

4. Details of the impact

The Pollution Pods were (and still are) an extraordinary success. The artist, NTNU and CapeFarewell (the climate change art organization) found a viable financial model for touring the Pollution Pods and since their first show in Trondheim in Summer 2017, the Pollution Pods have been in London (2018), Geneva (2018), Bremerhaven (2018), Vancouver (2019 – TED conference), Manchester (2019), Dorset (Portland, 2019), Melbourne (2019), New York (2019 – United Nations), Dorset (Brownsea Island, 2019), Madrid (2019, COP25), Glasgow (2021, COP26), and Dubai (2023, COP28). The tour – which was put on hold by the COVID pandemic – is now starting up again. In its 13 shows, the installation has attracted several ten-thousands of visitors and is thus probably the most visited environmental psychology inspired artwork. Among the visitors were world leaders at the United Nations and COPs, but also well-known activists like Greta Thunberg.

The Pollution Pods created a tremendous media echo in print- and online media, as well as radio and TV. A google search returns 4.330 sources naming "Pollution Pods" and Michael Pinsky, some of which are included below. The scientific papers above have been cited 245 times (3.1.2025, scholar-google).

In December 2019, the Pollution Pods were included in the list of the 100 artworks that defined the decade (ranked on place 71). In 2018, the researcher association awarded the Pollution Pods the Brain Power Award (shared second place) 2017.

5. Sources to corroborate the impact (indicative maximum of ten references)

Pollution Pods tour site: https://www.capefarewell.com/pollution-pods/

Pollution Pods on CNN: https://edition.cnn.com/style/article/michael-pinsky-pollution-pods/index.html

Greta Thunberg in the Pollution Pods: https://news.artnet.com/art-world-archives/michael-pinsky-pollution-pods-un-greta-thunberg-1658827

Pollution Pods on the United Nations Environmental Program website: https://www.unep.org/news-and-stories/story/turning-air-pollution-art

Pollution Pods on the World Health Organization website: https://www.who.int/news/item/24-09-2019-pollution-pods-connect-the-dots-between-air-pollution-climate-change-and-health-at-un-climate-action-summit

Pollution Pods at the TED2019: https://blog.ted.com/pollution-pods-a-tasting-menu-of-our-planets-air-quality-at-ted2019/

Pollution Pods at Climate Summits:

- COP25: https://theecologist.org/2019/nov/29/pollution-pods-cop25
- COP26: https://www.glasgowwestend.co.uk/the-pollution-pods-cop26-at-gartnavel/
- COP28: https://www.rfa.org/english/news/environment/pollution-pods-12132023032616.html

Hjernekraftprisen: https://www.forskerforbundet.no/om-forskerforbundet/hjernekraftprisen/vinnere/vinnere-av-hjernekraftprisen-2017#:~:text=Vinnere%20av%20Hjernekraftprisen%202017%20Vinneren%20av%20Hjernekraftprisen%202017,deler%20andreplassen%20og%20f%C3%A5r%2020000%20kroner%20hver.

Pollution Pods ranked 71 of the 100 artworks that defined the decade by artnet: https://news.artnet.com/art-world-archives/100-works-that-defined-the-decade-part-2-1738773

NTNU Department of Psychology case 2

Institution: Department of Psychology
Administrative unit: Norwegian University of Science and Technology
Title of case study: H-WORK. MULTILEVEL INTERVENTIONS TO PROMOTE MENTAL HEALTH IN SMEs AND PUBLIC WORKPLACES
Period when the underpinning research was undertaken: 01.01.2020 - 31.09.2023
Period when staff involved in the underpinning research were employed by the submitting institution: 01.01.2020 - 31.09.2023
Period when the impact occurred: 01.01.2020 - 31.09.2023 (and continuing)

1. Summary of the impact

The Horizon 2020 funded H-Work project's main results are the H-WORK Innovation Platform containing the HAT, HIT, and HET toolkits included in the roadmap, the benchmarking tool, the decision support-system and the economic calculator. Several policy briefs based on the results of the project have been published. In addition, the NTNU team got supplementary funding from NFR for dissemination of the results from H-WORK to Norway. Thus, the NTNU team translated the tools into Norwegian (policy briefs and roadmap) and developed an e-learning tool to guide HR/leaders, practitioners, and students who wants to learn more about how to create healthy workplaces.

2. Underpinning research

H-WORK, a Research and Innovation Action (RIA) project funded by the Horizon 2020 (grant agreement: 847386), was coordinated by the University of Bologna (UNIBO) and involved 14 partners across 9 countries from 01.01.2020 to 31.09.2023. NTNU's Department of Psychology led Work Package 3 (“COLLECT: Effect analysis of collected data”) and contributed to other packages. With additional funding from The Research Council of Norway (NFR), the NTNU team created an e-learning tool (“e-H-WORK”) and Norwegian translations of H-WORK tools (project period 01.04.2021.-31.03.2023).

This project addressed the growing concern over mental health issues in the EU, thus imposing a major burden on individuals, society, and economy across the EU countries. The H-WORK project aimed to design, implement, and validate effective multi-level assessment and intervention toolkits, evaluating individual and organisational outcomes of the adopted measures, and providing additional innovative products and services. The objectives included providing practical solutions and policy recommendations for employers, occupational health professionals, and policymakers.

The H-WORK project has developed various tools and resources to promote mental health and wellbeing at workplaces, especially for public organisations and small-to-medium (SME) businesses. These include:

• H-WORK Assessment, Intervention, and Evaluation Tools (HAT, HIT, HET): These toolkits, provide evidence-based knowledge on how to implement and evaluate interventions for different levels of the organisation (such as individual, team, leader, and organisational). They can be used by researchers and organisations to assess and improve mental health outcomes.

• A user-friendly roadmap: This document guides the users through the development and implementation of mental health promotion strategies at workplaces. It offers a stepwise and practical approach that can be helpful for SMEs and workplace health-related staff.

• An innovation platform and exploitation plan: This platform includes a benchmarking tool, a decision support system, and an ROI calculator that can help users evaluate the effectiveness and cost-benefit of the interventions. The platform also contains eleven policy briefs that provide useful suggestions and recommendations for different target groups, such as managers, EU policymakers, HR staff, and social partners.
• Scientific publications: The project has disseminated its results in 12 publications, most in GOLD Open Access. The findings have been presented in several international conferences.
Although the project was successfully approved by the European Commission 11.12.2023 the research team will still continue to monitor and evaluate its outputs and outcomes and seek ways to increase its reach and relevance for the stakeholders.

Supplementary funding, "H-WORK dissemination and learning platform (e-H-WORK):
The e-H-WORK supplementary funding supported the development of a dissemination and learning platform to leverage the H-WORK project's findings. The target group is managers and HR personnel in SMEs as well as the public sector, who plan to promote mental health and well-being in their own company, and who want to carry out this process themselves. The supplementary funding was used to translate the policy briefs and roadmap into Norwegian. It was also used to create an additional e-learning tool in Norwegian and English based on the theories and experience from the H-Work project. All resources, including the e-learning tool in Norwegian and English, will be available on a NTNU website, launching on April 22, 2024, for practitioners and researchers.

Key researchers and what positions they held at the administrative unit at the time of the research

- Siw Tone Innstrand, professor IPS, Work Package leader
- Marit Christensen, professor IPS, Work Package leader
- Per Øystein, professor IPS, researcher
- Karoline Grødal, research assistant IPS, 01.03.2020-31.07.2022.
- Josefina Pelaez Zuberbühler, research assistant IPS, 15.11.2022
- Leoni van der Vaart, post.doc IPS, started 13.03.2023
- Emmanuel Aboagye, Assistant professor, started 03.01.2023

Key contextual information about this area of research.
The focus for this research is small and medium sized enterprises and public organizations as they often are struggling more regarding economic incentives HR resources in order to deal with mental health issues in the workplace. The H-WORK stakeholders are employers, managers, scientific community, health professional, policy makers and general public.
The H-WORK project was conducted during the COVID-19 pandemic and received a three-month extension due to unforeseen challenges. Originally intended to be in-person, many of the mental health interventions had to be adapted to digital formats because physical implementation wasn't feasible at all intervention sites. Additionally, the pandemic placed several organizations, particularly hospitals in Spain and Italy, under extreme stress, intensifying the need for employee mental health support while simultaneously straining resources. This heightened crisis environment likely affected both the participation in and the effectiveness of the interventions, potentially influencing the data collection, response rates, and overall impact of the interventions as noted in point 4.

3. References to the research

The project has published 12 papers with more in progress, following the final data collection in autumn 2023. Below are six published publications where the NTNU team have been involved in:

Nielsen, K., De Angelis, M., **Innstrand, S. T**., & Mazzetti, G. (2023). Quantitative process measures in interventions to improve employees' mental health: A systematic literature review and the IPEF framework. *Work & Stress, 37*(1), 1-26. https://doi.org/10.1080/02678373.2022.2080775

Zuberbühler, J., & Salanova, M (2023). Strengths-based team coaching: A positive psychological intervention to enhance performance and well-being at work. In Theme booklet: Prevention and mental health at work (Ed. Werk, L., Vollborn, O., & Muschalla, B.). *Psychosoziale und Medizinische Rehabilitation*, 36:218-227. DOI: https://doi.org/10.2440/008-0006e

Pelzer, V., Nielsen, K., **Zuberbühler, J.** P., Muschalla, B., Kubik, R., Heber, E., & De Angelis, M. (2024). Managing well-being at work: multi-level interventions to promote productive and health workplaces. In: Thakre, N. and Uday Kumar Reddy, B., (eds.) Stress, Wellness, and Performance Optimization Promoting Sustainable Performance in the Workplace. Apple Academic Press, Inc, CRC Press, pp. 21-52. ISBN 9781774914069

Giusino, D., De Angelis, M., Mazzetti, G., **Christensen, M., Innstrand, S. T.,** Faiulo, I. R., & Chiesa, R. (2022). "We all held our own": Job demands and resources at individual, leader, group, and organizational levels during COVID-19 outbreak in health care. A multi-source qualitative study. *Workplace Health & Safety, 70*(1), 6-16. https://doi.org/10.1177/21650799211038499

Giusino, D., De Angelis, M., Mazzetti, G., Faiulo, I. R., **Innstrand, S. T., Christensen, M.,** & Nielsen, K., (2022). Mentally healthy healthcare: main findings and lessons learned from a needs assessment exercise at multiple workplace levels. In C.A. Bowers, D. C. Beidel, M. R. Marks, K. Horan, & J. Cannon-Bowers (eds.), Mental health and wellness in healthcare workers: Identifying risks, prevention, and treatment (pp. 143-171). IGI Global. ISBN 9781799888130 (open access: https://www.igi-global.com/chapter/mentally-healthy-healthcare/301481)

De Angelis, M., Giusino, D., Nielsen, K., **Aboagye, E., Christensen, M., Innstrand, S.T.,** Mazzetti, G., van den Heuvel, M., Sijbom, R.B.L., Pelzer, V., Chiesa, R., and Pietrantoni, L. (2020). H-WORK Project: Multilevel Interventions to Promote Mental Health in SMEs and Public Workplaces *Int. J. Environ. Res. Public Health*, 17, 8035; doi:10.3390/ijerph17218035

4. Details of the impact

The project's primary societal impact is the direct reduction of mental health issues in SMEs and the indirect benefit to future SMEs through the application of the developed tools.
Relevant innovation activities in this respect include policy briefs for better mental health in SMEs, a website featuring an economic impact calculator and a comprehensive roadmap, mapping various interventions against desired outcomes, and a series of review papers on the state-of-the art in this field. The project aligns with three expected impacts as outlines in the projects DoA*:

1. Improved Mental Health and Reduced Sickness Absence: H-WORK increased the knowledge of and availability of evidence-based interventions, managing work-related stress and psychosocial risks. While not significantly improving positive mental health aspects like job satisfaction, the interventions protected against negative outcomes, such as burnout, especially notable during the pandemic. The NTNU team's contribution to Impact 1 included developing new methods like needs analysis, products such as cognitive mapping exercises, a

roadmap, and an e-learning tool, and illustrating the protective and spillover effects on mental health and wellbeing from the interventions.

2. Positive Impact on Productivity and Economic Results: H-WORK's innovation platform includes an economic calculator, a decision support system, and a benchmarking tool. A policy brief specifically addresses economic benefits for SMEs. NTNU's contributions include increasing knowledge and awareness of mental health promotion using reflective questions in different assessment tools and exploring the interventions' protective and spillover effects.
3. Improved Mental Health Policies in Workplaces: The project influenced policies through a broader evidence base of effective interventions. Dissemination activities involved policymakers, producing policy briefs and recommendations for various stakeholders. NTNU played a vital role in developing these briefs and translating them into Norwegian using the supplementary funding from NFR.

The consortium focused on improving workplace mental health policies, providing scientific evidence, data for policy makers, and eleven policy briefs on various topics, ranging from digital interventions to the role of social partners and the use of AI in promoting well-being.

Facts and Figures:

- 440 mental health interventions, involving 1532 participants and 169 managers.
- 14 validated tools and over 30 psychosocial and economic metrics, translated into 7 EU languages.
- Innovation platform attracted over 2000 visitors and 1500 soft log-ins in five months.
- Over 300 downloads of the roadmap.
- Upcoming launch of a Norwegian website to further disseminate results, expecting to impact Norway's workforce.
- Results presented at international conferences and published in peer-reviewed journals.

The H-WORK project is being considered for inclusion in the European Commission's CORDIS website and as a best practice in response to the European Commission's call on mental health.

*The impact described is partly from the European Commissions "General project review consolidated report"

4. Sources to corroborate the impact

The project website https://h-work.eu/
The Innovation platform: https://h-work.eu/innovation-platform/
Roadmap: https://www.mentalhealth-atwork.eu/#roadmap
Economic calculator: https://www.mentalhealth-atwork.eu/
Policy briefs: https://www.mentalhealth-atwork.eu/#policy-briefs
e-learning tool: https://rise.articulate.com/share/AaLMRZhkoYs4BW79KloudTsQwHlSQNRE#/

Impact case guidelines

Each case study should include sufficiently clear and detailed information to enable the evaluation committee to make judgements based on the information it contains, without making inferences, gathering additional material, following up references or relying on members' prior knowledge. References to other sources of information will be used for verification purposes only, not as a means for the evaluation committee to gather further information to inform judgements.

In this evaluation, impact is defined as an effect on, change or benefit to the economy, society, culture, public policy or services, health, the environment or quality of life, beyond academia.

Timeframes

- The impact must have occurred between 2012 and 2022
- Some of the underpinning research should have been published in 2012 or later
- The administrative units are encouraged to prioritise recent cases

Page limit

Each completed case study template will be limited to **five pages** in length. Within the annotated template below, indicative guidance is provided about the expected maximum length limit of each section, but institutions will have flexibility to exceed these so long as the case study as a whole remains no longer than **five pages** (font Calibri, font size 11). Please write the text into the framed template under the sections 1–5 below. The guiding text that stands there now, can be deleted.

Maximum number of cases permitted per administrative unit

For up to 10 researchers: one case; for 10 to 30 researchers: two cases; for 30-50 researchers: three cases; for 50-100 researchers: four cases, and up to five cases for units exceeding 100 researchers.

Naming and numbering of cases

Please use the standardised short name for the administrative unit, and the case number for the unit (1,2,3, etc) in the headline of the case. Each case should be stored as a separate PDF-document with the file name: [Name of the institution and name of the administrative unit] [case number]

Publication of cases

RCN plans to publish all impact cases in a separate evaluation report. By submitting the case the head of the administrative units consents to the publication of the case. Please indicate below if a case may not be made public for reasons of confidentiality.

If relevant, describe any reason to keep this case confidential:

Please write the text here

NTNU_IPS case 3

Institution: NTNU
Administrative unit: Department of psychology, IPS
Title of case study: Psychological treatment of anxiety and depression
Period when the underpinning research was undertaken: 2012-ongoing
Period when staff involved in the underpinning research were employed by the submitting institution: entire period
Period when the impact occurred: consecutively

1. Summary of the impact (indicative maximum 100 words)

The projects explore effects of new psychological treatments for in RCTs for social anxiety, generalized anxiety disorder, depression, OCD and PTSD. Mental disorders represent one of the largest sources of loss quality adjusted life years and societal cost. At the end of treatment of choice 50% are recovery, and at 2-year follow-up only 25% are recovered. The new treatments increase recovery rates to 70-80%, that are upheld at up to 9 years follow-up. The treatments are taught to clinical psychology students and dissimilated to local and national mental health services. This addresses effectively one of the larger societal challenges.

2. Underpinning research (indicative maximum 500 words)

The studies produced in a series of randomized controlled trials (RCT) have increased the number of recovered patients for a series of anxiety disorders and depression with 20-30% recovery rates and has reduced the relapse rates of between 30-50%. This represents a major leap forward with regards to successfully treating anxiety and depression in 8-12 therapy sessions with substantial lasting effects. The basis for these RCTs is founded on a theory carefully developed over 30 years of research related to integrating findings and understanding from experimental cognitive psychology to clinical psychology undertaken by prof. Adrian Wells at University of Manchester, UK and labelled metacognitive theory. For patients suffering from mental disorders the theory postulates that cognitive functioning and attention is affected and governed by psychological processes and beliefs about cognition. The RCT's represents a large step forward and are groundbreaking within the field of psychological treatment anxiety and depressive disorders. The research group has completed one of the largest collections of RCTs' testing this model known between 2012 and present. And the work is on-going. It represents a new way of understanding anxiety and depression, it is implemented in the education of clinical psychology students, and disseminated to local and national mental health services. The transition from highly controlled RCT design to clinical use in naturalistic outpatient settings is also part of the work the research group is involved in. Preliminary findings indicate that the results from the RCTs' transition well to naturalistic outpatient settings with highly comparable results. It also seems to assure that patients with depression and anxiety return to work, which is very uncertain for recommended treatment for the same disorders.

- Key researchers have been prof. Hans M. Nordahl, prof. Roger Hagen, prof. Stian Solem, prof. Odin Hjemdal all have had PI roles in the different RCTs and related studies. Prof. Nordahl and prof. Hagen have change workplace, and prof. Solem and prof. Hjemdal have fixed senior positions at the same department within the same research group.
- A substantial part of the research has been undertaken in close collaboration with local mental health services.

3. References to the research (indicative maximum of six references)

1) Nordahl, H. M., Vogel, P. A., Morken, G., Stiles, T. C., Sandvik, P., Wells, A. (2016). Paroxine, cognitive therapy or their combination in the treatment of social anxiety disorder with and without avoidant personality disorder: A randomized clinical trial. *Psychotherapy and psychosomatics, 85(6): 346-356.* https://doi.org/10.1159/000447013
2) Nordahl, H. M., Borkovec, T. D., Hagen, R., Kennair, L. E. O., Hjemdal, O., Solem, S., Hansen, B., Haseth, S., & Wells, A. (2018). Metacognitive therapy versus cognitive-behavioural therapy in adults with generalized anxiety disorder. *British Journal of Psychiatry, 4,* 393-400. doi: 101192/bjo.2018.54
3) Solem, S., Kennair, L. E. O., Hagen, R., Havnen A., Nordahl, H. M., Wells, A., & Hjemdal, O. (2019). Metacognitive therapy for depression: A 3-year follow-up study assessing recovery, relapse, work force participation and quality of life. *Frontiers in Psychology,* https://doi.org/10.3389/fpsyg.2019.02908
4) Nordahl, H., Anyan, F., Hjemdal, O. (2022). Metacognition, cognition and social anxiety: A test of temporal and reciprocal relationships. *Journal of Anxiety Disorders, 86, 102516,* https://doi.org/10.1016/j.janxdis.2021.102516
5) Kennair, L. E. O., Solem, S., Hagen, R., Havnen, A., Nysæter, T. E., & Hjemdal, O. (2020). Change in personality traits and facets (NEO-PI-R) following metacognitive therapy or cognitive behavior therapy for generalized anxiety disorder: Results from a randomized controlled trial. *Clinical Psychology & Psychotherapy.* https://doi.org/10.1002/cpp.2541
6) Ryum, T., Svartberg, M., Stiles, T. C. (2021). Homework Assignments, Agenda Setting and the Therapeutic Alliance in Cognitive Therapy with Cluster C Personality Disorders: Synergetic or Antagonistic Ingredients?. *Cognitive Therapy and Research* (2021) https://doi.org/10.1007/s10608-021-10268-8

4. Details of the impact (indicative maximum 750 words)

The research is ongoing and part of a long-term strategy to research the effects and understand the processes of change involved in psychological treatment. It is a large societal challenge, as one in two people will experience a mental health problem during their lifetime. Mental ill health is a leading cause of global disease burden. Between 2010 and 2030, mental illness is projected to cost $ 16.1 trillion worldwide, putting it on par with cardiovascular disease. For example, depression and anxiety disorders account for 40.5 % and 14.6 % of the disability-adjusted life-years that are due to mental illness, which makes them the costliest mental health problems. In high-income countries only one third receive formal mental health care mostly due to limited capacity. Generally, for the treatment of choice for psychological therapy for common mental disorders only 50% recover, and 2-years after treatment only 25% remain recovered. Results are comparable for pharmaceutical treatment only with higher relapse rates if medication is discontinued.
Given the magnitude of mental health problems, limited access to treatment, and the large room for improvement in recovery and relapse rates, the goal of our research is to ameliorate this. The findings from our RCT research can be summarized to recovery rates of between 70-80% and relapse rates reduced to around 10-20% over treatment duration of 8-12 sessions across depression and anxiety. The new treatments are disseminated to students in clinical psychology at our department, which assures that future patients will have increased access to new and highly effective treatments. Ongoing studies are exploring implementation in naturalistic outpatient settings, and preliminary findings indicate similar recovery and relapse rates, and contributing to a higher proportion returning to work at the end of treatment compared to previous studies.
It seems to be one viable option to bring the treatment of mental health disorders in particular depression and anxiety a significant leap forward. The higher recovery rates indicate that more patients become non-symptomatic at end of treatment, and the lower relapse rates this can also collectively contribute to free-up much needed treatment resources within the health care system. Estimations of cost-effectiveness of the treatments are ongoing and preliminary findings indicate that the treatment is highly cost-effective.

5. Sources to corroborate the impact (indicative maximum of ten references)

1) Elin Ulleberg, director of the mental health clinic, St. Olavs Hospital, Nidaros DPS, email: elin.ulleberg@stolav.no
2) Ragne Gjengedal, Unit manager clinic for of research and innovation, Diakonhjemmet hospital, email: Ragne.Gjengedal@diakonsyk.no
3) Sverre Urnes Johnson, professor in clinical psychology, Department of psychology, University of Oslo, email: s.u.johnson@psykologi.uio.no
4) Liv Engvik, Unit manager, Division for mental health, St. Olavs. Hospital, email: liv.sigrun.engvik@stolav.no
5) Gunnar Morken, Professor in Psychiatry, Department of mental health, Faculty of Medicine and Health, NTNU, email: gunnar.morken@ntnu.no
6) Truls Ryum, associate professor, head of outpatient clinic at Department of psychology, NTNU, email: truls.ryum@ntnu.no

Oslo Metropolitan University, Faculty of Health Sciences (OsloMet HV) [1]

Institution: OsloMet
Administrative unit: Faculty of Health Sciences
Title of case study: Viral outbreak readiness
Period when the underpinning research was undertaken: 2020-2023
Period when staff involved in the underpinning research were employed by the submitting institution: 2018-2023
Period when the impact occurred: 2020-2021

1. Summary of the impact (indicative maximum 100 words)

Immediate implementation of whole genome SARS-CoV2 sequencing, viral phylogenetic analysis and contact tracing of health care workers to detect within-hospital SARS-CoV2 outbreaks in real time. Data was used to direct infection control measures when the COVID19 pandemic came to Norway. Publishing first in the field demonstrating the joint strengths of using viral genomics and epidemiological data to detect or refute hospital outbreaks.

2. Underpinning research (indicative maximum 500 words)

Outline of what the underpinning research produced

Development and implementation of a whole genome SARS-CoV2 sequencing approach to trace and prevent intra-hospital outbreaks. The initial output was real-time tracing to inform and direct essential infection prevention and control procedures to avoid nosocomial transmission in Akershus University Hospital serving 10% of the Norwegian population. In addition, one PhD thesis and two scientific papers were outputs of the research effort. The approach taken and know-how published was quickly adopted by public health authorities and other initiatives around the world. Deposition of data from the project guided and updated the global joint effort to trace and act against the spread of the COVID19 pandemic.

When: March 2020-Jan 2023

Who: GenMicroPat research group in collaboration with Akershus University Hospital.
Alexander Hesselberg Løvestad, PhD candidate from Nov 2018 to Jan 2023.
Ole Herman Ambur, Ass. Prof., Research group head, PhD supervisor and project participant, employed from Jan 2016 to date.

Contextual information

When Chinese scientist in January 2020 published the first **SARS-CoV2 genome** from the Wuhan epicenter strain, communities around the world received means to **trace** the spread of vial variants by whole genome SARS-CoV2 sequencing. Such **data was shared** by us and others through open global genome sequence repositories (GISAID/PANGOLIN). Within **six weeks** (May 2020) of detecting the first index case in Norway (March 2020) and during **a National close-down** we produced the first SARS-CoV2 whole genome sequences and were probably the first lab in Norway to do so. Such data has **high resolution** with 8000 data-points, one for each nucleotide of viral genome. In these first genomes we could observe by **phylogenomic analysis** from which national/local outbreaks the first imported cases came from (mainly China, Austria, Sweden and Spain). We learned that the virus mutates quickly and since new mutations tend to accumulate, that we could apply genomics directly to trace outbreaks and **nosocomial transmission**. Combining our **genomic data** with those of **contact tracing of health care workers** provided means to **confirm or refute expected outbreaks** within the hospital. One PhD student in the GenMicroPat group,

Alexander Hesselberg Løvestad, who worked on a completely different virus (a DNA virus, HPV) in his PhD project had the idea, skills and available infrastructure together with his PhD supervisor and collaborators at Ahus, - **a readiness** to undertake the implementation of real-time outbreak tracing in Ahus and demonstrate know-how and insights to the community.

3. References to the research (indicative maximum of six references)

Løvestad, A. H., Jørgensen, S. B., Handal, N., Ambur, O. H., & Aamot, H. V. (2021). Investigation of intra-hospital SARS-CoV-2 transmission using nanopore whole-genome sequencing. Journal of Hospital Infection, 111, 107-116.

Berggreen, Hanne, A. Hesselberg Løvestad, Karin Helmersen, Silje Bakken Jørgensen, and Hege Vangstein Aamot. "Lessons learned: use of WGS in real-time investigation of suspected intrahospital SARS-CoV-2 outbreaks."Journal of Hospital Infection 131 (2023): 81-88.

Løvestad, A. H. (2023). Viral genomics by next-generation sequencing–investigating intra-host genomic events in human papillomavirus and improving intra-hospital outbreak investigations of SARS-CoV-2. (PhD thesis, adjudicated and passed)

4. Details of the impact (indicative maximum 750 words)

An immediate response when the COVID-19 hit the World was necessary to both implement protective measures in hospitals and understand virus genomics and transmission. The outbreak-resolving strengths of combining whole genome SARS-CoV2 sequencing from third generation technology with epidemiological data was a new practice until we published Løvestad et al., 2021. Our demonstration of approach later became a global standard tracing the pandemic in real-time to “Ensure healthy lives and promote well-being for all at all ages” (UN, SDG3).

Berggreen et al 2023 concludes in describing the Løvestad et al., 2021: “*WGS is a valuable tool in hospital outbreak investigations when combined with traditional contact tracing. Inclusion of WGS data improved outbreak demarcation, identified unknown transmission chains, and highlighted weaknesses in existing infection control measures.*”

By studying viral genomics in a hospital, our group represented a local, national and global readiness upon which we swiftly acted. Establishing, implementing and demonstrating proof-of-concept for SARS-CoV-2 whole genome Nanopore sequencing in Norway during the first weeks of the pandemic allowed us to share new knowledge of technical applicability and virus characteristics with our academic and hospital environments and importantly also with the National Institute of Public Health (Norway), who then decided to follow the same sequencing approach in the national surveillance. The medical officer in charge of infection control (MD PhD Silje B. Jørgensen) and close collaborator in the project was equipped with both in-hospital personnel and tools to track outbreaks and implement personal (health care workers) and institutional (hospital) protective measures to prevent nosocomial transmission. Later, upon publishing our results in Journal of Hospital Infection (Løvestad et al., 2021) the insights we gained and shared has received global impact in four fields. 1. Nosocomial infections; 2. Hospital infection control; 3. Applicability of using third generation sequencing technology to study viruses and 4. SARS-COV2 evolution and emergence of variants. Publications citing our study (Løvestad et al., 2021) express these impacts as follows:

*"During the coronavirus disease (COVID-19) pandemic, nanopore sequencing played a critical role in **detecting** the severe acute respiratory syndrome coronavirus-2 virus genome **and containing the pandemic**."* (Watt et al., 2022)

"*Healthcare workers (HCWs) on the frontline have acquired COVID-19 in many different settings, often despite adequate availability and choice of appropriate personal protective equipment (PPE) []. To optimise the **safety of HCWs and patients**, it is critical for hospital infection control teams and, more broadly, healthcare systems to understand the drivers of infections in HCWs, through systematic investigations of the circumstances around these putative transmissions in healthcare settings. Internationally, genomics of SARS-CoV-2 has been a powerful tool for **understanding transmission links and outbreaks** […Løvestad et ., 2021…]*." (Greininger, 2022)

*Nanopore sequencing of SARS-CoV-2 cases in Norway illustrated the **complex nature of suspected hospital outbreaks** and ultimately confirmed 2 suspected outbreaks, revealed a third previously undetected outbreak, and refuted a separate suspected outbreak [Løvestad et al., 2021].* (Greininger, 2021)

*SARS-CoV-2 genomic sequencing can **refute or strengthen transmission hypotheses** from conventional nosocomial epidemiological investigations, and guide implementation of setting-specific control strategies* (Benoit et al, 2023)

*SARS-CoV-2 genome sequencing has elucidated **pathways of infection*** [Løvestad et al., 2021]" (Coope et al, 2022)

*"Whole-genome sequencing (WGS) has proven to be an **efficient tool** to track SARS-CoV-2 nosocomial outbreaks (Løvestad et al., 2021,[]). **Combined** with comprehensive **epidemiological investigations**, WGS of SARS-CoV-2 strains from HCWs and patients has provided a better understanding of transmission patterns.* (Leducq et al., 2022)

*"Whole-genome sequencing (WGS) has been **used widely** to elucidate transmission of SARS-CoV-2 in acute healthcare settings, and to guide infection, prevention, and control (IPC) responses."* (Hare et al., 2023)

*"Viral WGS helps to analyze the spread of pathogens by determining the transmission relationship between the virus and the patient to **reconstruct the transmission network**. At the same time, it can also monitor the emergence of dangerous variants and help to study the adaptation of pathogens in the host []."* (Cheng et al., 2023)

*"Having the **best data** is paramount to understanding an outbreak in order to stop ongoing transmission and prevent future outbreaks. In the past 5 years, the high-resolution view of transmission offered by analyzing pathogen whole-genome sequencing (WGS) is increasingly part of **hospital outbreak investigations**."* (Greininger et al. 2021)

5. Sources to corroborate the impact (indicative maximum of ten references)

Watt, A. E., Sherry, N. L., Andersson, P., Lane, C. R., Johnson, S., Wilmot, M., ... & Howden, B. P. (2022). State-wide genomic epidemiology investigations of COVID-19 in healthcare workers in 2020 Victoria, Australia: Qualitative thematic analysis to provide insights for future pandemic preparedness. The Lancet Regional Health–Western Pacific, 25.

Greninger, A. L., Dien Bard, J., Colgrove, R. C., Graf, E. H., Hanson, K. E., Hayden, M. K., ... & Lee, F. M. (2022). Clinical and infection prevention applications of severe acute respiratory syndrome

coronavirus 2 genotyping: an infectious diseases Society of America/American Society for Microbiology consensus review document. Clinical Infectious Diseases, 74(8), 1496-1502.

Leducq, Valentin, Jeanne Couturier, Benjamin Granger, Sarah Jolivet, Laurence Morand-Joubert, Jérôme Robert, Michel Denis et al. "Investigation of healthcare-associated COVID-19 in a large French hospital group by whole-genome sequencing." Microbiological Research 263 (2022): 127133.

Greninger, A. L., Dien Bard, J., Colgrove, R. C., Graf, E. H., Hanson, K. E., Hayden, M. K., ... & Lee, F. M. (2022). Clinical and infection prevention applications of severe acute respiratory syndrome coronavirus 2 genotyping: an infectious diseases Society of America/American Society for Microbiology consensus review document. Clinical Infectious Diseases, 74(8), 1496-1502.

Wong, R. C. W., Lee, M. K. P., Siu, G. K. H., Lee, L. K., Leung, J. S. L., Leung, E. C. M., ... & Lai, R. W. M. (2021). Healthcare workers acquired COVID-19 disease from patients? An investigation by phylogenomics. Journal of Hospital Infection, 115, 59-63.

Zheng, P., Zhou, C., Ding, Y., Liu, B., Lu, L., Zhu, F., & Duan, S. (2023). Nanopore sequencing technology and its applications. MedComm, 4(4), e316.

Hare, D., Dembicka, K. M., Brennan, C., Campbell, C., Sutton-Fitzpatrick, U., Stapleton, P. J., ... & Dunne, C. P. (2023). Whole-genome sequencing to investigate transmission of SARS-CoV-2 in the acute healthcare setting: a systematic review. Journal of Hospital Infection.

Cheng, L., Lan, L., Ramalingam, M., He, J., Yang, Y., Gao, M., & Shi, Z. (2023). A review of current effective COVID-19 testing methods and quality control. Archives of Microbiology, 205(6), 239.

Coope, R. J., Matic, N., Pandoh, P. K., Corbett, R. D., Smailus, D. E., Pleasance, S., ... & Marra, M. A. (2022). Automated Library Construction and Analysis for High-Throughput Nanopore Sequencing of SARS-CoV-2. The Journal of Applied Laboratory Medicine, 7(5), 1025-1036.

Oslo Metropolitan University, Faculty of Health Sciences (OsloMet HV) [2]

Institution: OsloMet
Administrative unit: Faculty of Health Sciences
Title of case study: Implementation falls prevention interventions
Period when the underpinning research was undertaken: 2016-2022 (2026)
Period when staff involved in the underpinning research were employed by the submitting institution: 2016-2022
Period when the impact occurred: 2020-2022

Summary of the impact (indicative maximum 100 words)
There is a need for implementation of existing evidence in clinical practice, teaching and research. FALLPREVENT is highly relevant in this context as it will reduce the gap between fall research and implementation of best practice for falls prevention among older adults (65+) in municipalities in Norway. Through co-creation and feasibility testing, we have developed an implementation intervention that currently is evaluated in a large ongoing cluster-randomized trial in 25 city districts/municipalities in Norway. We have also contributed to the development of national advice for falls prevention by the Norwegian Health Directorate.

2. Underpinning research (indicative maximum 500 words)
Falls and fall-related injuries are major contributors to the burden of disease in older people and costly for the society. Although the evidence for effective fall prevention interventions exists, uptake rates of for example simple exercise interventions in community is yet low.

The first part of FALLPREVENT was conducted in the period 2016 to 2019, focusing on barriers and facilitators to evidence-based practice (EBP). The findings are published in three papers. The overall findings delineate that EBP made older patients feel safe. The physiotherapists observed that the findings do not readily translate into clinical practice, and that both older users and physiotherapists underscored the importance that the evidence must be adapted and translated into user-friendly language.

To further develop an implementation intervention, a co-creation process with relevant stakeholders (health care providers, users (older “fallers”) and researchers was conducted in March 2020 to December 2022. In January 2023, this implementation intervention was tested in a feasibility study in two city districts. Together, the work laid the foundation for the development of an implementation intervention that is currently evaluated in an ongoing cluster-randomized controlled implementation trial. Alongside this project, there was an ongoing work to develop a local fall prevention check list led by the Health Agency in Oslo Municipality with participants from the city districts, from the Oslo Emercency Room and researchers from Aging, Health and Welfare. This work resulted in a standardized, evidence-based, check-list including screening procedures and suggestions for interventions to prevent falls linked to detected risk factors. The check-list is now implemented in the city districts of Oslo and used among older citizens in Oslo Municipality. Evaluation of the use of this check list is one of the projects in FALLPREVENT and the results will be published in 2024.

In 2022, there was a need to develop national advice for falls prevention, especially since new up-to-date, globally applicable guidelines was published in 2022. FALLPREVENT have collaborated with the Norwegian Directorate of Health. A new guideline has been developed by the Directorate (published in January 2024). Researchers from FALLPREVENT and the Research group Aging, health and welfare has been extensively involved in the work with this guideline, both in the planning phase and as participants in the resource group supporting the guideline development. The FALLPREVENT cluster-randomized implementation trial will evaluate the effectiveness of an implementation intervention to increase the adherence to these new national advice for falls prevention in municipalities in Norway. The knowledge from this study can guide implementation of guidelines also in the future.

Overall, we believe that the work from FALLPREVENT will have major impact on the knowledge on effective implementation strategies, and how to implement new guidelines in the municipalities in Norway and will prevent falls among older adults.

Context: This research was performed at OsloMet in close collaboration with the primary health services in Oslo Municipality and has now been extended to national collaboration with 25 municipalities/city districts in Norway as well as the Norwegian Directorate of Health.
Key persons: Professor Astrid Bergland, Associate Professor Therese Brovold, Professor Kristin Taraldsen and Professor Signe Flottorp (the Norwegian Public Health Institute)

3. References to the research (indicative maximum of six references)

1) Worum H, Lillekroken D, Ahlsen B, Roaldsen KS, Bergland A. Bridging the gap between research-based knowledge and clinical practice: a qualitative examination of patients and physiotherapists' views on the Otago exercise Programme. BMC Geriatr. 2019 Oct 21;19(1):278. doi: 10.1186/s12877-019-1309-6. PMID: 31638912; PMCID: PMC6805671.
2) Worum H, Lillekroken D, Ahlsen B, Roaldsen KS, Bergland A. Otago exercise programme-from evidence to practice: a qualitative study of physiotherapists' perceptions of the importance of organisational factors of leadership, context and culture for knowledge translation in Norway. BMC Health Serv Res. 2020 Oct 27;20(1):985. doi: 10.1186/s12913-020-05853-8. PMID: 33109177; PMCID: PMC7590709.
3) Worum H, Lillekroken D, Roaldsen KS, Ahlsen B, Bergland A. Physiotherapists' perceptions of challenges facing evidence-based practice and the importance of environmental empowerment in fall prevention in the municipality - a qualitative study. BMC Geriatr. 2020 Oct 29;20(1):432. doi: 10.1186/s12877-020-01846-8. PMID: 33121434; PMCID: PMC7596977.
4) Worum H, Lillekroken D, Roaldsen KS, Ahlsen B, Bergland A. Reflections of older people about their experience of fall prevention exercise in the community- a qualitative study exploring evidence-based practice. BMC Public Health. 2020 Nov 9;20(1):1671. doi: 10.1186/s12889-020-09630-4. PMID: 33167887; PMCID: PMC7650178.

4. Details of the impact (indicative maximum 750 words)

The first parts of the FALLPREVENT have mainly been conducted in the east country of Norway. FALLPREVENT participants from OsloMet have collaborated with the primary health care services in Oslo Municipality, especially when they developed a tool for assessment of falls and fall risk, that now is used by health personnel working in the city districts of Oslo.

On a national level we have contributed and collaborated with both the Health Agency in Oslo Municipality regarding local work with fall prevention and the Norwegian Directorate of Health in their work with the national advices for falls prevention. The national advices for falls prevention was published in January 2024, containing advices for municipalities, hospitals, and nursing homes. Furthermore, the ongoing study with 25 municipalities/city districts from four different regions in Norway, will evaluate the effectiveness of an implementation intervention aiming to increase the adherence to these national advices. Thus, the expected impact from this study is high, where we will provide knowledge on how to implement new guidelines in municipalities in Norway. The user perspectives and user involvement is also a strength through all phases of this project.

On an international level, the involvement of collaborators abroad in this project is important. We also have had meetings with researchers and health authorities in Sweden, to discuss the work in FALLPREVENT as this is interesting for their plans for updating national advices and guidelines on falls prevention. The project's dissemination and communication plans are thorough, and the project has been and will be presented on local, national, and international conferences and congresses.

Overall, the impact of the project will be to contribute to close the gap between evidence and practice in fall prevention focusing on older adult (65+) fallers who live in municipalities in Norway.

5. Sources to corroborate the impact (indicative maximum of ten references)

Norwegian Directorate of Health
https://www.helsedirektoratet.no/faglige-rad/fallforebygging-hos-eldre

Oslo Metropolitan University, Faculty of Health Sciences (OsloMet HV) [3]

Institution: OsloMet
Administrative unit: Faculty of Health Sciences
Title of case study: Understanding pain and promoting responsible use of OTC analgesics in adolescents.
Period when the underpinning research was undertaken: 2009 - 2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2009 - 2022
Period when the impact occurred: 2016-2022

1. Summary of the impact (indicative maximum 100 words)

The overall purpose has been to increase the public's and in particular health professionals', parents' and adolescents' knowledge about pain, pain management, and responsible use of OTC analgesics in adolescents through:

1. Public education – increased public knowledge of responsible use of OTC analgesics in adolescents through dissemination in various media
2. Educating health personnel
3. Monitoring adolescents' use of OTC analgesics
4. Influence health authorities and pharmaceutical industry so that information on the correct use of and risks associated with the use of OTC analgesics is easily available and adapted to young people.

2. Underpinning research (indicative maximum 500 words)

The underpinning research for this impact case started in 2009, when a research group consisting of researchers from OsloMet and the University of Oslo did the first study to map the use of OTC analgesics among adolescents in a region of Norway (SUS 1). We found the use of OTC analgesics to be surprisingly high, the adolescents had an understanding that the use of OTC was harmless, indications for use varied, and they had it readily available for use. Two papers were published in the *The Journal of the Norwegian Medical Association.* Following this, *the Norwegian Kidscreen-study* added questions on pain and pain management to the survey on health-related quality of life in children and adolescents. The study showed that 21% of Norwegian adolescents reported chronic pain that negatively affected social life and the ability to pursue hobbies, sleep, and presence at school. The Kidscreen-study resulted in a PhD comprising three scientific publications on pain and HRQOL (Haraldstad, 2011).

The findings from SUS 1 and Kidscreen was followed up in SUS 2, a PhD-project; *Frequent use of OTC analgesics among adolescents (10-19 years) – a warning sign of troubled lives* (Skarstein, 2018). Three studies are included, one quantitative study and two qualitative studies. The quantitative cross-sectional study showed that adolescents 15-16 years of age with high OTC analgesics use, had more widespread pain, lower self-esteem, less ambition for higher education, more often were engaged in binge drinking, and had higher school absenteeism, compared to adolescents using such medicines more seldom or never. We also identified that far more girls than boys reported continuous pain, accompanied by frequent OTC analgesic use. In qualitative interviews with young high consumers of OTC analgesics and their mothers we found that childhood experiences influence the adolescents' management of pain and their use of OTC analgesic. Further, that stressful childhood experiences, difficult family situations, and insecure peer relationships amplify their pain. The young people seemed to be psychosocially dependent

on their mothers. Mothers also had a significant influence on the young people's daily activities, assessment of pain, pain management and use of non-prescription painkillers.

In a study based on data from the Norwegian Young Data survey, including 349,528 adolescents 13-19 years we aimed to explore the relative roles and associations between on-label pain indication and psychological distress in weekly OTCA use. Thirty percent of females and 13 % of males used OTCA weekly. Headache was the strongest on-label pain predictor of weekly OTCA use, followed by abdominal pain. Depression and anxiety were the strongest psychological predictors of weekly OTCA use, and higher symptom levels and being female increased the strength of this association. Anxiety and depression also predict weekly OTCA use after controlling for physiological pain (Jonassen et al 2021).

In addition to the mentioned studies, we have continuously developed knowledge on the topic through various studies in close collaboration with the University of Agder. I.e ICanCope with Pain, a PhD project in which the purpose was to adapt and culturally examine the use of an app for pain management, as well as examine pain and quality of life in young people with long-term pain in upper secondary school (Grasaas, 2021). Another example is the longitudinal study Start Young aiming to generate new knowledge about HRQOL and pain among adolescents and their parents, as well as investigate potential family and regional patterns. A PhD student completed the doctorate in 2022 on this project (Mikkelsen 2022) The study is still ongoing.

https://www.oslomet.no/en/research/research-projects/pain-youth-over-counter-analgesics

- **Names of the key researchers**

Oslo Metropolitan University, Faculty of Health Sciences:

- Siv Skarstein. Associate Professor (Ph.d.-student year: 2012-2018). Oslo Metropolitan University, Faculty of Health Sciences https://www.oslomet.no/en/about/employee/siska/
- Sølvi Helseth. Professor and Vice-dean of Research, Oslo Metropolitan University, Faculty of Health Sciences. https://www.oslomet.no/en/about/employee/solvi/
- Kristin Haraldstad. Ph.d.-student (2007-2011) Oslo Metropolitan University
- Milada Småstuen. Professor (statisician), Oslo Metropolitan University. https://www.oslomet.no/en/about/employee/milasm/
- Rune Jonassen. Professor; Oslo Metropolitan University, Faculty of Health Sciences. https://www.oslomet.no/en/about/employee/runej/

Collaborators University of Agder:

- Kristin Haraldstad. Professor, Faculty of Health and Sport Sciences https://www.uia.no/en/kk/profile/kristiha
- Gudrun Rohde, Professor, Faculty of Health and Sport Sciences https://www.uia.no/en/kk/profile/gudruner
- Erik Grasaas. Faculty of Health and Sport Sciences https://www.uia.no/en/kk/profile/erikgr
- Hilde Timenes Mikkelsen, Associate Professor, Faculty of Health and Sport Sciences https://www.uia.no/en/kk/profile/hildeetm

Since 2011 there has been a close collaboration between researchers from the University of Agder (UIA) and OsloMet. The collaboration has included development of project applications, financing of activities, implementation of studies, publication of research results, visibility of research, teaching of health personnel and supervision of PhD candidates. There has been close collaboration with different user groups and stakeholders in developing the studies (e.g. adolescents, public health nurses, teachers and youth workers). In addition, voices of the users (adolescents, parents, teachers and public health nurses) have emerged and been published through qualitative studies.

From beginning of the project in 2009 there was a close collaboration with the Faculty of Medicine at University of Oslo, where Professor Emeritus Per Lagerløv was a central driving force behind the initial studies. Within OsloMet, researchers from Norwegian Social Research (NOVA), Faculty of Health Sciences (HV) and Faculty of Technology, Art and Design (TKD) have collaborated both on applications and studies. Within the Faculty of Health Sciences, the research groups of Mental Health and Quality of Life has collaborated and researchers from both groups are represented in most parts of the overall project. During the project period there has also been international collaboration with University of Oxford, Neuropsychological Research Department, University of Toronto and The Hospital for Sick Children in Toronto.

3. References to the research (indicative maximum of six references)

- Jonassen, R., Hilland, E., Harmer, C. J., Abebe, D. S., Bergem, A. K., & Skarstein, S. (2021). Over-the-counter analgesics use is associated with pain and psychological distress among adolescents: a mixed effects approach in cross-sectional survey data from Norway. BMC Public Health, 21(1), 1-12. https://doi.org/10.1186/s12889-021-12054-3
- Skarstein, S., Helseth, S., & Kvarme, L. G. (2020). It hurts inside: a qualitative study investigating social exclusion and bullying among adolescents reporting frequent pain and high use of non-prescription analgesics. BMC Psychology, 8(1), 1-9. https://doi.org/10.1186/s40359-020-00478-2
- Lagerløv, P., Rosvold, E. O., Holager, T., & Helseth, S. (2016). How adolescents experience and cope with pain in daily life: a qualitative study on ways to cope and the use of over-the-counter analgesics. BMJ Open, 6(3), e010184. https://doi.org/10.1136/bmjopen-2015-010184

  Skarstein, S., Lagerløv, P., Kvarme, L. G., & Helseth, S. (2016). High use of over-the-counter analgesic; possible warnings of reduced quality of life in adolescents-a qualitative study. BMC Nursing, 15(1), 1-11. https://doi.org/10.1186/s12912-016-0135-9
- Skarstein, S., Rosvold, E. O., Helseth, S., Kvarme, L. G., Holager, T., Småstuen, M. C., & Lagerløv, P. (2014). High-frequency use of over-the-counter analgesics among adolescents: reflections of an emerging difficult life, a cross-sectional study. Scandinavian Journal of Caring Sciences, 28(1), 49-56. https://doi.org/10.1111/scs.12039
- Haraldstad K, Sørum R, Eide H, Natvig GK, Helseth S. Pain in children and adolescents: prevalence, impact on daily life, and parents' perception, a school survey. Scandinavian Journal of Caring Sciences. 2011 Mar;25(1):27-36. https://doi.org/10.1111/j.1471-6712.2010.00785.x

3. Details of the impact (indicative maximum 750 words)

In Norway, both the sale of prescription pain medication and OTC analgesics, have increased markedly during the last decades. Paracetamol is recommended by the health authorities as the first choice in treating mild to moderate pain, and this medicine accounts for more than half of the Norwegian sales of non-prescription medicines for fever and pain in 2020. Frequency of use and ease of procurement engender a perception of OTC analgesics as relatively harmless. However, high consumption of OTC analgesics, such as paracetamol or ibuprofen carry a risk of worsening pain (medication-overuse headache) and cause damage the liver and kidneys. In addition, OTC analgesics cause a significant number of overdosing incidents among young people.

Approximately 20% of Norwegian adolescents experience persistent pain, with related problems increasing during adolescence and often manifesting in adulthood. Pain is a complex phenomenon with many different causal explanations that can impact young people's quality of life negatively. Adolescents' perceptions of pain, pain sensitivity, pain experiences and pain behaviour influence

their OTC analgesics use. Most children and other young people have access to OTC analgesics at home, and self-administration starts early in adolescence. Parents' attitudes towards OTC analgesics use can influence their children's use.

Throughout the project's various phases (2009-2022), knowledge has been developed to provide a better understanding of how young people experience and manage pain, as well as their knowledge of and attitudes towards OTC analgesic use. Results from the studies are being used continuously to spread knowledge about responsible OTC analgesics use among adolescents, parents, health professionals and health authorities. The knowledge has been disseminated via several channels, including scientific publications, various other media and national and international talks and lectures, including those for students in health sciences.
Associate professor Siv Skarstein (OsloMet) has become one of Norway's lead experts on the topic.

The overall purpose of this impact case has been to increase the public's and in particular health professionals', parents' and adolescents' knowledge about pain, pain management, and promote responsible use of OTC analgesics in adolescents *through public education, educating health personnel, monitoring adolescents' use and influence health authorities*.

1. **Public Education**. Increased public knowledge of responsible use of OTC analgesics in adolescents has occurred through massive dissemination in public media, like reports and debates on TV and radio, and articles in newspapers and weekly magazines during the last decade. The Directorate of Social Affairs and Health has in 2023-2024 run a campaign to increase the general public's knowledge of young people's use of OTC analgesics and to improve health professionals' competence in mapping and guiding young people with high consumption of OTC analgesics. Associate professor Siv Skarstein (OsloMet) has assisted with professional and research-based knowledge in this campaign at the request of the Ministry of Health. The researchers have also disseminated the research findings at parental meetings in schools.
2. **Educating health personnel**. The research group have disseminated the research findings at national and international conferences, congresses, and collaborative forums for health professionals, who work with children and young people. They have also published more than 20 scientific papers during the period, increasing the knowledgebase for education. Several researchers have with a health-related bachelor background have gained their PhDs within the overall project (4 completed and 1 in progress). These researchers are now teaching students, partly based on the research findings and their competence derived from this project. They have also gained insight into the use of OTC analgesics in children and young people which they can share with health professionals and researchers.
   Siv Skarstein has contributed to development of an internet learning program, aiming to increase employees in pharmacies competence in informing adolescents about proper OTC analgesics use (Pain and self-care). In addition, our research has influenced health authorities to make information of OTC analgesics use more available and targeted to adolescents, for example through the Norwegian Institute of Public Health.
3. **Monitoring adolescents' use of OTC analgesics**
   In 2014, NOVA (National Institute of Health and Welfare, OsloMet) incorporated questions about the use of OTC analgesics in the annual Norwegian Young Data survey (https://www.ungdata.no/english/). This has made it possible for us to follow the development of OTC analgesics use among Norwegian youth (13-18 years). Further, in 2020 NOVA implemented a national survey for 10-12 year olds, named Young Data Junior. Also including mapping of OTC analgesics use. We can now track the consumption trends of OTC analgesics young people from 10-18 years old. Further, researchers can identify OTC analgesics use in correlations with other trends in society, influence of crises like the Covid pandemic, and investigate geographical differences over time. We have recently conducted a study on

use of OTC analgesics among adolescents aged 10–12 years in 2023 (SUS 5). Preliminary findings indicate startling and worrying discoveries, yet to be published (Young-Youth).

4. **Influence health authorities and pharmaceutical industry** so that information on the correct use of and risks associated with the use of OTC analgesics is easily available, understandable, and adapted to young people. Knowledge provided in the research studies has impacted directly how authorities develop learning programmes and information campaigns on the topic. In addition, researcher Skarstein has supported the Norwegian Medical Product Agency, which again have imposed the medical companies to be more precise and informative in the text presented to the users within the leaf letter which follows the packages with OTC analgesics.

5. **Sources to corroborate the impact** (indicative maximum of ten references)

A selection of mass media publications involving researchers from OsloMet:

- Helsedirektoratet: – Løsningen blir en pille (dagbladet.no)
- https://www.abcnyheter.no/helse-og-livsstil/helse/2019/10/12/195617296/bekymret-for-ungdoms-bruk-av-smertestillende-medisiner-uheldig-og-farlig?nr=1
- https://www.bt.no/btmeninger/debatt/i/ALkmjz/unges-hoeye-forbruk-av-smertestillende-er-et-signal-om-at-noe-ikke-er-bra

Popular science articles involving researchers OsloMet (reaching out to health personnel, students and public):

- https://www.forskning.no/medisiner-partner-oslomet/forsker-advarer-mot-utbredt-pillekultur-blant-unge/272945
- https://www.forskning.no/barn-og-ungdom-helse/ett-av-fire-barn-mellom-10-og-12-ar-bruker-smertestillende-tabletter-ukentlig/2063694
- https://www.forskning.no/angst-barn-og-ungdom-depresjon/bruk-av-smertestillende-kan-vaere-et-signal-om-at-ungdom-sliter-psykisk/1940670
- https://sykepleien.no/meninger/2021/09/legemiddelforgiftning-hos-barn-og-unge-oker

An internet learning program for employees in pharmacies:

- E-læringskurs om smerte og egenomsorg - E-læringskurs for legemiddelrådgivere - Apokus - Apotekenes kompetanse og utviklingssenter

The Norwegian Young Data Survey (results from 2016 and Young Data junior 2022)

- https://oda.oslomet.no/oda-xmlui/bitstream/handle/20.500.12199/5106/Ungdata-Nasjonale-resultater-2016-web_korrigert_9.8..pdf?sequence=1&isAllowed=y
- https://oda.oslomet.no/oda-xmlui/bitstream/handle/11250/3011552/NOVA-rapport-6-2022.pdf?sequence=5&isAllowed=y

The Norwegian Public Health Institute (on OTC analgesics for children)

- https://www.helsenorge.no/medisiner/barn-og-medisiner/#reseptfrie-smertestillende-legemidler

Oslo Metropolitan University, Faculty of Health Sciences (OsloMet HV) [4]

Institution: OsloMet
Administrative unit: Faculty of Health Sciences
Title of case study: Impact on the education and professional role development of paramedics
Period when the underpinning research was undertaken: 2020-2023
Period when staff involved in the underpinning research were employed by the submitting institution: 2012-2024
Period when the impact occurred:2020-2023

1. Summary of the impact (indicative maximum 100 words)

This section should briefly state what specific impact is being described in the case study.

This case describes our research impact on the development of a new professional role, the state authorized Paramedicines (paramedics), and the education of these professionals in Norway. OsloMet established the first Norwegian bachelor's degree for paramedics in 2011 and our research have had great impact on the teaching of paramedics and on the role of the paramedics in clinical work.

2. Underpinning research (indicative maximum 500 words)

The GameSTROKE project (2019-2021) Training paramedics in identifying a broader range of acute stroke symptoms is crucial to get more patients rapidly to treatment. The Norwegian Air Ambulance Foundation, in collaboration with OsloMet, stroke experts, paramedics and paramedic students developed GameSTROKE, a smartphone application to teach and train paramedics in the NIHSS assessment (NIHSS = National Institutes of Health Stroke Scale), by digital simulation training. A study conducted at OsloMet in 2021 compared the feasibility and agreement between GameSTROKE and traditional in-person simulation. The results showed that the gamification approach incentivized more simulation training, resulted in faster stroke assessments with equal accuracy, and found digital simulation to be particularly beneficial during the pandemic, compared to traditional simulation training.

SYPACO (2020-2022). Paramedics play an important role in acute medical crises, including national health crises such as the COVID-19 pandemic. During the COVID-19 pandemic the paramedic bachelor's students were enrolled in the national COVID-19 response plan and our SYPACO project (2020-2022) documented that it is possible to safely include paramedic students in patient-related and non-patient related work. The results further showed that the education of essential healthcare personnel, such as paramedics could continue during a health crisis and that paramedic students can be valuable resources in times where healthcare personnel are needed.

Student-led simulation training (2021-2023). Experiences with simulation training with paramedic bachelor students indicated that students who had experience with simulation training and learning could benefit from practising student-led simulations as a supplement to teacher-led simulation. This was tested during the COVID-19 pandemic and seemed to work well. As a result, two researchers investigated the outcome of student facilitated simulation training and the results indicate that the level of reflection amongst student were equivalent for student facilitated simulations compared to teacher facilitated simulations.

Video streaming between caller and dispatcher in medical emergency calls (2021-2025)/Frequent callers (2022-2026) In 2020 our researchers took part in writing a report on the use of video in 113-calls (medical emergency calls) as part of a research collaboration between NAKOS (Nasjonal kompetansetjeneste for prehospital akuttmedisin), NKLM (Nasjonalt kompetansesenter for legevaktmedisin), KoKom (Nasjonalt kompetansesenter for helsetjenestens kommunikasjons beredskap) and SNLA (Stiftelsen Norsk Luftambulanse). This work resulted in

several new research projects involving the medical emergency call centra (EMCC), including two ongoing PhD projects at OsloMet. One of the OsloMet projects is investigating the use of video streaming in 113-calls, and one is investigating the phenomenon of frequent callers to the 113-center. Preliminary results from the video-streaming project indicate that the dispatchers experienced that the use of video streaming in medical emergency calls might contribute to a better comprehension of the situation, more precise resource allocation, as well as greater reassurance for the dispatcher and improved relationship between the dispatcher and the caller.

Safety during ambulance transits – use of force and coercion in the ambulance service (2019-2024) The number of ambulance assignments to people in mental health crises, with or without substance use issues, have been increasing. Based on clinical experienced challenges, our project has investigated how and why ambulance workers use coercion or coercive measures and how the laws and legislations should be interpreted in the prehospital setting.

EPaCuR (year 2019 – 2022) Three universities and one EMS provider in four Nordic countries received a grant from Erasmus+ (Application ID: 2019-1-IS01-KA203-051166) to initially work on an exemplary curriculum for a university bachelor's degree education for paramedics. During the project, the focus on an exemplary curriculum was found to be too detailed and was thus further developed to focus instead on a wider competency framework. This would enable any participating country to easily adapt its own potentially existing education to fit such a framework. The EPaCur report was published in year 2022.

- Maren Ranhoff Hov, Associate professor, 2020-Year to date (YTD)
- Astrid Karina Harring, Assistant professor, 2020-YTD., PhD student 2023-YTD
- Trine Møgster Jørgensen, head of department (2020-YTD), associate professor, 2012-YTD
- Magnus Hjortdahl, associate professor, 2020-YTD
- Siri Idland, assistant professor year 2017-2018, PhD student 2021-YTD
- Carl Christiansen, assistant professor 2012-YTD
- Jeanette Viggen Andersen, Assistant professor 2019 – YTD
- Nina Øye Thorvaldsen, Assistant professor 2020-YTD, PhD student 2022-YTD
- Kristin Häikiö, associate professor, 2020-YTD.

The paramedic department, where this impact case is based, was established in 2012 being the first bachelor program in paramedic in Norway.

3. References to the research (indicative maximum of six references)

- Harring, Astrid Karina V. ; Røislien, Jo; Larsen, Karianne; Guterud, Mona; Bugge, Helge Fagerheim; Sandset, Else Charlotte; Kristensen, Dorte Vesterager; Hov, Maren Ranhoff. Gamification of the National Institutes of Health Stroke Scale (NIHSS) for simulation training—a feasibility study. (2023). [Original research paper] Advances in Simulation. Vol. 8. https://doi.org/10.1186/s41077-023-00245-4
- Thorvaldsen, Nina Øye ; Bergem, Anne Kristine; Holst, Øyvind ; Häikiö, Kristin (2022). Bruk av tvang under ambulansetransport. Tidsskrift for Den norske legeforening. Vol. 142. https://doi.org/10.4045/tidsskr.22.0086
- Häikiö, Kristin ; Andersen, Jeanette Viggen ; Bakkerud, Morten ; Christiansen, Carl ; Rand, Kim; Staff, Trine. A retrospective survey study of paramedic students' exposure to SARS-CoV-2, participation in the COVID-19 pandemic response, and health-related quality of life. (2021) [Original research paper]. Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine. Vol. 29. https://doi.org/10.1186/s13049-021-00967-2
- Idland, Siri ; Iversen, Emil ; Brattebø, Guttorm; Kramer-Johansen, Jo; Hjortdahl, Magnus. From hearing to seeing: medical dispatchers' experience with use of video streaming in medical emergency calls - a qualitative study. (2022). [Original research paper] BMJ Open. Vol. 12. https://doi.org/10.1136/bmjopen-2022-063395

- Dúason, Sveinbjörn; Ericsson, Christoffer; Jónsdóttir, Hrafnhildur Lilja; Andersen, Jeanette Viggen ; Andersen, Thomas Lynge. European paramedic curriculum—a call for unity in paramedic education on a European level. (2021) [Original research paper]. Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine. Vol. 29. https://doi.org/10.1186/s13049-021-00889-z
- Christiansen, Carl ; Andersen, Jeanette Viggen ; Dieckmann, Gerhard Peter. Comparing reflection levels between facilitator-led and student-led debriefing in simulation training for paramedic students. (2023) [Original research paper]. Advances in Simulation. Vol. 8. https://doi.org/10.1186/s41077-023-00273-0

4. Details of the impact (indicative maximum 750 words

Enabling paramedics to do effective, efficient, and safe assessments of acute or critically ill and injured people outside of the hospitals enables an earlier medical assessments, earlier medical treatment and more effective medical prioritization and allocation of medical resources. A high-quality, early, medical assessment is likely to facilitated better patient outcomes, less use of in-hospital resources, and a safe transition of patients to their best effective level of care with less unnecessary delays.

As part of the Paramedic Norwegian Acute Stroke Prehospital Project (ParaNASPP), GameSTROKE is now being implemented in several health trusts, offering a flexible and cost-effective solution for skill acquisition and maintenance and competence enhancement, compared to the traditional implementation of new methods in the Emergency Medical Services. Gamification enabled easier access to training, and consequently more training and knowledge development. Improved knowledge and improves communication with in-hospital staff will prevents under-triage of patients with stroke and is likely to improve patients' health and future quality of life.

Simulation training and repetitive training on complex assessments are important to prepare students for real life work and for skill acquisitions. However, it is expensive and requires significant use of resources (time, room facilities, teachers and expensive equipment). The results from the GameSTROKE project and the student-led simulation project have had impact on the teaching of teaching paramedic students and have been used for competence enhancement among paramedics in clinical work. It has led to more cost-effective simulation and more simulation training while documenting similar or better learning outcomes among students. In addition to OsloMet, the Arcada University of Applied Sciences, in Finland, have shown interest in student-led simulation and are planning on testing the same concept in their simulation centre this year.

The establishment of a new bachelor's degree clearly impacts on the role of the paramedic. Paramedics with a bachelor's degree are bringing more medical knowledge to the patients outside of hospitals and consequently gaining more responsibility. Based on the results of the SYPACO project, paramedic students are now allowed to work in ambulance services after completing two out of three years of the BSc education, including having passed the drivers' license test for emergency vehicles. A direct impact is that the department of prehospital work at OsloMet now have integrated BSc students as part of the Oslo University Hospital preparedness lists in our common agreement for future health crises. Their competence is hereby acknowledged among ambulance services and other healthcare services.

Especially the paramedic's role in meetings with persons in a mental health crisis has gained interest in the society the last few years, following some incidents where the police have been involved in cases with adverse outcomes. The results from the Safety during ambulance transit project has impacted the teaching of paramedic students at OsloMet and have had impact on competence enhancement of paramedics in clinical work in ambulance services in Norway. The results led to discussions between legal experts, paramedics and police regarding the use of police,

and healthcare resources, identifying that the legal preparatory work in areas involving involuntary transportation of patients to mental health care, the use of coercion, and traffic safety for patients and escorting personnel has not been considered in relation to the prehospital context. The project resulted in two ongoing PhD projects owned by OsloMet and a textbook that is being published in January/February 2024. The textbook aims to enhance competence among paramedic students and other relevant groups of students and/or healthcare personnel in how to communicate with people in acute crises. The Paramedic association have arranged discussions and seminars regarding this subject and the subject has been discussed in public newspapers. The subject has also been published and debated in the Norwegian journal Ambulanseforum. The book is the first paramedic textbook in Norwegian, aiming to cover the learning outcomes in the paramedic programs in Norway. This complies with the European Paramedic Competency Framework, published in the report from the EpaCuR project.

The EPaCurE project and the wider competency framework is now being conveyed to Danmark as the department of prehospital work – paramedic, at OsloMet, has been asked for advice regarding the establishment of a bachelor's program in paramedic sciences in København. In Finland, the EPaCur framework has high relevance and applicability for paramedic educational competencies in contemporary times. Through the EPACUR-project, the Paramedic department at OsloMet is also involved in a Nordic collaboration aiming to develop a common content for the bachelor's degrees in paramedic.

A direct impact following the research and development work at the EMCCs (the video streaming project among others) is the establishment of a further education program in emergency medical dispatch (Videreutdanning i medisinsk nødmeldetjenester), which started in 2022. The evaluation of this program indicate that the content of the program is covering actual clinical needs and fills the knowledge gaps that is experienced by those who work clinically at the EMCCs and medical out-of-hours patient clinics. The clinical requests for more education in these areas and the future need of more medical personnel has also led to the planning and work towards a future master's program in advanced paramedic sciences at OsloMet. Such a program will strengthen the medical emergency care to the growing number of older people with complex health conditions, improve the care to the growing number of patients with mental health issues and/or substance use issues, and support and relieve other healthcare workers in other parts of the health services.

Sources to corroborate the impact (indicative maximum of ten references)

- **https://www.oslomet.no/studier/hv/evu-hv/medisinsk-nodmeldetjeneste**
- **https://norskluftambulanse.no/nyheter/gaming-oppdage-hjerneslag/?fbclid=IwAR3a_ol0W_aLpwfGtdebOCnUx2v5xuNetszQge4zoQtig5n86Zcp4xuuea0**
- **https://norskluftambulanse.no/nyheter/test-dine-slagkunnskaper-pa-forskningsdagene/**
- **https://issuu.com/norskluftambulanse/docs/snla_5-web (s.20-22)**
- https://ambulanseforum.no/artikler/nytt-studie-bruk-av-tvang-under-ambulansetransport, https://ambulanseforum.no/artikler/tvangshjemler-kan-fore-til-mer-tvang
- https://www.dagensmedisin.no/uten-tvangshjemmel-kan-liv-og-helse-settes-i-fare/510939
- https://ec.europa.eu/programmes/erasmus-plus/project-result-content/f64741e9-bd34-44c5-b76f-4170a478ddbc/EPaCur_Report_and_Framework__2022.pdf
- https://ambulanseforum.no/artikler/paramedisinstudenter-hadde-bedre-livskvalitet-enn-den-ovrige-befolkningen-under-pandemien
- file:///C:/Users/haikio/Downloads/Evalueringsrapport%20for%20pilotprosjekt%20om%20bruk%20av%20video%20i%20medisinsk%20n%C3%B8dmeldetjeneste%20(2).pdf
- https://www.hertervigforlag.no/produkt/prehospitale-moter-med-mennesker-i-krise-laerebok-for-ambulansepersonell/

Oslo Metropolitan University, Faculty of Health Sciences (OsloMet HV) [5]

Institution: OsloMet
Administrative unit: Faculty of Health Sciences
Title of case study: "Healthy Start": A nutrition education material that facilitates a healthy transition and integration for newly resettled immigrants.
Period when the underpinning research was undertaken: 2015-2020
Period when staff involved in the underpinning research were employed by the submitting institution: 2015-2020
Period when the impact occurred: 2015- (as Healthy Start is currently used its impact is still occurring)

1. Summary of the impact (indicative maximum 100 words)

The Healthy Start Food and Health (HSFH) is a nutrition education material targeting newly resettled immigrants and professionals working in close contact with this group. Its impacts are:

1) It contributes to knowledge-based health services for newly resettled immigrants.
2) It contributes to the societal need to improve health communication towards the immigrant population.
3) It promotes food security and integration by facilitating the transition into a new food environment.
4) It contributes to knowledge-based education and build capacity among professionals in Public Health Nutrition.

2. Underpinning research (indicative maximum 500 words)

Nutrition is an important determinant of health. Some immigrant groups are more likely to develop non-communicable diseases; moreover, food insecurity is high among asylum seekers and newly resettled immigrants. Having competencies facilitating a healthy transition into a new food environment is important. A measure to reach this goal is enabling those working with newly resettled immigrants to communicate about nutrition and health in a way that is suitable for this group. In 2014, responding to the national strategy aiming to achieve equity and equality in health, the Oslo Health Authority initiated the development of nutrition education material to be used in the Introduction Programme, leading to the Healthy Start Food and Health (HSFH) initiative. HSFH is a research-practice collaboration involving stakeholders from the public sector, academia, and non-governmental organizations. Researchers from the Public Health Nutrition group at OsloMet have been closely involved from the beginning and have been engaged in developing, revising, and evaluating this initiative from 2014 to 2021.

HSFH, was developed following the "Intervention Mapping" approach, and it combines theoretical and practical aspects related to food and nutrition[1]. It incorporates principles of cultural sensitivity and was reviewed following the Suitability Assessment of Material approach. HSFH contains information on topics that are relevant for a healthy diet, supported by a teacher's guideline and an activity booklet. It was launched in May 2016 in a public seminar. The material became available on the website in 2017. https://www.sunnstartnorge.no/.

A big "ace" in this project has been the stakeholders' involvement in all stages of the project. In addition to the Agency of Health and OsloMet, involved advisors of the Introduction programme, and NGOs as Diabetesforbundet, Flerkulturelt råd for Oslo og Akershus (FROA), and Bydelsmødre [the name of these organizations as others further in the text is left in Norwegian as there is not an adequate translation). The HSMH "core group" (the Agency of Health and OsloMet) have worked systematically to anchor and expand the use of HSMH. Two projects were financed in the period 2016-2020. "Healthy Start at Asylum Reception Centers" was funded in 2016 by the Directorate of Integration and Diversity (IMDi). Taking place in four reception centers, it focused on promoting food security, family activities around food, and involvement of the local civil society. This project also partially financed the first cross-sectional study conducted in Norway on food security in reception centers[2], the first one of this kind in Norway. HSMH was further financed by the DAM Foundation in the period 2017-2020 (extended to 2021 due to Covid 19). During that period, 166 employees and volunteers received courses and guidance in using the HSMH material. In addition, 6 different initiatives were carried out[3]. 1) In the autumn of 2017, a cooking course (combining theory, social activities, and the Norwegian language) was held over 6 weeks with residents from the Ila reception center[4]. 2) In autumn 2018-spring of 2019, twelve sessions were carried out for participants of the language café "Møteplassen" in the district of Grünerløkka, Oslo 3) In February 2019, a two-day cooking course was conducted for unaccompanied minors. 4) In the spring of 2019, an in-depth course on the use of HSMH was conducted in collaboration with "Bydelsmødre". 5) In the autumn of 2019, a theory course over 6 weeks was carried out at the Norwegian Labour and Welfare Administration (NAV) Stovner[5]. 6) In the autumn of 2020, adapted material was used in short courses at the Stovner's "frisklivsentral". Given the small context of these initiatives a qualitative approach was preferred for the evaluation and participant observation and qualitative interviews with participants in Healthy Start initiatives were conducted by OsloMet researchers and students, both during and after the different initiatives. An exception is the survey that was conducted one year after the launch of the HSFH website, to get an insight into the use and evaluation of the material[6]. Both the qualitative and quantitative evaluation indicate that HSFH has a positive impact.

- **Names of the key researchers and what positions they held at the administrative unit at the time of the research**

- Laura Terragni, professor at OsloMet, is head of the project and became part of the Healthy Start team in 2015. She has followed HSMG from the beginning and has led the project on food security in reception centers, she supervised 5 master students and involved researchers from Cornell University with expertise in nutrition education.
- Sigrun Henjum, was Professor at OsloMet and has been particularly involved in the project on food security in reception centers from 2016. She was supervisor for two master students and involved researchers from UC Davis, USA during 2018-2019.
- Gun Roos, was a senior researcher at OsloMet, she joined the HSMH project in 2020, following the experience with NAV at Stovner and -together with Terragni-disseminated the methodology and the findings from HSMH as a case study for the Food2Gather project, funded by the European Union's Horizon 2020.

- Any relevant key contextual information about this area of research.

The HSFHG project well represents key research areas of the Public Health Nutrition Research Group (https://www.oslomet.no/en/research/research-groups/public-health-nutrition), whose main aim is "to contribute with knowledge that helps to promote a healthy and sustainable diet, prevent nutrition-related diseases, and reduce social health inequalities". A main strength of this project has been the long lasting collaboration between members of the research group and the

Agency of Health. The project provide the opportunity to collaborate with other research centres and institutions, like Consumer Research Norway, the Norwegian Institute of Public Health, Cornell University, and UC Davis in USA We are currently part of an application Food access among vulnerable EU population promoted by COST (European Cooperation in Science and Technology. Terragni and Henjum, together with master students, are now investigating food security among Ukrainians population.

3. References to the research (indicative maximum of six references)

Output 1,2,4 are scientific articles published in peer-reviewed journals. Outcome 5 is a podcast; 3 & 6 are two reports that have been published as part of OsloMet Skriftserie.

1) Terragni, L., Garnweidner-Holme, L., Vingmark Næss, T., & Hussain, A. (2018). A healthy start: Development of nutrition education for newly resettled immigrants and refugees living in Norway. International Journal of Home Economics, 11(1), 80–95. https://search.informit.org/doi/abs/10.3316/informit.915188406858811
2) Henjum, S., Morseth, M. S., Arnold, C. D., Mauno, D., & Terragni, L. (2019). "I worry if I will have food tomorrow": A study on food insecurity among asylum seekers living in Norway. BMC Public Health, 19(1), 592. https://doi.org/10.1186/s12889-019-6827-9
3) Barbala, I., Terragni, L., Haug, H., Eriksen, A.M*., Sunn start mat og helse for innvandrere 2017-2020* [Healthy Start food and health for immigrants, activities 2017-2020 Sluttrapport, Stiftelsen Dam, Oslo https://oda.oslomet.no/oda-xmlui/handle/11250/2978208
4) Barbala, I., Haug, H., Kaur Grewal, N., Eriksen A.M., & Terragni, L. (2019) Mat for fremtiden. Erfaringer med et matlagingskurs blant asylsøkere ved et integreringsmottak[Food for the future: experiences with a cooking course among Asylum seekers living in a reception center]; *Norsk Tidskrift for Ernæring* 17 (4) 8-17. https://doi.org/10.18261/ntfe.17.4.2
5) Terragni, L & Roos, Gun (2022) "Bringing language class to life with food in Norway", Part of the 12-part podcast series of the Food2Gather project. https://uni.oslomet.no/food2gather/resources/podcasts/
6) Schwaiger E., Grewal, N., & Terragni, L. (2019). *Sunn Start. Bruk, Brukervennlighet og nytteverdi av Sunn Start- et forebyggende og helsefremmende undervisning- og veiledningsmateriell tilpasset personer med migrasjonsbakgrunn* [Healthy Start: Use, utility and user-friendliness of teaching material tailored for people with immigrant background]. OsloMet Skriftserie 2019/5, OsloMet, Oslo. https://skriftserien.oslomet.no/index.php/skriftserien/article/view/660/173

4. Details of the impact (indicative maximum 750 words)

IMPACT 1: Building knowledge-based health services.

A main challenge – and frustration- for researchers is when promising health projects fail to survive in the "real world". The main impact of HSMH is that it managed to overcome the piloting phase and it is anchored in the activities of health and social care service. After almost ten years HSMH is still up and running and its use has been disseminated to other settings than those originally planned. Indicators of the extent of the impact are that 1) the HSFH approach has been applied to two other health education themes: Healthy Start Mental Health and Healthy Start Dental Care; other topics, as Sexual Health and Maternal and Child Health, are under consideration[1]. 2) in addition to the Introduction Programme and reception centers, HSMH has been used by Bydelsmødrene, NAV Yrkesrettet Norskopplæring (YNO) and frisklivssentralen to communicate with immigrants with low Norwegian proficiency (A1/A2 level)[2,3] 3) HSMH has also reached a national scale as it was mentioned as an example in the Norwegian National Action Plan for a

Healthier Diet 20217-2021 (p.70), and both the Directorate of Health and the Directorate of Integration and Diversity have recommended its use (https://www.imdi.no/planlegging-og-bosetting/kommunens-arbeid/helse/) 4) Currently the Oslo's Directorate of Education (UDE) is collaborating with the Oslo Agency of Health for including the HS modules in the sessions of the Introduction program focusing on "Livsmestring i et nytt land"(Personal communication).

IMPACT 2: Facilitating of nutrition communication.

HSMH aimed to build capacity among people working with newly resettled immigrants to communicate about food and health [2,3,4,.] Data collected one year after the creation of the HSMH website indicated that it was uniquely downloaded by 522 organizations/people[2]. Findings from the survey among downloaders who were asked to participate indicated that HSMH was used by 77 organizations across the country[2]. A large majority (82%) stated that "the Healthy Start material had made it easier for me to create an understanding of these topics among participants"[2]. In the qualitative interviews done with a sub-group of survey participants, it was stated that "*Healthy Start is just a gift for us ("en gavepakke"). We have a short time [to talk about health] and this material has been very good for us*"[2].

In the period 2017-2020 – when HSFH received funding from Dam Foundation. During the project 166 people (84 health or social care professionals and 82 volunteers) have been trained in the use of the HSFH[3]. Qualitative evaluation of these experiences confirms the positive experience of using HSMH[3]. A volunteer from Bydelsmødrene stated for instance that "*I've used it in schools and kindergartens. What we all like best is the picture where you see how many sugar cubes are in Coke! It is the slide we use the most. It makes a difference when you see how much it really is. And it becomes very easy for me to explain as well. And then people are like: Yep, you're right*"[3].

IMPACT 3 Promoting food security and integration.

HSMH aimed also to promote food security. The alarming findings of the study we conducted on food security in reception centers[5,], as part of the HSMH project, were disseminated in seminars and on the media and contributed to creating awareness and attention towards this topic[6,7,] We hold meetings with the Norwegian Directorate of Immigration (UDI)[7] and with the Norwegian Organization for asylum seekers (NOAS). Newspapers mentioned this study also some years later, in 2022, in relation to the conditions of the Ukrainian refugees (https://www.dagbladet.no/meninger/umenneskelig/77074986).

The evaluation of the HSMH initiatives addressed towards asylum seekers and refuges indicated that participation in these initiatives improved familiarity with the new food environment, more varied diets [3,4]. "*There are many challenges you can experience as a newly arrived immigrant and therefore it is very important to have a place like the "møteplassen", where we can get more information. It is important that we learn about the diet and lifestyle here in Norway; how we can prepare food and what we can eat, as this can be challenging. We often don't know where to find the food we are used to from our home country and don't know how to prepare Norwegian food*." (Participant to the language cafe organized "møteplassen")[3].

For many participants in the project coming from war, political instability, and dictatorship, food became a way of investing in a better future and developing a sense of belonging[9] to their new country. *"Now I like spaghetti. Even rice: sometimes I cook it with different vegetables. I like it. We try to cook for the future, we want to cook Norwegian food. Now we mix and eat both Eritrean and Norwegian food" (P*articipant in the course at Ila's reception centre)[3].

IMPACT 4: Enriching knowledge-based education

Participation in this project has strengthened the cooperation with health and social care services of the Oslo Municipality, providing the opportunity for a mutual exchange of expertise. Our bachelor's and master's students in Public Health Nutrition have particularly benefited from this collaboration [2,3,4,5,10]. Seven had their internship at the Norwegian Health Authority, four bachelor's

theses and five master's theses were written in connection with this project. Two of the students were hired by the Health Authority.

5. Sources to corroborate the impact (indicative maximum of ten references)

1) Helseetaten, Oslo Kommune, *Sunn Start*, retrieved 24th January 20224 from https://www.sunnstartnorge.no/
2) Schwaiger E., Grewal, N., & Terragni, L. (2019). Sunn Start. Bruk, Brukervennlighet og nytteverdi av Sunn Start- et forebyggende og helsefremmende undervisning- og veiledningsmateriell tilpasset personer med migrasjonsbakgrunn [Healthy Start: Use, utility and user-friendliness of teaching material tailored for people with immigrant background]. OsloMet Skriftserie 2019/5, OsloMet, Oslo. https://skriftserien.oslomet.no/index.php/skriftserien/article/view/660/173
3) Barbala, I., Terragni, L., Haug, H., Eriksen, A.M., Sunn start mat og helse for innvandrere 2017-2020 [Healthy Start food and health for immigrants, activities 2017-2020 Sluttrapport, Stiftelsen Dam, Oslo. https://oda.oslomet.no/oda-xmlui/handle/11250/2978208
4) Barbala, I., Haug, H., Kaur Grewal, N., Eriksen A.M., & Terragni, L. (2019) Mat for fremtiden. Erfaringer med et matlagingskurs blant asylsøkere ved et integreringsmottak[Food for the future: experiences with a cooking course among Asylum seekers living in a reception center]; Norsk Tidskrift for Ernæring 17 (4) 8-17. https://doi.org/10.18261/ntfe.17.4.2
5) Henjum, S., Morseth, M. S., Arnold, C. D., Mauno, D., & Terragni, L. (2019). "I worry if I will have food tomorrow": A study on food insecurity among asylum seekers living in Norway. BMC Public Health, 19(1), 592. https://doi.org/10.1186/s12889-019-6827-9
6) Terragni, L; Henjum S. (2019) Mat på asylmottak: «Det viktigste er at barna får mat, det er ikke like viktig med oss voksne.», pod Mat på asylmottak: «Det viktigste er at barna får mat, det er ikke like viktig med oss voksne.» OsloMet Podcast serie, Oslo https://podcasts.apple.com/us/podcast/mat-p%C3%A5-asylmottak-det-viktigste-er-at-barna-f%C3%A5r-mat/id988493567?i=1000463694269
7) Terragni, L. (2019). Sårbare grupper i «lykkeland» Kosthold og matsikkerhet på Norske asylmottak». I seminaret Velkommen hit? Asylmottak og rettighetsarbeid i en ny tid; arrangert av Norsk Folkehjelp, February. Litteraturhuset, Oslo (invited speaker).
8) Terragni, L.; Henjum, S. (2018). Hvordan kan vi forbedre matsituasjon på asylmottak? Implikasjoner av studien og veien videre. [How can we ameliorate the food situation in asylum reception centres?] Presentation of results from the study on food security at the seminar organised with the Norwegian Directorate of Immigration (UDI) and the Directorate of Integration and Diversity (IMDi). Oslo, September 2019.
9) Roos G. & Terragni, L. (2022). The role of food in creating a sense of normality and belongings in precarious lives. Paper presented at "A Sense of Home - European Symposium on Food, Migration and Belonging". Utrecht, 19–21 April 2022.
10) Terragni, L., Garnweidner-Holme, L., Vingmark Næss, T., & Hussain, A. (2018). A healthy start: Development of nutrition education for newly resettled immigrants and refugees living in Norway. International Journal of Home Economics, 11(1), 80–95. https://search.informit.org/doi/abs/10.3316/informit.915188406858811

[Østfold University College, Faculty of Health, Welfare and Organisation] [1]

Institution: Østfold University College
Administrative unit: Faculty of Health, Welfare and Organisation
Title of case study: Integrated Services for Patients with Dual Diagnosis (ROPIT)
Period when the underpinning research was undertaken: 2018-2021
Period when staff involved in the underpinning research were employed by the submitting institution: 2018-2021
Period when the impact occurred: 2018-2022

1. Summary of the impact (indicative maximum 100 words)

The impact of this study includes a better understanding of mechanisms that prevent a successful integration of services for patients with concurrent addiction and mental health problems according to national policies and guidelines, at the municipal level. Further, the knowledge and experience gained through this project are included in relevant professional studies at Østfold University College. Together, this may have an impact on both organization and management of these services, as well as increased awareness and knowledge on this topic among future professionals.

2. Underpinning research (indicative maximum 500 words)

This section should outline the key research insights or findings that underpinned the impact, and provide details of what research was undertaken, when, and by whom. This research may be a body of work produced over a number of years or may be the output(s) of a particular project. References to specific research outputs that embody the research described in this section, and evidence of its quality, should be provided in the next section. Details of the following should be provided in this section:

- The nature of the research insights or findings which relate to the impact claimed in the case study.
- An outline of what the underpinning research produced by the submitted unit was (this may relate to one or more research outputs, projects or programmes).
- Dates of when it was carried out.

The organization of the services and management structure in the field varied greatly for several reasons: i) the size of the municipality, ii) the continuation of the arrangements and professional traditions that characterized the local service system before the goal of integrated services was launched and iii) the municipalities interpreted national guidelines differently – guidelines that were relatively vague.

The variation in organization reflects the municipalities' autonomy to organize services based on local needs, but the services in question were also subject to prioritization of other policy areas by the local municipalities. Many of the employees – both managers and service providers - felt being on their own in handling how to design the services.

Across all three municipalities, some common challenges were identified:

Firstly, user participation was a problem when considering individual preferences and needs. The services were not able to meet the needs, often restricted by financial shortcomings and few voluntary organizations that could contribute (especially in the smaller municipalities).

Secondly, based on data from managers, service providers and users, coordination with the specialist services often failed – especially regarding admissions and discharges (too many, and often severely ill patients, exceeded the capacity of the services at the municipal level). Furthermore, the organization of the specialist services in two pillars (addiction/psychiatry) and a lack of resources at this level, created systemic challenges for the services for this group of patients at the municipal level. This could explain why particularly seriously ill patients were discharged too early or discharged without sufficient information transfer to municipal actors.

Thirdly, municipal services became a last resort in the users' care pathway - with both professional and financial challenges, and no possibility of evading responsibility.

The research results have been published in national and international peer-reviewed journals as well as a peer-reviewed anthology *Statlig politikk og lokale utfordringer: Organisering av tjenester innen rus og psykisk helse* edited by Bjørkquist and Ramsdal was published October 2021. Here, all project participants published one or more chapters.

The data collection took place from late 2018 to late 2021. Dissemination of results to the field of practice, participation in seminars for managers and professionals, and scientific conferences as well as scientific publications occurred continuously in the period 2019-2022.

The project team:

- Bjørkquist, Catharina, professor (project lead 2019-2021)
- Ramsdal, Helge N., professor (project lead 2018-2019)
- Hansen, Gunnar V., professor (project member)
- Fineide, Mona J., ass. professor (project member)
- Haug, Erna, senior lecturer (project member)
- Fugletveit, Ragnhild, ass. professor (project member)
- Røste, Rannveig, ass. professor (project member)
- Løken, Therese D., doctoral student (project member)

3. References to the research (indicative maximum of six references)

This section should provide references to key outputs from the research described in the previous section, and evidence about the quality of the research. All forms of output cited as underpinning research will be considered equitably, with no distinction being made between the types of output referenced. Include the following details for each cited output:

Bjørkquist, C., & Hansen, G. V. (2018). Reducing service barriers to people with dual diagnosis in Norway. *Cogent Social Sciences*. https://doi.org/10.1080/23311886.2018.1561237

Bjørkquist, C., & Ramsdal, H. N. (Eds.). (2021). *Statlig politikk og lokale utfordringer: Organisering av tjenester innen rus og psykisk helse* [Scientific antology]. Cappelen Damm Akademisk. https://doi.org/10.23865/noasp.140

Bjørkquist, C., & Ramsdal, H. (2021). Structural disavowal and personal inundation of responsibility – a local perspective on pressure on mental health front-line professionals. *European Journal of Social Work*, 1-12. https://doi.org/10.1080/13691457.2021.1882399

Fineide, M. J., Haug, E., & Bjørkquist, C. (2021). Organisational and Professional Integration Between Specialist and Primary Healthcare Services: A Municipal Perspective. *International Journal of Integrated Care*, *21*(2). https://doi.org/http://doi.org/10.5334/ijic.5606

Løken, T. D., Helgesen, M. K., & Bjørkquist, C. (2022). Collective Competence as an Enabler for Service Integration in Health and Social Care Services. *Journal of Multidisciplinary Healthcare*, *15*, 2817-2830. https://doi.org/10.2147/JMDH.S387719

Løken, T. D., Helgesen, M. K., Vike, H., & Bjørkquist, C. (2022). Being bound and tied by the ropes of frugality: a case study on public management values and service integration. *Journal of Health Organization and Management*, *36*(9), 95-111. https://doi.org/10.1108/JHOM-10-2020-0401

4. Details of the impact (indicative maximum 750 words)

This project addressed one of the most difficult questions in the modern welfare state: how to organize services for people with concurrent addiction and mental health problems in ways that make these services more coordinated. Overall, the project has provided arenas for reflection on organization and professional practice as well as opportunities for local service development.

From an academic standpoint, it has been critical to underline the need for an explicit positioning in political science and organizational theoretical perspectives within the research field related to addiction and mental health problems.

The results indicate that there is a need for flexible structures, coordination mechanisms and multi-professional approaches, as well as increased financial contributions.

Decentralization, coordination, and user participation may be regarded as central characteristics of national policies and the organization of services for people with complex needs. We argue that these characteristics provide a framework for, and represent conditions for, the service development for patients with such disorders. The characteristics are understood as an entangled processes, which constitute elements in the emergence of a «new paradigm» in the services: what is described as a focus on community-based services. The process of changes at the local level shows that institutional characteristics related to working with this patient group are important for understanding how the change processes are organized.

Drawing from the experiences of users, service providers, managers, and international researchers, we have intended to extend knowledge on how to improve the relevant services and design models of interprofessional teaching, adopting an organization theory approach. We have aimed to maintain user involvement through the data-gathering methods (individual in-depth interviews and focus group interviews) with users and family caregivers. Further, user involvement was maintained by including one representative from the national user organization for substance abuse (RIO) in the reference group. This representative helped with the development of a case that was used in the last round of focus group interviews. Lastly, one peer-support worker employed in one of the municipalities participated in a focus group interview with other professionals. As such, the voices of current and former service users and family caregivers have had an impact on the findings of this study.

The project sought to meet the objectives through broad participation from the professional community at the faculty, mostly aimed at Master in Coordination of Health and Welfare Services. This has resulted in both formal competence enhancement and a more unified and consolidated professional environment. This will eventually have a significant impact on future professionals in the field. Due to the complexity of challenges and needs among people with concurrent substance addiction and mental health problems, the knowledge and experiences from this study may also be highly relevant when working with other groups of patients in our society.

For the students, the project implied that the teaching was directly linked to theoretical perspectives, findings and discussions from the project. For the Østfold University College, the project also entailed that the experience gained from the prioritized research area Working life, professions and service development was continued in a way relevant to the faculty.

In late 2021, the project developed a brief, flexible course which focused on policies, coordination of measures, and delivery of services in the addiction and mental health field. The aim was to make these courses available to municipalities, individual service providers, user organizations, and others to help build expertise in adapting policies and developing services and organizations in municipal addiction and mental health services. However, difficulties in implementation arose in 2021-2022 partly due to the general education plan for mental health work.

To conclude the project, a final conference was organized in October 2021, gathering participants from the national and international research community in the coordination and addiction and mental health policy field. Representatives from the three municipalities, including professionals and managers, took part, several of whom presenting. Additionally, recordings of posts suitable for educational purposes were made.

5. Sources to corroborate the impact (indicative maximum of ten references)

The researchers have taken part in a Scandinavian network for research related to treatment and organization of services for people with addiction and mental health problems, SKANROP, previously Meeting the Dragon as well as more general healthcare and organization research settings:

Bjørkquist, C., Fineide, M. J., & Løken, T. D. (2023). *Mange – og varierende veier til kommunale helse- og velferdstjenester* [Konferanse]. SKANROP, Hamar. (Originally set to June 2022 but postponed to June 2023)

Fineide, M. J., & Haug, E. (2019). *Sirkulære prosesser - utfordringer når ulike institusjonelle logikker møtes i behandling av mennesker med dobbeltdiagnoser*. Meeting the Dragon, København, 6.-7.06.2019.

Hansen, G. V. (2019). *Er en bolig alltid et hjem?*. Meeting the Dragon, København, 6.-7.06.2019.

Løken, T.D., 2021. Organizing financial resources in the municipality: a case study on integrated services provision to persons with dual diagnosis. *International Journal of Integrated Care*, 21(S1), p.119.DOI: https://doi.org/10.5334/ijic.ICIC20289

The researchers have presented and taken part in various national seminars where professionals, users and peer-support workers attended in addition to the research community. Some selected presentations are:

Bjørkquist, C. (2022). *Muligheter og utfordringer i organisering av lokalbaserte tjenester. Statlig politikk vs. lokale utfordringer på ROP-området*. Rus og psykisk helsedag med Statsforvalteren, Høgskolen på Vestlandet og fagfletet, Haugesund. 25.08.2022

Fineide, M. J. (2022). *Hva med idealet om integrerte tjenester for mennesker med ROP lidelser?* Seminar med praksisfeltet, Litteraturhuset, Fredrikstad. 07.03.2022

Løken, T. D. (2021). «Offentlige styringsverdier og vilkår for integrerte og personorienterte tjenester». Skuddårsseminaret: From double trouble to dual recovery – om rehabilitering, livskvalitet og hverdagsliv til personer med samtidige psykisk helse- og ruslidelser., USN, digital/Drammen. 25.02.2021

The results have been presented in the media through interviews, opinion pieces and podcasts. A selection is:

Bjørkquist, C. (2021). *Stort mangfold i hvordan tjenester på ROP-feltet organiseres* [Interview]. Nasjonalt kompetansesenter for samtidig rusmisbruk og psykiske lidelser. https://rop.no/aktuelt/stort-mangfold-i-hvordan-tjenester-pa-rop-feltet-organiseres/

Fineide, M. J., & Ramsdal, H. (2018). Sviktende samhandling år utover pasienter og brukere. *Fredrikstad blad, kronikk.* https://www.f-b.no/debatt/hogskolen-i-ostfold/psykisk-helse/sviktende-samhandling-gar-ut-over-pasienter-og-brukere/o/5-59-1291566

Løken, T. D. (2021). Alvorlig psykisk syke mennesker blir kasteballer med døden til følge. *Forskersonen.no* https://www.forskersonen.no/kronikk-meninger-psykisk-helse-og-rus/alvorlig-psykisk-syke-mennesker-blir-kasteballer-med-doden-til-folge/1950417

One of the keynote speakers at the final conference invited members of the ROPIT project to the Third Meeting Science Symposium; 19.-20.05.2022 where the Ph.D. student presented a paper. Our participation resulted in an Erasmus exchange from Belgium in late 2022.

Løken, T. D. (2022). *Interdependent collaboration in municipal health and social care organizations*. 3rd Meetings Science Symposium, Brussel, 19.-20.05.2022.

[Østfold University College, Faculty of Health, Welfare and Organisation] [2]

Institution: Østfold University College
Administrative unit: Department of Nursing, Health and Laboratory Science (SHB); Faculty of Health, Welfare and Organisation (HVO)
Title of case study: Development of a model for nurses' role in interprofessional pharmaceutical care (DeMoPhaC)
Period when the underpinning research was undertaken: 1st Oct. 2018 – 30th Sept. 2021
Period when staff involved in the underpinning research were employed by the submitting institution: 1st Oct. 2018 – 30th Sept. 2021
Period when the impact occurred: 1st Oct. 2018 – 30th Nov. 2023

1. Summary of the impact (indicative maximum 100 words)

The main impact of this study is the initiation of a strong international network of expertise on "Nurse and Pharmaceutical Care (PC)". It also contributed with a more unified and competency based education for nurses through the NuPhaC-EU framework on nurses' role in PC. Further, a competency test was developed for students to evaluate and benchmark their competency. The study contributed to increased transparency and equality for nurses in PC, as well as a stronger accordance with the current research, education, practice and policy. Finally, it also contributed to labour mobility of nurses and nurse students within the EU.

2. Underpinning research (indicative maximum 500 words)

This section should outline the key research insights or findings that underpinned the impact, and provide details of what research was undertaken, when, and by whom. This research may be a body of work produced over a number of years or may be the output(s) of a particular project. References to specific research outputs that embody the research described in this section, and evidence of its quality, should be provided in the next section. Details of the following should be provided in this section:

- The nature of the research insights or findings which relate to the impact claimed in the case study.
- An outline of what the underpinning research produced by the submitted unit was (this may relate to one or more research outputs, projects or programmes).
- Dates of when it was carried out.

A first study in 4888 nurses, 974 physicians and 857 pharmacists showed providing patient education and information (PEI), monitoring medicines adherence (MMA), monitoring adverse/therapeutic effects (ME) and prescribing medicines were considered integral to nursing practice by 77%, 85%, 81% and 23% respectively. Most respondents were convinced that quality of PC would be improved by increasing nurses' involvement in ME (95%), MMA (95%), PEI (91%) and prescribing (53%). Mean scores for the reported quality of collaboration between nurses and physicians, collaboration between nurses and pharmacists and interprofessional communication were respectively <7/10, ≤4/10, <6/10 for all four aspects of PC.

In **a second** study, in 340 interviews, health care providers reflected on the preferential role for nurses in PC. Nurses' autonomy varied across Europe (none, limited, a few tasks, in case of emergency, a broad range of tasks and responsibilities). Respondents reported when nurses would assume more pharmaceutical care responsibilities this could have a positive effect on quality of care and patient outcomes. However, when translating the preferential role for nurses into clinical practice several contextual factors such as education, team characteristics, country-

specific regulations, and types of medications for which nurses are held responsible have to be taken into account.

In **a third** study, a scoping review was performed to corroborate the evidence and to extract the responsibilities and tasks described in literature. Seven responsibilities were identified: management of therapeutic and side effects of medications; management of medication adherence; management of patient medication self-management; management of patient education/information about medications; prescription management; management of medication safety; and care coordination. Within these seven responsibilities 26 tasks were described.
The first three studies resulted in the development of the NUPHAC-EU framework. Following its' development, the framework was evaluated by 923 nurses, 240 physicians, and 199 pharmacists. No responsibilities, tasks or contextual factors had to be removed after evaluation.

In **a fourth** study, through literature review and a Delphi procedure, competences required for nurses to take up the responsibilities and tasks of the NuPhaC-EU framework were described. The expert panel reached consensus on the relevance of 60 competences for 22 nursing tasks.

In **a fifth** study, applying the NuPhaC-EU framework and related competences, the level of integration into nursing curricula and the extent to which nurse students master these competences at different educational levels was questionned in 1939 students. The results showed that the embedding of PC courses in nurse curricula should be extended. PC knowledge of final year students was assessed as limited with regard to the expectation of the labour market.

Finally, considering the studies performed in the DeMoPhaC project, **a position paper** was published on the implementation of more interprofessional, integrated, evidence-based PC, together and with a shared focus on what is best for the patient.

Project Reference: 2018-1-BE02-KA203-046861
Web site: https://www.nuphac.eu/erasmus-demophac

Vigdis Abrahamsen Grøndahl, professor
Ann Karin Helgesen, professor

References to the research (indicative maximum of six references)

- De Baetselier, E., Dijkstra, N. E., Batalha, L. M., Ferreira, P. A. C., Filov, I., Grøndahl, V. A., ... & Dilles, T. (2022). Nurse students' competences in interprofessional pharmaceutical care in Europe: Cross-sectional evaluation. *Nurse Education in Practice*, *65*, 103485. https://doi.org/10.1016/j.nepr.2022.103485
- De Baetselier, E., Dilles, T., Batalha, L. M., Dijkstra, N. E., Fernandes, M. I., Filov, I., ... & Van Rompaey, B. (2021). Perspectives of nurses' role in interprofessional pharmaceutical care across 14 European countries: A qualitative study in pharmacists, physicians and nurses. *PloS one*, *16*(5), e0251982. ttps://doi.org/10.1371/journal.pone.0251982
- De Baetselier, E., Van Rompaey, B., Batalha, L. M., Bergqvist, M., Czarkowska-Paczek, B., De Santis, A., ... & Dilles, T. (2020). EUPRON: nurses' practice in interprofessional pharmaceutical care in Europe. A cross-sectional survey in 17 countries. *BMJ open*, *10*(6), e036269. http://dx.doi.org/10.1136/bmjopen-2019-036269
- De Baetselier, E., Van Rompaey, B., Dijkstra, N. E., Sino, C. G., Akerman, K., Batalha, L. M., ... & Dilles, T. (2021). The NUPHAC-EU Framework for Nurses' Role in Interprofessional Pharmaceutical Care: Cross-Sectional Evaluation in Europe. *International journal of environmental research and public health*, *18*(15), 7862. https://doi.org/10.3390/ijerph18157862

- Dijkstra, N. E., De Baetselier, E., Dilles, T., Van Rompaey, B., da Cunha Batalha, L. M., Filov, I., ... & Sino, C. G. (2021). Developing a competence framework for nurses in pharmaceutical care: A Delphi study. *Nurse Education Today*, *104*, 104926. https://doi.org/10.1016/j.nedt.2021.104926
- Dilles, T., Heczkova, J., Tziaferi, S., Helgesen, A. K., Grøndahl, V. A., Van Rompaey, B., ... & Jordan, S. (2021). Nurses and pharmaceutical care: interprofessional, evidence-based working to improve patient care and outcomes. *International journal of environmental research and public health*, *18*(11), 5973. https://doi.org/10.3390/ijerph18115973

4. Details of the impact (indicative maximum 750 words)

The DeMoPhaC project allowed us to build a stronger international network of expertise on 'Nurse and Pharmaceutical Care'. This was done in a partnership with representatives of 14 European countries and in collaboration with students. This will strengthen the international network on pharmaceutical care in nursing and facilitate collaboration on nurse education, research, practice and policy.

The NuPhaC-EU framework on nurses' role in interprofessional PC was developed. This framework shows the responsibilities and tasks in PC for nurses expected by health care providers in clinical practice. The NuPhaC EU-framework is an essential step towards more competency based education.

A website with a competency test was created, allowing nurse students to evaluate and benchmark their competences.

This project contributed to a more well-functioning labour mobility of nurses within the EU.

Besides connections with nurse experts, we have also established connections with other professional groups and associations internationally. We have discussed collaboration with PCNE (Pharmaceutical Care Network Europe), which is a strong international pharmacist network. In February 2020 we were invited in the 'soapbox' (members only session) of their international conference, to present DeMoPhaC and NuPhaC, and to define strategies for collaboration between the organizations. In March 2020 we were invited to present DeMoPhaC and NuPhaC for Eurodurg, and to set up formal collaboration. International collaboration with physicians is more difficult as they are less organized with the focus on pharmaceutical care. We have established a formal connection with the European Geriatric Medicine Society – Special Interest Group Pharmacology. Furthermore, we are connecting with Espacomp (European Society Patient Compliance to Medication).

5. Sources to corroborate the impact (indicative maximum of ten references)

Regulations on national guidelines for nursing education:
https://lovdata.no/dokument/SF/forskrift/2019-03-15-412
When working on the new regulation for nursing education, pharmaceutical care and treatment were highlighted.

Grøndahl, Vigdis Abrahamsen; Nome, Carina Marie; Stenbjerg, Julie Kjølhede; Arnesen, Marie Helen; Aardalen, Tina; Helgesen, Ann Karin. Pharmaceutical care in nursing homes - a qualitative study about interprofessional collaboration and patient safety. NuPhaC Winter Conference 2021; 2021-12-10 - 2021-12-11

OUS_UiO_BAR: Impact case number 1

Institution: Oslo University Hospital
Administrative unit: Division of Paediatric and Adolescent Medicine
Title of case study: Bronchilitis All-SE Study
Period when the underpinning research was undertaken: 2010-2013
Period when staff involved in the underpinning research were employed by the submitting institution: 2007-2024
Period when the impact occurred: 2012-2014

1. Summary of the impact (indicative maximum 100 words)

2. The treatment of acute bronchiolitis, the most common cause of acute hospitalisations in children, was changed based on the results of the Bronchiolitis All-study, SE-Norway. Prior to the study, the Norwegian guidelines recommended to use inhaled adrenaline frequently, up to every hour in children hospitalised with acute bronchiolitis. This typically resulted in the administration of 15-20 inhalations per child. The study's negative result led to a recommendation against the use of adrenaline, which in turn was successfully implemented in clinical practice.

3. Underpinning research (indicative maximum 500 words)

This multicentre, double-blind, randomized clinical trial (the Bronchiolitis All-study, SE-Norway) included infants with acute bronchiolitis who were admitted to the paediatric departments of eight hospitals in South-Eastern Norway from January 2010 through May 2011. They were followed to two years of age, ending in early 2014. In accordance with a 2-by-2 factorial design, children were randomly assigned to receive inhaled racemic adrenaline or inhaled saline and to receive the assigned treatment either on demand or on a fixed schedule. Any use of oxygen therapy, nasogastric-tube feeding, or ventilatory support was recorded. The primary outcome was the length of the hospital stay.

The mean age of the 404 infants included in the study was 4.2 months, and 59.4% were boys. Length of stay, use of oxygen supplementation, nasogastric tube feeding, ventilatory support, and relative improvement in the clinical score from baseline (before any inhalation/randomisation) were similar in the infants treated with inhaled racemic adrenaline and those treated with inhaled saline ($P>0.1$ for all comparisons).

On-demand inhalation, as compared with fixed-schedule inhalation, was associated with a significantly shorter estimated mean length of stay. In the treatment of acute bronchiolitis in infants, inhaled racemic adrenaline is not more effective than inhaled saline. However, the strategy of inhalation on demand appears to be superior to that of inhalation on a fixed schedule.

Key researcher at Oslo University Hospital was research group leader and project manager professor Karin Lødrup Carlsen and medical doctor/PhD candidate and national coordinator Håvard Ove Skjerven. The other participating 7 hospitals in South-Eastern Norway had their own local PIs employed at the respective hospitals: Østfold (JO Hunderi and Jon Lunde), Vestre Viken (SK Brügmann-Pieper), Vestfold (AC Brun and C Siva), Telemark (H Engen), Sørlandet (L Eskedal), Innlandet Lillehammer (T Vikin), Innlandet Elverum (LB Rolfsjord).

3. References to the research (indicative maximum of six references)

Skjerven HO, Hunderi JO, Brügmann-Pieper SK, Brun AC, Engen H, Eskedal L, Haavaldsen M, Kvenshagen B, Lunde J, Rolfsjord LB, Siva C, Vikin T, Mowinckel P, Carlsen KH, Lødrup Carlsen KC (2013)
Racemic adrenaline and inhalation strategies in acute bronchiolitis
N Engl J Med, 368 (24), 2286-93

Skjerven HO, Rolfsjord LB, Berents TL, Engen H, Dizdarevic E, Midgaard C, Kvenshagen B, Aas MH, Hunderi JO, Bains KE, Mowinckel P, Carlsen KH, Carlsen KC (2015)
Allergic diseases and the effect of inhaled epinephrine in children with acute bronchiolitis: follow-up from the randomised, controlled, double-blind, Bronchiolitis ALL trial
Lancet Respir Med, 3 (9), 702-8

4. Details of the impact (indicative maximum 750 words)

Acute bronchiolitis in infants is the most common disease in paediatric acute wards, leading to hospitalisation in 2-3% of all children born. In Norway alone, it accounts for approximately 1500 hospitalisations each year. For decades, the routine treatment in Norway and other countries was inhaled adrenaline, recommended up to every hour, estimated to 15 inhalations per child per hospital stay. In addition, inhaled adrenaline was used in outpatient settings in emergency clinics and hospital wards. However, the evidence for this practice was weak, with no large placebo controlled trials published. The Bronchiolitis All-SE trial was the first to test the effect of inhaled adrenaline versus placebo in hospitalised children with acute bronchiolitis with clinically relevant outcomes including the length of hospital stay.

The study, which was published in NEJM in 2013, has received 83 citations.
The negative result of the trial led to an end to this recommendation in Norway, as well as in other countries. The Norwegian “Veileder i akutt pediatri” changed in 2013, removing inhaled adrenaline from routine use. The American Academy of Pediatrics updated their clinical practice guideline in 2014, no longer recommending the use of bronchodilators. The Bronchiolitis All-SE trial was the only large RCT on hospitalised patients published prior to these changes.

A retrospective observational study of electronic medical records showed that the use of adrenaline in 2017 was reduced to 5% of patients (from 59% in 2009) in hospitalised patients and 16% (from 67% in 2009) in the primary care setting. The study was conducted in Oslo, but the patients are equally common in all paediatric departments in the country.

All paediatric departments benefit from the implemented results of the study. No formal health economic analysis has been performed, but conservative estimates suggests that at least 10000 less inhalations are given in Norway each year as a direct consequence of the study, saving expenses to medication as well as nurses’ time to prepare and administer the medication. Reducing the exposure of an unnecessary drug that may cause stress to a child, and prolonged length of hospital stay, is also beneficial.

The study was run on nine hospitals in the South-eastern Norway, involving attending doctors, nurses as well as bioengineers round the clock for two years. The external funding of the study was minimal, only accounting for a 20% study nurse position for 4 months at each study site. The national coordinator was funded through an engagement as PhD research fellow at the University of Oslo, while remaining personnel costs was in kind at each hospital.

5. Sources to corroborate the impact (indicative maximum of ten references)

American Academy of Pediatrics (AAP) guidelines:
Shawn L. Ralston, Allan S. Lieberthal, H. Cody Meissner, Brian K. Alverson, Jill E. Baley, Anne M. Gadomski, David W. Johnson, Michael J. Light, Nizar F. Maraqa, Eneida A. Mendonca, Kieran J. Phelan, Joseph J. Zorc, Danette Stanko-Lopp, Mark A. Brown, Ian Nathanson, Elizabeth Rosenblum, Stephen Sayles, Sinsi Hernandez-Cancio, Shawn L. Ralston, Allan S. Lieberthal, H. Cody Meissner, Brian K. Alverson, Jill E. Baley, Anne M. Gadomski, David W. Johnson, Michael J. Light, Nizar F. Maraqa, Eneida A. Mendonca, Kieran J. Phelan, Joseph J. Zorc, Danette Stanko-Lopp, Mark A. Brown, Ian Nathanson, Elizabeth Rosenblum, Stephen Sayles, Sinsi Hernandez-Cancio; Clinical Practice Guideline: The Diagnosis, Management, and Prevention of Bronchiolitis. Pediatrics November 2014; 134 (5): e1474–e1502. 10.1542/peds.2014-2742
https://www.nejm.org/doi/10.1056/NEJMoa1301839

Norwegian guidelines: Akuttveilederen i pediatri
https://www.helsebiblioteket.no/innhold/retningslinjer/pediatri/akuttveileder-i-pediatri/7.lunge-og-luftveissykdommer-inkludert-luftveisinfeksjoner/7.4-akutt-bronkiolitt#undefined

Klem N, **Skjerven HO**, Nilsen B, Brekke M, Vallersnes OM.
Treatment for acute bronchiolitis before and after implementation of new national guidelines: a retrospective observational study from primary and secondary care in Oslo, Norway.
BMJ Paediatr Open. 2021 May 20;5(1):e001111. eCollection 2021.PMID: 34104804
doi: 10.1136/bmjpo-2021-001111.

OUS_UiO_BAR: Impact case number 2

Institution: Oslo University Hospital and University in Oslo
Administrative unit: BAR
Title of case study: PreventADALL (Preventing Atopic Dermatitis and ALLergies in children)
Period when the underpinning research was undertaken: 2013-2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2013-2022
Period when the impact occurred: 2018-2022

1. Summary of the impact (indicative maximum 100 words)

In this largest study to date on primary prevention of atopic dermatitis (AD) and food allergy, introducing peanut, cow's milk, wheat and egg between 3 and 4 months reduced the relative risk of food allergy at 3 years by around 60%, while neither early food introduction nor regular emollients from 0.5-9 months of age reduced the risk of AD at 1 and 3 years.

Being the first population-based study showing primary food allergy prevention by early food introduction, the results substantially contributed to a meta-analysis of 23 trials that concluded with high-evidence that early introduction prevents food allergy. The evidence documents the need to consider the benefits of immunological tolerance development by introducing allergenic foods during revision of infant feeding guidelines.

2. Underpinning research (indicative maximum 500 words)

The lack of primary prevention effect on AD in the PreventADALL (Skjerven et al Lancet 2020) contradicted two earlier small pilot studies, but together with a similar study in infants at high-risk of AD (Chalmers Lancet 2020) as well in individual patient data meta-analyses (Kelleher et al Cochrane 2020) lead to the current conclusion that regular emollients from 2 weeks of age are not recommended to prevent AD. Allergic/atopic and other non-communicable diseases (NCD) are likely to have origins in early life, possibly with shared risk or beneficial factors. As allergic diseases were among the first to increase, but were followed by other immune-related NCDs, the PreventADALL was designed to a) determine if interventions in the first year of life could prevent atopic disease, and b) to explore early life origins of NCDs, primarily allergic, but also other NCDs such as obesity, cardiovascular and others.

The PreventADALL study is a primary prevention, factorially designed randomised controlled general population-based of 2400 mother-child pairs in Norway (OUS and Østfold Hospital trust) and Karolinska Institute, Sweden. Participants (2697women) were enrolled in mid-pregnancy from Dec 2014-October 2017 and their newborn infants were randomised at birth to no intervention, regular emollients from 2 weeks-9 months of age, introduction of peanut, cow's milk, wheat and egg between 3 and 4 months of age or both interventions. The exploratory arm of PreventADALL has focused on extensive clinical, biologic, health-, life-style and demographic data collection from mid-pregnancy to 3 years of age, with further follow-up to adult age.

Extensive clinical follow-up investigations (n= 2394) at 3, 6, 12, 24 and 36 months of age (completed in 2020) included anthropometric measures, skin assessment, blood pressure measurements, skin prick tests (allergy 6, 12, 36 months), lung function (3, 12, 35 months) and biosampling (blood, feces and meconium, vernix, skin swabs, urine, blood, breast-milk) for skin and gut microbiome, allergy assessments, genetics/epigenetics, immune function (12 and 36 months) as well as electronic questionnaires for general, life-style, nutritional and health-related information at 18+34 week-pregnancy and child age 3, 6, 9, 12, 18, 30 and 36 months. Furthermore, data include general and extended foetal ultrasound measures around 18 weeks pregnancy from all participants, with corresponding and further lung-specific ultrasound

measures at 30-week pregnancy in 450 fetuses which have been continued with corresponding anthropometric measures from birth through 3 years of age in the off-spring. Also, placenta function biomarkers in mid-pregnancy are analysed for all women.
The PreventADALL is initiated and coordinated by the unit, (ORAACLE) which is responsible for all infra-structure and management of the project. Also, the unit collects data from around 2/3 of study participants and is involved in every research output from the project.
Each collaborating institution is responsible for their own funding, while data management, biobank and coordination are within the unit. The unit is involved with supervision of most, but not all PhD candidates, while Master projects are usually supervised by appropriate collaborators. The project PIs are core researchers in all papers, involved in research aims, analytic approaches and results as well as writing the papers.
The PreventADALL has a strong collaboration across research groups, departments and divisions within OUS and UiO, as well as across national, regional and international institutions. In particular, the rapid enrollment within 20 months of almost 2700 women from a general population in connection with the 18-week routine ultrasound screening, would not have been possible without the diligent and enthusiastic cooperation of the obstetric unit staff at the participating hospitals. Furthermore, through close collaboration with the obstetrics and fetal units, the study has unique insight and available state-of-the-art knowledge for interpreting data as well as defining the most important research questions related to early life factors that may impact NCD development. By nature of longitudinal prospective studies, the scientific impact will become apparent stepwise, with the first phase (mid-trimester fetal life -3 year child age) being the focus in this evaluation.
The multi-disciplinary scientific representation and collaboration within the steering group as well as thematic PIs ensures the necessary scientific strategic focus necessary for high-quality, cutting-edge scientific work in the PreventADALL.
The steering group is key to all aspects of the project, including research strategies, providing synergies and collaboration across thematic areas, supervision and publication and dissemination. Thematic PIs are core to ensure synergies across research personnel collaboration, as well as contributing with relevant scientific approaches to other research areas and topics within the PreventADALL. All central researchers participate in developing specific research questions, provide necessary resources to ensure methodological and analytic data acquirement, as well as serve as collaborating or central authors on publications, as appropriate. The organization of the project is thus core to the success of ensuring priorities and delivering high-quality research across a broad area of multi-disciplinary, translational, epidemiologic and clinical research.

3. References to the research (indicative maximum of six references)
Original articles related to impact described above

Skjerven HO, Lie A, Vettukattil R, Rehbinder EM, LeBlanc M, Asarnoj A, Carlsen KH, Despriee ÅW, Färdig M, Gerdin SW, Granum B, Gudmundsdóttir HK, Haugen G, Hedlin G, Håland G, Jonassen CM, Landrø L, Mägi CO, Olsen IC, Rudi K, Saunders CM, Skram MK, Staff AC, Söderhäll C, Tedner SG et al. (2022)
Early food intervention and skin emollients to prevent food allergy in young children (PreventADALL): a factorial, multicentre, cluster-randomised trial
Lancet, 399 (10344), 2398-2411

Skjerven HO, Rehbinder EM, Vettukattil R, LeBlanc M, Granum B, Haugen G, Hedlin G, Landrø L, Marsland BJ, Rudi K, Sjøborg KD, Söderhäll C, Staff AC, Carlsen KH, Asarnoj A, Bains KES, Carlsen OCL, Endre KMA, Granlund PA, Hermansen JU, Gudmundsdóttir HK, Hilde K, Håland G, Kreyberg I, Olsen IC et al. (2020)

Skin emollient and early complementary feeding to prevent infant atopic dermatitis (PreventADALL): a factorial, multicentre, cluster-randomised trial
Lancet, 395 (10228), 951-961

Wärnberg Gerdin S, Lie A, Asarnoj A, Borres MP, **Lødrup Carlsen KC**, Färdig M, Konradsen JR, Monceyron Jonassen C, Olsson Mägi CA, Rehbinder EM, Rudi K, Skjerven HO, Staff AC, Söderhäll C, Tedner SG, van Hage M, Vettukattil R, Nordlund B (2021)
Impaired skin barrier and allergic sensitization in early infancy
Allergy, 77 (5), 1464-1476

Tedner SG, Söderhäll C, Konradsen JR, Bains KES, Borres MP, Carlsen KH, Carlsen KCL, Färdig M, Gerdin SW, Gudmundsdóttir HK, Haugen G, Hedlin G, Jonassen CM, Kreyberg I, Mägi CO, Nordhagen LS, Rehbinder EM, Rudi K, Skjerven HO, Staff AC, Vettukattil R, van Hage M, Nordlund B, Asarnoj A (2021)
Extract and molecular-based early infant sensitization and associated factors-A PreventADALL study
Allergy, 76 (9), 2730-2739

Nilsen M, Lokmic A, Angell IL, Lødrup Carlsen KC, Carlsen KH, Haugen G, Hedlin G, Jonassen CM, Marsland BJ, Nordlund B, Rehbinder EM, Saunders CM, Skjerven HO, Snipen L, Staff AC, Söderhäll C, Vettukattil R, Rudi K (2021)
Fecal Microbiota Nutrient Utilization Potential Suggests Mucins as Drivers for Initial Gut Colonization of Mother-Child-Shared Bacteria
Appl Environ Microbiol, 87 (6)

Edre KMA, Rehbinder EM, Carlsen KL, Carlsen KH, Gjersvik P, Hedlin G, Jonassen CM, LeBlanc M, Nordlund B, Skjerven HO, Staff AC, Söderhäll C, Vettukattil R, Landrø L, study group (2019)
Maternal and paternal atopic dermatitis and risk of atopic dermatitis during early infancy in girls and boys
J Allergy Clin Immunol Pract, 8 (1), 416-418.e2

Rehbinder EM, Advocaat Endre KM**, Lødrup Carlsen KC,** Asarnoj A, Stensby Bains KE, Berents TL, Carlsen KH, Gudmundsdóttir HK, Haugen G, Hedlin G, Kreyberg I, Nordhagen LS, Nordlund B, Saunders CM, Sandvik L, Skjerven HO, Söderhäll C, Staff AC, Vettukattil R, Værnesbranden MR, Landrø L, study group, Carlsen MH, Lødrup Carlsen OC, Granlund PA et al. (2019)
Predicting Skin Barrier Dysfunction and Atopic Dermatitis in Early Infancy
J Allergy Clin Immunol Pract, 8 (2), 664-673.e5

4. Details of the impact (indicative maximum 750 words)

Randomised trial of primary prevention of Atopic dermatitis and food allergy:
The lack of primary prevention effect of the skin intervention, as well as significantly reduced risk of food allergy by early complementary feeding among a general population of infants are novel and have in a major way contributed to the updated knowledge base through meta-analyses. The impact of the results of primary prevention of food allergy is likely to be observed during revised updated guidelines of infant nutrition in 2024.

Infant lung function:
Use of tidal flow volume (TFV) loops to measure lung function in awake infants have not been standardised, prior to the PreventADALL study. By measuring TFV in almost 1000 3-month old infants we first demonstrated high inter-observer correlation by assessing flow-volume curves

using a newly developed standard operating procedure, and subsequently showed significant lower flow-volume ratios among sleeping compared to awake infants (Bains et al ERJ open 2022). Infants born to inactive pregnant mothers were more likely to have low lung function (Gudmundsdottir ERJ open 2022), a finding highlighted by the European Respiratory Society during the annual congress in 2021 due to novelty and importance.

Gut microbiota: By exploring the infant gut microbiota, we identified potential nutritional drivers for bacterial colonization, and observed its maturation towards adulthood. We found that as the microbiota matures, butyrate levels increase with key bacteria's involvement, underlining their importance in gut health and the need for further exploration as butyrate plays a crucial role in regulating immune responses (Nilsen et al Genes 2020).

Infant skin: It is suggested that the skin plays an important role in development of atopic dermatitis and allergy development. The study has expanded this knowledge, showing that

- almost 50% of 3-month-old infants from a general population had clinically documented dry skin, and that dry skin, even in the absence of eczema was associated with reduced skin barrier function at this time as well as doubled the risk of having atopic dermatitis at 6 months of age (Rehbinder et al. BJD 2019 and JACI pract 2019).
- reduced skin barrier function at 3 months of age, even in the absence of eczema significantly increased the risk of allergic sensitisation at 6 months, and was a major risk factor for development of specific IgE antibodies associated with food allergy, mainly peanut, milk and egg allergy (Wärnberg Gerdin, S., et al. Allergy, 2022). Collectively, our findings underpin the role of the skin in sensitisation and early allergy development.

Allergy development: Findings from the PreventADALL showed that already at 3 months of age

- 7% of the infants had specific IgE-antibodies against food allergens, which were associated with maternal IgE-antibodies against food allergens during pregnancy (Tedner, S. G., et al. Allergy, 2021).
- IgE antibodies towards major food allergens were shown among 25-45% of the sensitized infants, underpinning the importance of early sensitisation and subsequent increased risk of food allergy prior to introduction to complementary feeding.
- Thus, a likely window of opportunity for preventing the development from no IgE to sensitisation, as well as from IgE-sensitisation to tolerance rather allergy development may be short, and before 6 months of age, which is currently the recommended time of introducing complementary feeding in Norway.

4. Sources to corroborate the impact (indicative maximum of ten references)

Kelleher MM, Cro S, Van Vogt E, Cornelius V, Lodrup Carlsen KC, Ove Skjerven H, Rehbinder EM, Lowe A, Dissanayake E, Shimojo N, Yonezawa K, Ohya Y, Yamamoto-Hanada K, Morita K, Cork M, Cooke A, Simpson EL, McClanahan D, Weidinger S, Schmitt J, Axon E, Tran L, Surber C, Askie LM, Duley L et al. (2021)
Skincare interventions in infants for preventing eczema and food allergy: A cochrane systematic review and individual participant data meta-analysis
Clin Exp Allergy, 51 (3), 402-418

R. Scarpone, P. Kimkool, D. Ierodiakonou, J. Leonardi-Bee, V. Garcia-Larsen, M. R. Perkin, et al.
Timing of Allergenic Food Introduction and Risk of Immunoglobulin E-Mediated Food Allergy: A Systematic Review and Meta-analysis
JAMA Pediatr 2023 Vol. 177 Issue 5 Pages 489-497

OUS_UiO_BAR: Impact case number 3

Institution: University of Oslo and Oslo University Hospital
Administrative unit: BAR
Title of case study: The role of the oxytocin system in health and wellbeing
Period when the underpinning research was undertaken: 2013-2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2013-currently
Period when the impact occurred: 2019-ongoing

1. Summary of the impact (indicative maximum 100 words)

The role of the hormone oxytocin in childbirth and breastfeeding has been known for over a century. More recently, there has been increasing research attention on oxytocin's role in social behaviour. However, the full extent of oxytocin's function is not well known, not to mention the potential for oxytocin as an individualised support for various diseases and conditions. This gene expression study by Quintana and colleagues (2019) confirmed existing hypotheses and helped develop new hypotheses, regarding oxytocin's function. In particular, this study helped reveal the role of oxytocin in behavioural flexibility, which has contributed to three upcoming randomised controlled trials.

2. Underpinning research (indicative maximum 500 words)

The experimental manipulation of oxytocin receptors expression levels can influence behaviour. Thus, identifying the location of oxytocin receptors in the human brain can help inform the extent of oxytocin's function. Before our study, the only existing data on oxytocin receptor expression in the human brain was limited to a small number of brain region sites. In our study, we created a high-resolution map of oxytocin receptors in the human brain across hundreds of brain regions. To understand the functional significance of the location of these receptors, we matched this map against brain activation maps from a meta-analysis of over 15k brain imaging meta-analyses. This means that we were able to see which activation maps that correspond to specific mental states, most closely correlated with oxytocic receptor expression. Altogether, we confirmed some of oxytocin's known functions (e.g., social behaviour), and provided evidence for functions that have received little research attention in the context of oxytocin research (e.g., reward, anticipation, taste, learning).

This research program was designed by Associate Professor Daniel S. Quintana, Senior Researcher Terje Nærland (Both at the paediatric division) and Professor Lars T. Westlye and Professor Ole A. Andreassen. This study built on data from two previous oxytocin clinical trials led by Quintana, Westlye, Nærland, and Andreassen (Quintana et al., 2019; 2017). Together, data from this gene expression study and prior clinical trials has provided the basis for two more oxytocin clinical trials, which will begin in 2024.

3. References to the research (indicative maximum of six references)

Main reference:

1. Quintana, D.S., Rokicki, J., van der Meer, D., Alnæs, D., Kaufmann, T., Córdova-Palomera, A., Dieset, I., Andreassen, O.A., Westlye, L.T., 2019. Oxytocin pathway gene networks in the human brain. Nature Communications 10, 668.

https://doi.org/10.1038/s41467-019-08503-8

Related work by KG Jebsen Centre for Neurodevelopmental Disorders/ Paediatric division authors:

2. Rokicki, J., Kaufmann, T., Glasø de Lange, A.-M., van der Meer, D., Bahrami, S., Sartorius, A.M., K. Haukvik, U., Eiel Steen, N., Schwarz, E., Stein, D.J., Nærland, T., Andreassen, O.A., Westlye, L.T., Quintana, D., 2022. Oxytocin receptor expression patterns in the human brain across development. Neuropsychopharmacology 47, 1550–1560. https://doi.org/10.1038/s41386-022-01305-5

3. Quintana, D.S., Westlye, L.T., Alnæes, D., Kaufmann, T., Mahmoud, R.A., Smerud, K.T., Djupesland, P.G., Andreassen, O.A., 2019. Low-dose intranasal oxytocin delivered with Breath Powered device modulates pupil diameter and amygdala activity: a randomized controlled pupillometry and fMRI study. Neuropsychopharmacology 44, 306–313. https://doi.org/10.1038/s41386-018-0241-3

4. Quintana, D.S., Westlye, L.T., Rustan, Ø.G., Tesli, N., Poppy, C.L., Smevik, H., Tesli, M., Røine, M., Mahmoud, R.A., Smerud, K., Djupesland, P.G., Andreassen, O.A., 2015. Low dose oxytocin delivred intranasally with Breath Powered device affects social-cognitive behavior: a randomized 4-way crossover trial with nasal cavity dimension assessment. Transl. Psychiatry 5, e602. https://doi.org/10.1038/tp.2015.93

5. Quintana, D.S., Westlye, L.T., Hope, S., Nærland, T., Elvsåshagen, T., Dørum, E., Rustan, Ø., Valstad, M., Rezvaya, L., Lishaugen, H., 2017. Dose-dependent social-cognitive effects of intranasal oxytocin delivered with novel Breath Powered device in adults with autism spectrum disorder: a randomized placebo-controlled double-blind crossover trial. Transl. Psychiatry 7, e1136. https://doi.org/10.1038/tp.2017.103

6. Winterton, A., Bettella, F., Beck, D., Gurholt, T.P., Steen, N.E., Rødevand, L., Westlye, L.T., Andreassen, O.A., Quintana, D.S., 2022. The oxytocin signalling gene pathway contributes to the association between loneliness and cardiometabolic health. Psychoneuroendocrinology 144, 105875. https://doi.org/10.1016/j.psyneuen.2022.105875

4. Details of the impact (indicative maximum 750 words)

This research group has been investigating oxytocin's role in health and wellbeing for over a decade. The impact of the group's work is exemplified by a range of high-impact publications, which have formed the foundation for three upcoming clinical trials, which are funded by the Research Council of Norway, South-Eastern Norway Regional Health Authority, and the Kavli trust.

One trial is investigating the effects of one month oxytocin administration on day-to-day functioning and behavioural flexibility. The other trials are specifically investigating oxytocin's effects on learning, and the neurobiological correlates of changes in learning using EEG. By including an EEG measure of brain activity, this trial will evaluate whether oxytocin's effects on learning are associated with changes in synaptic plasticity.

Most oxytocin trials have historically only included males, thus the inclusion of both males and females in these trials will provide a greater understanding of oxytocin's effects in both sexes and facilitate the evaluation of potential sex differences in response to oxytocin. It is currently unclear which intranasal oxytocin dosage is the most effective in modulating cognition and behavior. Thus, another strength of these two trials on oxytocin's effects on learning is that they will compare two different dosages of intranasal oxytocin against placebo.

The results from the randomised controlled trials have the potential to provide evidence supporting a personalised support for disorders and conditions associated with difficulties relating to social behaviour and behavioural rigidity. Individuals with these disorders or conditions have the potential to benefit from this work. This work has also contributed to the development of a highly cited theory of oxytocin's purpose in health and wellbeing, which has since been tested and successfully corroborated by different international labs. These trials have led to collaborations with various universities around the world, including Heidelberg University (Germany), KU Leuven (Belgium), McGill University (Canada), and Leiden University (Netherlands).

This research on the role of oxytocin in health and wellbeing has led to institutional (University of Oslo Prize for Young Researchers, 2022), national (Royal Norwegian Society of Sciences and Letters Award for Young Researchers - The I.K. Lykkes Prize, 2021), and international awards (International Society for Psychoneuroendocrinology Dirk Hellhammer Award, 2022) for Quintana.

5. Sources to corroborate the impact (indicative maximum of ten references)

Theory article
Quintana, D.S., Guastella, A.J., 2020. An allostatic theory of oxytocin. Trends in Cognitive Sciences 24, 515–528. https://doi.org/10.1016/j.tics.2020.03.008

Support from the Kavli Trust to perform a randomised controlled trial:
https://kavlifondet.no/en/2020/11/university-of-oslo-awarded-kavli-trust-grant-for-new-autism-treatment-trial/

Quintana and Nærland in the leading Newsletter for International Autism research
https://www.spectrumnews.org/opinion/viewpoint/how-to-improve-oxytocin-research-for-autism/

An article on vox.com on the varied roles of oxytocin:
https://www.vox.com/science-and-health/2019/2/13/18221876/oxytocin-morality-valentines

The University of Oslo Young researcher award:
https://www.sv.uio.no/psi/english/about/news/uio-young-researcher-award-to-daniel-quintana.html

The ISPNE Dirk Hellhammer award:
https://www.ispne.net/dirk-hellhammer-award

The Royal Norwegian Society of Sciences and Letters Award for Young Researchers - The I.K. Lykkes Prize: https://www.dknvs.no/priserutmerkelser/vitenskapelige-priser/tidligere-vinnere/

OUS_UiO_BAR: Impact case number 4

Institution: Oslo University Hospital and University in Oslo
Administrative unit: BAR
Title of case study: Enterovirus in type 1 diabetes and celiac disease.
Period when the underpinning research was undertaken: 2012-2023
Period when staff involved in the underpinning research were employed by the submitting institution: 2012-2023
Period when the impact occurred: 2015-2023

1. Summary of the impact (indicative maximum 100 words)

Type 1 diabetes and celiac disease share genetic background and frequently occur in the same individuals. Enterovirus is a group of viruses frequently found in biological samples without causing symptoms but may also cause disease particularly in newborns and immunocompromised. Seroconversion as a sign of recent enterovirus infection has been associated with subsequent onset of type 1 diabetes in some but not all studies. Our studies have identified enterovirus as the only virus in pancreatic sections in newly onset type 1 diabetes. Further, in a landmark study from 2023 we found that antiviral treatment against enterovirus could preserve insulin secretion after diagnosis. In the first observational study on enterovirus and celiac disease, infection was significantly more frequent in cases who later developed celiac disease compared to matched controls.

2. Underpinning research (indicative maximum 500 words)

The main objective of the Diabetes Virus Detection study (*DiViD*) was to collect pancreatic tissue from living subjects very soon after the diagnosis of type 1 diabetes to investigate the presence of viruses. Pancreatic tissue was obtained by laparoscopic pancreatic tail resection in six patients aged 18-40 years in 2013. Due to postoperative complications, though none of these experienced permanent injuries, further recruitment was terminated. The pancreatic tissue samples have been extensively characterized. The DiViD study has so far resulted in around 40 peer-reviewed articles and several theses.

Key researchers in this initial study were PhD student/consultant paediatrician Lars Krogvold and professor Knut Dahl-Jørgensen, who also designed the following intervention study.

An intervention trial was a crucial next step to study whether enterovirus infections could be in the causal pathway towards development of type 1 diabetes. The main objective of the RCT *DiViD intervention study* was to determine the effect of antiviral treatment on beta cell function in children and adolescents from onset of type 1 diabetes. The study recruited 96 newly diagnosed children and adolescents with type 1 diabetes from 2018 to 2020, recruiting from paediatric departments in Norway and Denmark. Results describing the primary endpoint was published in 2023. Two antiviral agents (pleconaril and ribavirin) used in combination was shown to significantly preserve pancreatic beta cell function 12 months after start of treatment when compared to placebo and measured by C-peptide mixed meal tolerance test. More articles regarding secondary and exploratory endpoints will be published in coming years.

For the endpoint of celiac disease, we used data and biobank samples collected in the MIDIA study since 2000. Children with HLA DQ2/DQ8 and a high risk of type 1 diabetes and celiac disease, were

recruited. Monthly fecal samples from 3-36 months were analysed for enterovirus and parechovirus by PCR methods. Parechovirus together with enterovirus belongs to a group of small RNA viruses (picorna). Endpoint was seroconversion for antitransglutaminase IgA as sign of celiac disease after analysis of serum samples collected at 3, 6, 12, 18 and 24 months and thereafter annually. The study was conducted by researchers from Norwegian Institute of Public Health (PI was LC Stene, German Tapia) and University of Oslo (C Kahrs, K Lundin), the co-PI for celiac disease changed position from NIPH to UiO in 2020.

3. References to the research (indicative maximum of six references)

Lars Krogvold, Bjørn Edwin, Trond Buanes, Gun Frisk, Oskar Skog, Mahesh Anagandula, Olle Korsgren, Dag Undlien, Morten C. Eike, Sarah J. Richardson, Pia Leete, Noel G. Morgan, Sami Oikarinen, Maarit Oikarinen, Jutta E. Laiho, Heikki Hyöty, Johnny Ludvigsson, Kristian F. Hanssen and **Knut Dahl-Jørgensen**
Detection of a low-grade enteroviral infection in the islets of langerhans of living patients newly diagnosed with type 1 diabetes (2015)
Diabetes 64(5):1682–1687
https://doi.org/10.2337/db14-1370

Lars Krogvold, Angelo Genoni, Anna Puggioni, Daniela Campani, Sarah J. Richardson, Christine S. Flaxman, Bjørn Edwin, Trond Buanes, **Knut Dahl-Jørgensen**, Antonio Toniolo
Live enteroviruses, but not other viruses, detected in human pancreas at the onset of type 1 diabetes in the DiViD study (2022)
Diabetologia 65:2108–2120
https://doi.org/10.1007/s00125-022-05779-2

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Detection of Antiviral Tissue Responses and Increased Cell Stress in the Pancreatic Islets of Newly Diagnosed Type 1 Diabetes Patients: Results From the DiViD Study (2022)
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BMJ 2019 Vol. 364 Pages l231
https://www.ncbi.nlm.nih.gov/pubmed/30760441

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Parechovirus Infection in Early Childhood and Association With Subsequent Celiac Disease
Am J Gastroenterol 116(4); p788-795

https://journals.lww.com/ajg/abstract/2021/04000/parechovirus_infection_in_early_childhood_and.32.aspx

4. Details of the impact (indicative maximum 750 words)

The Diabetes Virus Detection study (DiViD) was the first to examine fresh pancreatic tissue at the diagnosis of type 1 diabetes for the presence of viruses. Minimal pancreatic tail resection was performed 3– 9 weeks after onset of type 1 diabetes in six adult patients. The presence of enteroviral capsid protein 1 (VP1) and the expression of class I HLA were investigated by immunohistochemistry. Enterovirus RNA was analyzed from isolated pancreatic islets and from fresh-frozen whole pancreatic tissue using PCR and sequencing. Nondiabetic organ donors served as controls. VP1 was detected in the islets of all type 1 diabetic patients (two of nine controls). Hyperexpression of class I HLA molecules was found in the islets of all patients (one of nine controls). Enterovirus-specific RNA sequences were detected in four of six patients (zero of six controls). The results were confirmed in various laboratories. Only 1.7% of the islets contained VP1+ cells, and the amount of enterovirus RNA was low.

The results provide evidence for the presence of enterovirus in pancreatic islets of type 1 diabetic patients, which is consistent with the possibility that a low-grade enteroviral infection in the pancreatic islets contributes to disease progression in humans.

We further explored multiple human virus species using innovative methods, including virus passage in cell cultures. The results, based on sensitive assays, confirmed that the pancreases of all DiViD cases contain EVs but no other viruses. The detected EV strains can be passaged in series from one cell culture to another in the form of poorly replicating live viruses encoding antigenic proteins recognised by multiple EV-specific antibodies. Thus, the early phase of type 1 diabetes is associated with a low-grade infection by EVs, but not by other viral agents.

These observations resulted in the antiviral intervention study, which supported the concept that enterovirus is a modifiable factor in the pathway leading to beta cell loss and cessation of insulin production in susceptible individuals.

The DiViD studies have been led from OUS/UiO BAR, but with collaboration across paediatric departments in Norway and Denmark. Specimens have been obtained nationally, but some of the laboratory studies performed in collaboration with leading research environments in Finland and Italy. Dissemination has been in leading journals in biomedicine and presented in prestigious international meetings.

The research on viral infections before the onset of celiac disease are observational and admittedly small studies, which need further corroboration. The findings for enterovirus have been replicated in two subsequent studies from other groups. Currently, we have started a collaboration with these two groups (in the EU-funded HEDIMED study, characterizing the exposome in immune-mediated diseases). This project will gain more in-depth understanding by application of different methods including intestinal organoids and intestinal biopsies to further explore whether low-grade viral infections are in the causal pathway in celiac disease.

Enterovirus infections can be prevented (with a new vaccine) and treated (with antiviral medications). If proven to be beneficial, this would be a novel therapy for two common autoimmune diseases in childhood which so far have not been possible to prevent or cure.

5. Sources to corroborate the impact

Type 1 diabetes-early life origins and changing epidemiology
J. M. Norris, R. K. Johnson and L. C. Stene
Lancet Diabetes Endocrinol 2020 Vol. 8 Issue 3 Pages 226-238
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7332108/pdf/nihms-1603295.pdf

Exposomic determinants of immune-mediated diseases: Special focus on type 1 diabetes, celiac disease, asthma, and allergies: The HEDIMED project approach (2022).
J. E. Laiho, O. H. Laitinen, J. Malkamaki, L. Puustinen, A. Sinkkonen, J. Parkka, Hyoty, H.
Environ Epidemiol 2022 Vol. 6 Issue 3 Pages e212.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9187189/pdf/ee9-6-e212.pdf

Metagenomics of the faecal virome indicate a cumulative effect of enterovirus and gluten amount on the risk of coeliac disease autoimmunity in genetically at risk children: the TEDDY study
K. Lindfors, J. Lin, H. S. Lee, H. Hyoty, M. Nykter, K. Kurppa, et al.
Gut 2020 Vol. 69 Issue 8 Pages 1416-1422
https://gut.bmj.com/content/gutjnl/69/8/1416.full.pdf

Coeliac disease: what can we learn from prospective studies about disease risk?
M. Stahl, S. Koletzko, C. Andren Aronsson, K. Lindfors, E. Liu, D. Agardh, et al.
Lancet Child Adolesc Health 2024 Vol. 8 Issue 1 Pages 63-74
https://www.thelancet.com/journals/lanchi/article/PIIS2352-4642(23)00232-8/fulltext

Oslo University Hospital and University of Oslo, Division of Cancer Medicine - Case 1

Institution: Oslo University Hospital and University of Oslo
Administrative unit: Division of Cancer Medicine (DCM)
Title of case study: Impact of underpinning cancer research – Consequences of its organisation in the RCN CoE Centre for Cancer Biomedicine (CCB) and the subsequently developed portfolio
Period when the underpinning research was undertaken: 01.01.2008- 31.12.2017
Period when staff involved in the underpinning research were employed by the submitting institution: 01.01.2008 – 31.12.2017
Period when the impact occurred: 01.01.2012 – 31.12.2022

1. Summary of the impact (indicative maximum 100 words)

CCB, a Norwegian Centre of Excellence by RCN funded in the 2nd cycle of CoEs, achieved ground-breaking insight into the biological mechanisms of cancer development, as well as biological factors that can aid diagnosis and guide precision cancer medicine. Results from the centre were published in leading journals, including as many as 13 articles in *Nature* and *Science*, of which 8 had CCB scientists as corresponding authors. The educational program of the centre led to 61 PhD degrees. The wider impact of CCB is illustrated by the fact that CCB scientists have headed several additional joint high-impact projects and centres during and after the CCB period. These include the Norwegian Centre of Excellence, CanCell, the two KG Jebsen Centres for Colorectal Cancer Research and Blood Cancer Research, the lighthouse project, DoMore!, two consecutive OUH Strategic Research Areas on Colorectal Cancer, the National Nanoparticle Project, NanoCan, the two ERC Advanced Grant Projects, "PI3K-III complex" and "CODE", the National Microscopy Infrastructure Network, NALMIN, the two RCN "Toppforsk" grants, «Modeling tumor heterogeneity in colorectal cancer management» and "Deciphering tumor-host biology", and the Norwegian Cancer Genomics Consortium (as work package leaders).

2. Underpinning research (indicative maximum 500 words) The vision of CCB was to unite basic and translational cancer research for the benefit of future patients. In other words, interdisciplinary collaborations in cancer research were the main rationale for establishing CCB. The basic cancer research (exemplified in papers 1 and 6-9 in Section 3) involved cell and developmental biology whereas the translational research (exemplified in papers 2-5 and 10) included cancer genomics, epigenetics and transcriptomics, and with extensive involvement of researchers of several medical professions. Experts in bioinformatics and biostatistics were important for analyzing complex data that "bridged" the basic and translational research. As an important step in the ambitions to achieve impact beyond academia, bringing scientific discoveries from bench to bedside and foster commercial interest, CCB scientists filed as many as 36 patent applications for their scientific innovations. These have so far resulted in 24 granted patents, ranging from applications of novel biomarkers for cancer diagnosis and personalized therapy to novel informatics and bioinformatics tools and apps for smartphones. Commercial development of these products may ultimately benefit health care personnel as well as cancer patients. CCB also had an active educational and early career development portfolio. During CCB´s lifetime, 61 PhD students finished their degree, and 10 young scientists obtained permanent positions as group leaders or associate professors.

3. References to the research (CCB scientists in bold)

The majority of selected references showcase the interdisciplinary collaborations enabled within CCB. Furthermore, the long-term funding provided by the centre was essential for the opportunity to raise the ambitions of several projects.

1.**Ågesen TH, Sveen A, Merok MA, Lind GE**, Nesbakken A, **Skotheim RI, Lothe RA** (2012). ColoGuideEx: a robust gene classifier specific for stage II colorectal cancer prognosis. *Gut* 61: 1560-1567

This paper presented ColoGuideEx, a 13-gene expression classifier for evaluation of patient prognosis. ColoGuideEx enables prediction of disease relapse after surgery for stage II colorectal cancer, which has consequences for personalized treatment decisions regarding adjuvant chemotherapy.

The two shared first authors were PhD students in CCB whereas the last and corresponding author was PI and co-director of CCB. A CCB bioinformatician and a CCB clinical associate contributed extensively to the study. All work was performed in CCB.

2. **Brodtkorb M**, Lingjærde OC, **Huse K,** Trøen G, Hystad M, Hilden VI, **Myklebust JH**, Leich E, Rosenwald A, Delabie J, Holte H, **Smeland EB** (2014). Whole-genome integrative analysis reveals expression signatures predicting transformation in follicular lymphoma. *Blood* 13:1051-1054.

This paper addresses the problem that transformation of follicular lymphoma to a more aggressive disease is associated with rapid disease progression and death. The study identifies genes regulating B-cell survival and activation as key players in transformation of follicular lymphoma, thus pinpointing novel therapeutic targets.

The first author was PhD student in CCB whereas the last (and corresponding) author was PI in CCB. The biostatistics group in CCB contributed with statistical analyses of big data, a CCB visiting professor contributed with pathology analyses, and a CCB associate clinician contributed with biobanking and clinical evaluations. The research was carried out in CCB.

3. **Vietri M, Schink KO, Campsteijn C, Wegner CS, Schultz SW, Christ L, Thoresen SB, Brech A, Raiborg C and Stenmark H** (2015). Spastin and ESCRT-III coordinate mitotic spindle disassembly and nuclear envelope sealing. *Nature* 522: 231-235

This paper establishes a mechanism for disassembly of the mitotic spindle at mitotic exit and sealing of the newly formed nuclear envelope. Interference with this mechanism is shown to cause DNA damage, which is associated with cancer development. The paper was dedicated commentary articles in both *Nature* and *Science*, which is rather exceptional.

The first author was a PhD student in CCB (she received H.M. the King's gold medal for her PhD), and the last author is PI and director of CCB. The other corresponding author, CC, was a project leader in CCB. All co-authors of this paper were also CCB members. The research was carried out in CCB.

4. **Raiborg C, Wenzel EM, Pedersen NM**, Olsvik H, **Schink KO, Schultz SW, Vietri M**, Nisi V, Bucci C, **Brech A**, Johansen T and **Stenmark H** (2015). Repeated ER-endosome contacts promote endosome translocation and neurite outgrowth. *Nature* 520: 234-238

This paper establishes a novel concept in cell biology, namely that contact sites between endosomes and the endoplasmic reticulum fuel motor-driven translocation of endosomes towards the plasma membrane, and that fusion of endosomes with the plasma membrane promotes protrusion outgrowth. This is relevant both for neurobiology and cancer. The paper was dedicated commentary articles in *EMBO Journal* and *Bioessays*.

The first author was project leader in CCB and the last author was PI and director of CCB (both these author were corresponding authors). Except for two national and two international collaborators, all co-authors were CCB members. About 95% of the research was carried out in CCB.

5. **Katheder N, Khezri R, O'Farrell F, Schultz SW, Jain A, Rahman MM, Schink KO**, Theodossiou T, Johansen T, Juhasz G, Bilder D, **Brech A, Stenmark H and Rusten TE** (2017). Microenvironmental autophagy promotes tumour growth. *Nature* 541: 417-420

This paper demonstrates that tumours induce autophagy, cellular self-eating, in the tumour microenvironment. This causes production of amino acids that fuel further tumour growth. If autophagy in the microenvironment is inhibited by genetic or pharmacological means, the tumour shrinks, opening possibilities for new therapeutic strategies. The paper was covered by national TV news and was dedicated commentary articles in *Developmental Cell*, *Cell Metabolism* and *Science Signaling*.

The first author was PhD student in CCB and the corresponding author was a project leader in one of the CCB groups (he now has his own group in a new CoE, CanCell). Except for two national and two international collaborators, all co-authors were CCB scientists. The research was carried out in CCB.

6.Sveen A, **Johannessen B**, **Tengs T**, **Danielsen SA**, **Eilertsen IA**, **Lind GE**, **Berg KCG**, **Leithe E**, Meza-Zepeda LA, Domingo E, Myklebost O, Kerr D, Tomlinson I, Nesbakken A, **Skotheim RI**, **Lothe RA** (2017). Multilevel genomics of colorectal cancers with microsatellite instability-clinical impact of JAK1 mutations and consensus molecular subtype 1. Genome Med. 9:46

Novel mutations were identified and associated with immune modulation in colorectal cancers with the hypermutation phenotype microsatellite instability. Integrative "omics"-analyses were used to identify substantial tumor heterogeneity in this "immune-hot" subtype. Truncating *JAK1* mutations were proposed as a resistance mechanism for immune checkpoint inhibition. This has later been confirmed in other studies. Selected "Research Highlight" by the Journal Editors, who emphasized the potential consequences for immunotherapy (Samstein and Chan *Genome Med*; 9: 45).

The three, shared first authors were CCB scientists and the senior and corresponding author was PI and co-director of CCB. All work was performed in CCB and included international partners and collaborators in the Norwegian Cancer Genomics Consortium.

4. Details of the impact (indicative maximum 750 words)

The underpinning research in CCB, described in Sections 2 and 3, had impact for a number of centres, projects and beneficiaries:

- Establishment of a new Norwegian Centre of Excellence, Centre for Cancer Cell Reprogramming (CanCell). This centre with a budget from the Research Council of 167 MNOK was established in 2018 by CCB director Harald Stenmark and involves 3 scientists trained in junior positions in

CCB (Anne Simonsen, Tor Erik Rusten and Jørgen Wesche) as PIs. Cell biological discoveries made in CCB (for instance, papers no. 3-5 in Section 3) formed the basis for CanCell´s research program, which is funded by the Research Council until end of 2028. Beneficiaries: University of Oslo (project owner), Oslo University Hospital (consortium partner), patient societies (blood cancer, prostate cancer, childhood cancer, sarcoma, lung cancer).

- Establishment of a new KG Jebsen Centre for Translational Research, the KG Jebsen Colorectal Cancer Research Centre. This centre was established by CCB co-director Ragnhild A. Lothe and involved 3 scientists trained in junior positions at CCB (Rolf I. Skotheim, Guro E. Lind and Anita Sveen) as PIs. Translational research discoveries made in CCB (for instance, papers no. 1 and 6 in Section 3) were continued in the KG Jebsen Centre´s research program. Beneficiaries: Oslo University Hospital (project owner), University of Oslo (consortium partner), NORILCO (patient society).

- Establishment of a new KG Jebsen Centre for Translational Research, the KG Jebsen Centre for B-Cell Cancer (2018-2024). CCB PI Erlend B. Smeland was involved in establishing the centre, and June H. Myklebust, a junior scientist in CCB, is a PI of the KG Jebsen Centre. Some of the research in the centre is based on findings in paper 2 in Section 3. Beneficiaries: Oslo University Hospital (project owner), University of Oslo (consortium partner), Blood Cancer Society.

- Establishment of a new Lighthouse Project, Domore!. This centre with a budget from the Research Council of 60 MNOK was established by CCB PIs Håvard Danielsen (director) and Knut Liestøl (co-director) and was largely based on research Danielsen´s group performed in CCB. Two scientists trained in junior positions at CCB (Tarjei Hveem and John Arne Nesheim) were WP leaders. The DoMore! project (2016-2021) contributed to the digitalization of pathology and paved the way for the transition from digital pathology to in silico pathology, in addition to introducing AI and Deep Learning into tissue diagnostics. Beneficiaries: Oslo University Hospital. Patients with prostate, colorectal or lung cancer. The Norwegian Cancer Society. DoMore Diagnostics (a spin-off company).

- Establishment of a Strategic Research Area of Oslo University Hospital, SMART Colorectal Cancer. This multi-disciplinary priority area was established by CCB co-director Ragnhild A. Lothe and CCB Associate Member Arild Nesbakken. This interdisciplinary research program benefits from translational research resources and discoveries made during the CCB period (for instance, paper 1 and 6 in Section 3). The Priority Area addressed several challenges in the treatment of colorectal cancer, a cancer with poor prognosis if not diagnosed early. Such challenges include introduction of novel biomarkers for early detection, prediction of benefit of surgery after metastasis, and prediction of benefit of chemotherapy in conjunction with surgery. The translational research program is continued in a second consecutive Strategic Research Area, TEAM-ACT, focusing on personalized treatment modelling in patient-derived tumor organoids. Beneficiaries: Oslo University Hospital, NORILCO (patient organization).

- Establishment of a National Research Project under “Nanotechnology and New Materials”, “Biodegradable Nanoparticles in Cancer Diagnosis and Therapy (NanoCan)”. This project (2013-2019) with a budget from the Research Council of 30 MNOK was established by CCB PI Kirsten Sandvig and involved CCB junior scientist Tore-Geir Iversen as WP leader. Beneficiaries: Oslo University Hospital (project owner), University of Oslo (consortium partner), NTNU (consortium partner), SINTEF (consortium partner).

- Establishment of a National Infrastructure, Norwegian Advanced Light Microscopy Imaging Network (NALMIN). This national network was established in 2016 by CCB director Harald

Stenmark with an original budget from the Research Council of 52 MNOK. The network was awarded new funding from the Research Council (NALMIN-II) in 2022 with 71.5 MNOK and has a planned duration until 2032. Current nodes are located at University of Oslo (two nodes at Faculty of Medicine, one node at Faculty of Mathematics and Natural Sciences), Oslo University Hospital, University of Bergen, NTNU, and University of Tromsø. NALMIN is member of a European Research Infrastructure Consortium, Euro-BioImaging. Beneficiaries: University of Oslo (project owner), Universities of Bergen, Trondheim and Tromsø (consortium partner), Oslo University Hospital (consortium partner), all Norwegian life scientists who need to perform advanced light microscopy.

- Acquisition of an ERC Advanced Grant, "The PI3K-III complex: Function in cell regulation and tumour suppression". The grant of 2.27 MEUR was obtained by CCB director Harald Stenmark in 2008 and had a duration until 2012. The background for the grant were results obtained in the early phase of CCB. Beneficiaries: University of Oslo (project owner), Oslo University Hospital (consortium partner).

- Acquisition of an ERC Advanced Grant, "Coincidence detection of proteins and lipids in regulation of cellular membrane dynamics (CODE)". The grant of 2.5 MEUR was obtained by CCB director Harald Stenmark and has a duration of 2018-2024. The grant was based on results obtained in CCB, especially papers no. 3-4 in Section 3. Beneficiaries: University of Oslo (project owner), Oslo University Hospital (consortium partner).

- Acquisition of a Toppforsk Grant funded by the Research Council and University of Oslo with 25 MNOK, «Modeling tumor heterogeneity in colorectal cancer management». The grant was obtained by CCB co-director Ragnhild Lothe and partly involved a continuation of results and resources developed during CCB, such as papers 1 and 6 in Section 3. Beneficiaries: University of Oslo (project owner), Oslo University Hospital (consortium partner).

- Acquisition of a Toppforsk Grant funded by the Research Council and University of Oslo with 25 MNOK, "Deciphering tumor-host biology". The grant was obtained by Tor Erik Rusten, who was a project leader in CCB and obtained one of two associate professorships provided by the University of Oslo as part of CCB´s exit strategy. The grant had a duration of 2018-2023 and was largely based on results obtained in paper no. 5 in Section 3. Beneficiaries: University of Oslo (project owner), Oslo University Hospital (consortium partner).

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5. Sources to corroborate the impact (indicative maximum of ten references)

See the following links for sources

Centres of Excellence

KG Jebsen Centres

OUS Priority Areas

Lighthouse Projects

National Research Infrastructures

Nanotechnology and New Materials

ERC Projects

Toppforsk Grants

Oslo University Hospital and University of Oslo, Division of Cancer Medicine Case 2

Institution: Oslo University Hospital and University of Oslo (UiO)
Administrative unit: Division of Cancer Medicine (DCM)
Title of case study: OUS Immune Oncology (OUS-IO): From Discovery Research to Clinical Translation
Period when the underpinning research was undertaken: 2012-2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2012-2022
Period when the impact occurred: 2012-2022 and beyond

Summary of the impact
The OUS-IO impact case demonstrates significant advancements in cancer immunotherapy, particularly in identifying novel tumor antigens, T cell receptors, CARs, and overcoming immune suppression in tumors. The quality of the underpinning research has led to partnerships in international consortia supported by competitive funding schemes from EU, ERC, NIH and CRUK and most recently paved the way for a new Centre of Excellence in Precision Immunotherapy, PRIMA. We also describe the successful establishment of a novel national infrastructure for manufacturing of advanced therapy medicinal products (ATMPs), and a clinical trial engine within MATRIX, an RCN-funded Centre of Excellence in Clinical Research. The impact is further illustrated in strong industry partnerships, and significant contributions to clinical trials, positioning OUS as an international leader in precision immunotherapy research.

2. Underpinning research (indicative maximum 500 words)
In this impact case, we highlight scientific and infrastructural advances that together have contributed to the establishment of an internationally leading research environment at OUS in the very competitive area of immune-oncology (IO).

i) Scientific Breakthrough 1: New technologies for discovery of novel classes of tumor antigens and T cell receptors (TCRs)(ref 3), and identification of new CARs: Johanna Olweus (JO) and her team developed a breakthrough concept, inducing healthy donor T cells to recognize mutations ignored by the patient immune system (**Science 2016**, IF = 47) and **Nat Protoc 2019**, IF = 17). They used the technology to generate a TCR reactive to a shared mutation in acute myeloid leukemia (**Nat Cancer 2023** (IF=23). They also demonstrated targeting of tumor-associated self-antigens (**PNAS 2014**, IF = 11.1, including the novel target TdT in T/B-acute lymphoblastic leukemia (**Nat Biotechnol 2021** (IF = 46). They further showed that translational mistakes in cancer cells can represent novel immunotherapy targets, as co-authors in two collaborations (**Nature 2021**, and **Nature 2022** (IF=64). Two additional independent CAR-T cell programs, one co-lead by Else-Marit Inderberg (EMI) and Sebastien Walchli (SW), is focusing on novel CARs against Sarcoma and Malignant Lymphoma, and one led by Jon-Amund Kyte (JAK) is focusing on solid tumors (**Blood Adv 2019** (IF=7,6), **JBC 2021** (IF=5,5), **Nat Comm 2023**) (IF=16,6).
ii) Scientific Breakthrough 2: Overcoming suppressive mechanisms driving functional disarming and exhaustion of immune effector cells: During her post-doc at Stanford, OUS scientist Chloe Steen (CS), currently in June Myklebust (JM) Lab, developed a deep-learning framework to decode transcriptional signatures and cellular communities in the TME **Cell 2021** (IF=67) and **Cancer Cell 2021** (IF = 50). Another tool developed by Karl-Johan Malmberg (KJM) and his team allows integration of high-resolution flow cytometry or mass cytometry data with clinical meta-data to interrogate phenotypic and functional states across large cohorts of patients in diagnostic biopsies or longitudinally during therapeutic interventions **Med 2021** (IF = 17). Together these publications

demonstrate great variability in the types of multicellular tumor ecosystems in different patients with the same cancer type, but also identify targets for immunomodulation, including regulatory T cells and myeloid-derived suppressor cells. In this context, Kjetil Taskén (KT) has investigated mechanisms of activation of human Tregs and examined the role of several drug classes (PI3Ki, MEKi, STAT3i, FAKi) as Treg inhibitors for potential drug repurposing in **Science Signaling 2021** (IF=9.7), **J Clin Oncol 2016** (IF=45) and **Nat Chem Biol 2012** (IF= 14.8).

iii) Clinical breakthrough: Development of IO clinical programs based on in-house developed concepts and infrastructure to support them: KJM leads a team-based international clinical program harnessing the intrinsic cytolytic potential of NK cells (**Clin Cancer Res 2018,** IF = 11,5). Arne Kolstad was PI (JO co-PI) for the first-in-human cell therapy trial LYMVAC I (NCT01926639) in follicular lymphoma, demonstrating T-cell-mediated tumor regression (**Blood 2015,** IF 22)**.** To enable in-house development of new cell and gene therapies from i) *(see above),* the Centre for Advanced Cell and Gene Therapy (**ACT centre**), led by Anna Pasetto (AP) opened May 2021. It is further supported by a new Clinical Center of Excellence **MATRIX** with a dedicated clinical trial engine led by JAK. In addition to these ATMP programs, JAK has led two randomized trials (ALICE and ICON), evaluating addition of immune checkpoint inhibitors (ICI) to chemotherapy in metastatic breast cancer (mBC). ALICE (**Nat Med 2022**, IF = 83) is the first trial to show benefit from adding immune check point therapy (ICI) to chemotherapy in PD-L1-negative metastatic breast cancer. This finding supports the use of selected chemotherapy to make "immune-cold" tumors responsive to ICI.

Karl-Johan Malmberg (KJM), M.D., Ph.D., Prof. Director, Center of Excellence; Precision Immunotherapy Alliance (PRIMA) 2023-28, and Dept of Cancer Immunology, UiO & OUS.
Johanna Olweus (JO), M.D:, Ph.D., Prof. Head Dept of Cancer Immunology, Director, Center of Excellence; Precision Immunotherapy Alliance (PRIMA) 2029-33, OUS and UIO.
Kjetil Taskén (KT), M.D., Ph.D., Prof., Head Institute for Cancer Research, DCM, OUS, and UiO.
Jon-Amund Kyte (JAK), M.D., Ph.D., Head of the Clinical Trial Unit, Dept. Oncology, OUS
June Myklebust (JM), Ph.D. Deputy head, Dept of Cancer Immunology, OUS and UiO
Anna Pasetto (AP), Ph.D., Director Center for Advanced Cell and Gene Therapy, OUS and UiO
Else-Marit Inderberg (EMI), Head of Translational Research Unit, Dept. Oncology, OUS
Sebastien Walchli (SW), Senior Researcher, Section for Cell Therapy, Dept. Oncology, OUS
Chloe Steen (CS), Ph.D., Scientist, Department of Cancer Immunology, OUS
Åslaug Helland (ÅH), M.D., Ph.D., Professor, Centre Leader MATRIX – Norwegian Ctr for Clinical Cancer Research, Research Director, OUS Comprehensive Cancer Centre
Arne Kolstad, M.D., Senior Consultant. Previous leader of Strategic research area in cancer immunotherapy, Dept. Oncology, OUS
Trevor Clancy (TC), Former Scientist at OUS, Former CSO at NEC Oncoimmunity.

3. References to the research (Authors from OUS in bold)

Reference 1:

Authors: **Muhammad Ali**, **Eirini Giannakopoulou**, Yingqian Li, Madeleine Lehander, Stina Virding Culleton, **Weiwen Yang**, **Cathrine Knetter**, Mete Can Odabasi, **Ravi Chand Bollineni**, Xinbo Yang, **Zsofia Foldvari**, **Maxi-Lu Böschen**, **Eli Taraldsrud**, **Erlend Strønen**, Mireille Toebes, Amy Hillen, Stefania Mazzi, Arnoud H. de Ru, George M. C. Janssen, **Arne Kolstad**, **Geir Erland Tjønnfjord**, **Benedicte A. Lie**, Marieke Griffioen, Sören Lehmann, Liv Toril Osnes, **Jochen Buechner**, K. Christopher Garcia, Ton N. Schumacher, Peter A. van Veelen, Matthias Leisegang, Sten Eirik W. Jacobsen, Petter Woll & **Johanna Olweus**.
Title: T cells targeted to TdT kill leukemic lymphoblasts while sparing normal lymphocytes
Year: 2022 ***Nature Biotechnol,*** **IF = 46** *2022 https://www.nature.com/articles/s41587-021-01089-x*

Reference 2:

Authors: **Strønen E**, Toebes M, Kelderman S, van Buuren MM, **Yang W**, van Rooij N, Donia M, **Böschen ML**, **Lund-Johansen F, Olweus J*,** Schumacher TN*. **Shared senior and corresponding authors*
Title: Targeting of cancer neoantigens with donor-derived T cell receptor repertoires.
Year: 2016 ***Science*** **IF=47** https://www.science.org/doi/10.1126/science.aaf2288
Commentary articles in: Science, N Engl J Med, and in Mol Ther **2016**

Reference 3:
Authors: **Ask, E.H., Tschan-Plessl, A., Gjerdingen, T.J**., **Saetersmoen, M.L., Hoel, H.J., Wiiger, M.T., Olweus, J**., Wahlin, B.E., Lingjaerde, O.C., Horowitz, A., Cashen, A.F., Watkins, M., Fehniger, T.A., Holte, H., Kolstad, A. and **Malmberg, K.J.**
Title: A Systemic Protein Deviation Score Linked to PD-1(+) CD8(+) T Cell Expansion That Predicts Overall Survival in Diffuse Large B Cell Lymphoma.
Year: 2021 ***Med*** **IF = 17** *DOI: 10.1016/j.medj.2020.10.006*
https://pubmed.ncbi.nlm.nih.gov/35590201/

Reference 4:
Authors: **Steen CB***, Luca BA*, Esfahani MS, Nabet BY, Sworder BJ, Kurtz DM, Liu CL, Azizi A, Khameneh F, Advani RH, Natkunam Y, **Myklebust JH**, Diehn M, Gentles AJ, Newman AM, Alizadeh AA.
Title: The Landscape of Tumor Cell States and Ecosystems in Diffuse Large B Cell Lymphoma.
Year: 2021
Cancer Cell **IF = 50** /2021/ DOI: 10.1016/j.ccell.2021.08.011.
https://www.cell.com/cancer-cell/fulltext/S1535-6108(21)00451-7

Reference 5:
Authors: **Lone AM**, Giansanti P, **Jørgensen MJ**, Gjerga E, Dugourd A, Scholten A, Saez-Rodriguez J, Heck AJR, **Taskén K.**
Title: Systems approach reveals distinct and shared signaling networks of the four PGE_2 receptors in T cells.
Year: 2021 ***Science Signal*** **IF = 9,7** */2021/*DOI: 10.1126/scisignal.abc8579 /

Reference 6:
Authors: **Røssevold AH, Andresen NK**, Bjerre CA, Gilje B, Jakobsen EH, Raj SX, Falk RS, Russnes HG, Jahr T, Mathiesen RR, Lømo J, Garred Ø, **Chauhan SK, Lereim RR, Dunn C**, Naume B, **Kyte JA**[1].
[1]*corresponding author*
Title: Atezolizumab plus anthracycline-based chemotherapy in metastatic triple-negative breast cancer: the randomized, double-blind phase 2b ALICE trial/
Nature Medicine **IF = 87** /2022/ DOI: 10.1038/s41591-022-02126-1. *URL:*
https://www.nature.com/articles/s41591-022-02126-1

4. Details of the impact

A long-term commitment to develop a translational immune oncology program at OUS. The research described in this impact case builds on long-term strategic investments in immunotherapy research at the Division of Cancer Medicine, OUS. During early years (1990-2010), the main focus of immunotherapy research at this unit was on various types of cancer vaccines, including against mutated KRAS (exemplified by a report in **The Lancet, 1995**), eventually leading to spin off companies including Ultimovacs and Circio Holdings ASA (formerly Targovax ASA), with ongoing Phase II programs in combination with ICT.

During the past decade (2012-2022), the focus has shifted towards support for cutting-edge immunology research aiming to gain new insights into the fundamental principles that dictate immune recognition of cancer. This includes discovery research in T-, B- and NK cell biology and development of new computational frameworks for analysis of complex data from large scale sequencing efforts and heterogenous patient samples. The strategic focus on high quality research has resulted in increased numbers of publication in top journals, with first/senior authorships in journals including, **Science**, **Science Signalling**, **Nature Medicine**, **Nature Protocols**, **Nature Biotechnology**, **Nature Cancer**, **Nature Communications**, **Nature Reviews Immunology (in press 2024)**, **Cell**, **Cancer Cell**, **Med**, **Clinical Cancer Research** and numerous publications in **Blood**. Further illustrating the quality of the output, the scientists listed in this impact case have all been successful in acquiring external funding both from national and international sources, including long-term support from **RCN** - Research Council of Norway, **NCS** – Norwegian Cancer Society, **HSØ** – Helse Sør-Øst / South-Eastern Norway Regional Health Authority, **ERC**- European Research Council, EU HE Horizon Europe, **CRUK**. Cancer Research UK and **NIH** – National Institute of Health.

Different constellations of scientists in the OUS-IO case have over the period jointly competed successfully for various national and international network grants and center of excellence schemes. These include ITN network grants: MATURE-NK, a Eurostars grant NK-ENGAGE, and a TRANSCAN-3 grant NK-4-GBM, EU-Horizon 2020 consortium GeneTiga 2022-26. ERPerMed IPerGlio (GBM). Melomanes. Together with some of the world´s foremost experts in artificial intelligence at MIT, in structural biology at Stanford Univ. and in genetics at Harvard, JO is a partner in the MATCHMAKERS consortium, awarded a CRUK/NIH Grand Challenge 25 M$ grant in Dec. 2023.

Innovation and impact of the research in terms of exploitation in the industry sector: Another illustration of the impact made is the extensive collaboration with industry. We reports extensive Partnership with **FATE Therapeutics** on NK cells (KJM) 2017-23 3,3 M$, **Oncopeptides** NK engagers (KJM) 2021- 150k$/y, **Roche** and **BMS** on immunotherapy trials (JAK) 2017-23 (free drugs + 12.8 MNOK), **Nanostring** on biomarkers (JAK) 2018-23 (free assays), **NEC Oncoimmunity** on neoantigen validation (JAK; 2021-23; 3 MNOK) and with **Thermo Fisher** and other leading technology developers for cell therapy (KJM, JAK, EMI), including the CellFit project 23 MNOK all ongoing. JO past collaboration with **Kite/Gilead** 2018-21 (300.000 EUR). Trevor Clancy, a computational scientist and bioinformatician, and employed part time at OUS until 2020, together with Richard Stratford, developed innovative software solutions to guide the discovery of clinically relevant neoantigen-based personalized cancer vaccines. Their startup (OncoImmunity AS) was acquired in 2019 by the multinational NEC Corporation.

A translational pipeline for cutting edge discovery research and clinical implementation of new biological insights in cancer immunotherapy: The impact of the current case goes beyond the reporting period. Firstly, KJM and JO, together with five other PIs, including JM, was awarded a 10-year Center of Excellence grant of 155MNOK from the Research Council of Norway (RCN): The Precision Immunotherapy Alliance (PRIMA). PRIMA was launched June 2023. PRIMA will develop new therapeutic concepts to be translated into first-in-man cell and gene therapy trials. Secondly, the formation of a new Centre for Advanced Cell and Gene Therapy (ACT) launched May 2021, supported by a private donor consortium and the recruitment of Dr Anna Pasetto as the Director in April 2022. The ACT centre has established a single point-of-entry with transparent review of new protocols, acquired new instrumentation for cell isolation and gene editing under full GMP. The center has established a pricing model and already attracted both academic and industry customers and is expected to be self-financed by the end of 2026. Thirdly, ÅH, KT and JAK are in the management team of a new Norwegian Centre for Cancer Research (MATRIX), supported by

the RCN. Within MATRIX, ÅH leads WP2 (w WP2b focus on IO) and JAK leads a dedicated work package (WP4) focusing on establishing a clinical trial engine. This support function will contribute to make the initiation of new cell therapy trials more efficient. **Altogether, PRIMA, ACT and MATRIX provide a seamless pipeline from discovery research to clinical translation, with potential of placing Norway at the international forefront in this rapidly evolving field.**

5. Sources to corroborate the impact

Reference 1: Ultimovacs and Targovax Spin-offs based on the historic focus on cancer vaccines at the unit. A clinical investigator initiated study for patients with mesothelioma (NIPU), were presented orally at ESMO 2023. Here patients were randomised to the checkpoint inhibitors ipilimumab and nivolumab +/- the UV1 vaccine from Ultimovacs.

Reference 2: IO-Centers awarded based on scientific excellence: KJM, JO, JAK and KT have had (or have) leadership roles in national centers related to the impact case in immunotherapy, granted on merits of scientific excellence. These include 2 K.G. Jebsen centers (B-cell malignancies , ongoing, Cancer Immunotherapy 2013-19, one Center of Excellence (PRIMA, ongoing), and a clinical Center of Excellence (MATRIX), and two OUS focus areas (Cancer Immunotherapy and Strat-Cell, ongoing).

Reference 3: The impact of the TCR discovery platform and TCR-T cell program: OUTSOURCE: An ERC Consolidator grant to Johanna Olweus 2020-25. A publication describing the TdT TCR generated in the project was published in Nat Biotechnol 2022 (IF = 68). A commentary on the paper was published in Cancer Discovery (IF=37). Recently, JO published another article in Nature Cancer (IF=23), and received and ERC Proof-of-concept grant, based on work performed in the OUTSOURCE project in 2020-22 .

Reference 4: Examples of Clinical IO trials based on in-house concepts published in prestigious journals: JAK was PI for the ALICE trial published in Nature Medicine. https://www.matrix-fkb.no/en/news/data-from-the-alice-trial-published-in-nature-medicine
AK was PI (JO co-PI) for the LYMVAC I trial in follicular lymphoma (NCT01926639), demonstrating T-cell-mediated tumor regression Blood 2015, (IF 22). KJM led the first allogeneic NK cell therapy trial against AML and MDS. Clinical Cancer Research 2018, (IF = 13,8).

Reference 5: A National Center for Advanced Cell and Gene Therapy (ACT). ACT opened thanks to a generous private donation of 50 mNOK (years 2021-2026) from SAMfond (lead donor), the Norwegian Cancer Society, and RADFORSK investeringsstiftelse.

Reference 6: Clinical Center of Excellence MATRIX, funded 2022-30, promoting clinical trials for patients with a strong medical need. MATRIX comprises hospitals across Norway.

Reference 7: Examples of Industry collaboration, licensing of IP within the OUS-IO case: Malmberg and Fate Therapeutics. Media coverage 2018 of collaboration between Olweus and Kite Pharma

Reference 8: Successful exit of AI neoantigen prediction softaware startup. NEC OncoImmunity https://www.nec.com/en/press/201907/global_20190729_01.html

Reference 9: Zelluna, an Oslo-based IO company delivering innovative TCR-NK cell therapy based on discovery research at the unit.
https://www.zelluna.com/news

Oslo University Hospital, Division of Cancer Medicine, Case number 3

Institution:	Oslo University Hospital (OUS)
Administrative unit:	Division of Cancer Medicine (DCM) and OUS Comprehensive Cancer Ctr.
Title of case study:	Development of national precision cancer medicine (PCM) implementation initiative
Period when the underpinning research was undertaken: 2012-2018 (and also w later papers)	
Period when staff involved in the underpinning research were employed by the submitting institution: From 1999 and earlier and till today	
Period when the impact occurred: 2019-2022 and beyond	

4. Summary of the impact

Until 2019, Norwegian cancer patients had very limited access to **molecular cancer diagnostics and precision cancer medicine (PCM)** in the health care. However, the introduction of genomic medicine in cancer in Norway had paved the way (see pt. 2 below). From 2019, a bottom-up and top-down coordinated effort lead by DCM, OUS, involving oncology, hematology and pathology environments nationally, has resulted in (i) the formation of the national **Infrastructure for Precision Cancer Diagnostics, InPreD**, which runs extended gene panel analyses and other techniques and organises a **national molecular tumor board** (MTB) as part of the health care services, (ii) the **IMPRESS-Norway** clinical trial for PCM, currently with 24 drugs in algorithm, including patients at all hospitals in Norway treating cancer patients, (iii) **the CONNECT Public-Private partnership** (18 pharma, 12 public and NGO partners), and (iv) the **Norwegian Centre for Clinical Cancer Research, MATRIX** for new PCM diagnostics and treatment. In addition, collaboration with >20 international partners on trials and data aggregation is established and we lead or co-lead PCM projects funded by EU4Health under the Europe Beating Cancer plan and Horizon Europe under the EU Mission Cancer (**PCM4EU**, **PRIME-ROSE** a.o.) and have taken a significant position in PCM in Europe.

2. Underpinning research

Genomic medicine was developing in Norway from 1999 with the Norwegian Microarray Consortium (NMC) by DCM scientists a.o., funded by RCN as a national platform for functional genomics from 2002 and from 2007 as a RCN national infrastructure for sequencing, **NorSeq**, headed by OUS (see also Impact Case on Genomic Medicine, by OUS Division of Laboratory Medicine). Early involvement of DCM researchers in genomic medicine in cancer involved development and characterization of gene expression-based classifiers such as the PAM50/Prosigna assay (PNAS, 2001), validated in a national trial (EMIT-EBC) and included as standard-of-care for breast cancer, and ColoGuideEx/ColoGuidePro for evaluation of patient prognosis and enabling personalized treatment decisions (Gut, 2012; Clin Cancer Res., 2012).

At this time, **precision cancer medicine (PCM)** was still in its infancy, but at the initiative of researchers in DCM, OUS, the RCN funded a national initiative, the **Norwegian Cancer Genomics Consortium** (NCGC) from 2012 to 2018. NCGC contributed to genome-wide sequencing of >1000 tumor-normal pairs of different cancer diagnoses (nine major types), established **large-scale tumor sequencing (NGS)** in Norway with laboratory and computational procedures (Bioinformatics, 2018 ao), and enhanced the knowledge of cancer-specific genomic aberrations, for example in lymphoma, sarcoma, colorectal cancer, prostate cancer and ovarian cancer as well as of the germ line genetic structure (Blood, 2014, Oncotarget, 2016, Genome Med., 2017, Eur. Urol., 2019, Eur J Hum Genet, 2021 JCI Insight, 2024 ao). Genomic characterization of other cancer types such as lung- and breast cancer, as well as melanoma was also performed (Lung Cancer, 2014, Int J Cancer, 2017, PNAS, 2012, Nature, 2016, Transl. Oncol., 2019). In addition, the RCN funded the **MetAction** project (2012-18), the first clinical trial in Norway, led from DCM, OUS, where the intervention was selected based on broad molecular profiling (NCT02113384) (26

screened and 13 treated patients, Acta Oncol 2020). Importantly, this piloted early molecular- and computational pipelines for clinical translation of PCM and contributed competence in molecular analyses, computational pipelines for interpretation of genomic variants, and composition of multidisciplinary tumor boards (ESMO Open, 2017). In parallel, other PCM trials (TREM-study, ALUR) also helped build competence (Lung Cancer, 2020, ESMO Open, 2022). Furthermore, the **BigMed** project (RCH lighthouse project, 2017-2021) provided a computational environment, a firm bioinformatics pipeline and capacity necessary to set up PCM bioinformatics. Together, this competence-building paved the way for the next steps. However, Norwegian patients did not have access to advanced molecular diagnostics or PCM in a broader context in 2018, which warranted strong efforts from 2019 to establish a PCM implementation initiative and ecosystem for the involvement of all relevant stakeholders, to have an impact on health care and to improve cancer patient access to frontier research results, see pt 4 below.

Names of the key researchers and positions held at the adm. unit at the time of the research.

- Kjetil Taskén, MD, Ph., Prof., Head, Inst. Cancer Res. (ICR), DCM, OUS, and UiO (2018-), led OUS and natl. PCM implementation initiative (2019-), Director OUS-CCC PCM Centre (2021-), Coordinator PRIME-ROSE (2023-), MATRIX WP1 lead (2022-), Trial Mgm. Com. (TMC) IMPRESS-Norway (2020-).
- Åslaug Helland, MD (oncologist), PhD, Prof., Research Director, OUS-CCC (2019-), National PI IMPRESS-Norway (2020-), Ctr Director & WP2 lead MATRIX – Norwegian Ctr for Clinical Cancer Res (2022-), PI in several lung cancer studies using a PCM strategy.
- Hege Russnes, MD (pathologist), PhD, Prof, Head of Sect. for Exp. Pathology, National Coordinator for InPreD, responsible pathologist MetAction (2012-18), Head NorPreM (all 2019-), MATRIX WP1 co-lead, TMC IMPRESS-Norway
- Sigbjørn Smeland, MD (oncologist), PhD, Prof, Head of DCM (from 2010-) and Head of OUS-CCC (2017-), OUS & UiO, Sponsor IMPRESS-Norway (2020-), Chair of Board of CONNECT PPP (2021-)
- Eivind Hovig, Prof, PhD, Director UiO Ctr for Bioinformatics (2018-), Director Bioinformatics CF ICR, DCM, OUS, ELIXIR Node Oslo, PI and Bioinformatics Director NCGC ao. (2012-), InPreD-OUS working group (2019-), Trial Steering Com (TSC), IMPRESS-Norway (2020-)
- Leonardo Meza-Zepeda, PhD, Head Dept of Core Facilities, ICR, DCM (2014-), Director Genomics CF & NorSeq-Cancer (2014-), PI and Technology Platform Director NCGC ao. (2012-), InPreD-OUS working group (2019-), TSC IMPRESS (2020-)
- Ola Myklebost, Prof, PhD, Dept Tumor Biol, ICR, OUS (till 2017), Director NCGC (2012-18)
- Ragnhild A. Lothe, Prof, PhD, Head Dept Mol Oncol, ICR, OUS (2006-), PI NCGC (2012-18), Director of K.G.Jebsen Colorectal Cancer Research Centre (2014-2020), Leader of OUS strategic priority area, colorectal cancer (2014-24), TSC IMPRESS (2021-), PI EVIDENT trial (part of MATRIX) (2022-)
- Gunhild M. Mælandsmo, Prof, PhD, Head Dept Tumor Biol, ICR, OUS (2003-), PI MetAction (2012-18)
- Anne-Lise Børresen-Dale, Prof, PhD, Head Dept Cancer Genet, ICR, OUS (till 2015), PI MetAction
- Kjersti Flatmark, Prof, PhD, Dept Tumor Biol, ICR, OUS (2010-), PI MetAction (2012-18)
- Jon Amund Kyte, Prof MD, PhD, MATRIX WP4 lead, TMC IMPRESS-Norway
- Live Fagereng, PhD, Strategy Advisor, ICR, DCM, OUS (2018-), Study Coordinator, IMPRESS-Norway 2020-21, Coordinator OUS-CCC PCM Centre (2021-), Project Manager PRIME-ROSE (2023-)
- Elisa Bjørgo, PhD, MATRIX Coordinator (2022-)
- Vigdis Nygård, PhD, molecular biologist, coordinating the mol. biol. team in MetAction (2012-18) and at InPreD (2019-)
- Tonje Lien, PhD, biostatistician, coordinating the bioinformatics and IT team at InPreD (2019-)
- Kajsa Johansson, MSc, Study Coordinator, IMPRESS Norway (2022-)
- A **broad set of key collaborators nationally** including researchers in national projects and InPreD teams at all six University Hospitals, IMPRESS-Norway PIs and study teams at all 17 Hospital trust and 24 sites running the trial, 30 partners with board representatives and work package leaders and Members in CONNECT (eg 117 consortium authors in Nat. Med., 2022).
- A **broad set of key collaborators internationally** including study teams in 10 national DRUP-like PCM trials running or starting and staff associated with 17 partners in **PCM4EU**, and 24 partners in **PRIME-ROSE** (eg 102 consortium authors in paper to Acta Oncol, 2024 with description of initiative).

Any relevant key contextual information about this area of research.

- See also OUS Division of Laboratory Medicine **Impact Case on Genomic Medicine** and page 3…
- The Department of Core Facilities at ICR runs seven platforms, including the Genomics (GCF) (NorSeq-Cancer) and Bioinformatics Core Facilities (BCF) at ICR, DCM, OUS
- The **Norwegian Consortium for Sequencing and Personalized Medicine** is a national research infrastructure financed by the RCN and part of the Norwegian road map for research infrastructures. NorSeq aims to provide cost-effective, cutting-edge genomics, high-throughput sequencing analysis, and competence for research to facilitate the development and implementation of personalized medicine in Norway. The **NorSeq-Cancer node** (Genomics CF), runs a specialized node for cancer sequencing and has been instrumental in the establishment and transfer of competence to build competence in genomics in Infrastructure for Precision Diagnostics (InPreD). Today, InPreD collaborates with NorSeq-Cancer to evaluate and implement the next generation of diagnostics tests (e.g., liquid biopsies and HRD testing).

3. References to the research

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4. Details of the impact

A transdisciplinary effort to strengthen research and implementation of PCM was started in DCM, OUS in 2019 and the working group defined three main goals: (1) to establish equal access to advanced molecular diagnostics, enabling stratification for clinical trials; (2) to increase the volume of precision cancer medicine trials and initiate a large national precision cancer medicine trial; and (3) to work on mechanisms to implement precision cancer medicine within standard-of-care.

The work was escalated to the OUS-CCC and subsequently to a national arena as we formed a national precision cancer medicine (PCM) implementation initiative.

Working with the oncology, hematology and pathology environments across Norway, with the authorities including the regional health care systems, the Ministry of Health and other national stakeholders including the Norwegian Cancer Society, internationally with the other Nordic countries and with the Netherlands (specifically, the DRUP trial), as well as with industry, we succeed in creating an interconnected set of initiatives & projects (described in Nat. Med., 2022):

i) The **InPreD national Infrastructure for Precision Diagnostics** that offers 500-gene panel testing for patients with advanced disease for stratification into clinical trials and includes a permanent national molecular tumor board (piloted 2020, operative from Q2 2021, test reimbursed as health care to stratify patients to trials). Implements molecular diagnostics to enhance trial inclusion (incl. DNA methylation, liquid biopsies, WGS/WTS and complex biomarkers);
ii) The **IMPRESS-Norway clinical trial** (modelled after the DRUP study in the Netherlands) that uses a combined umbrella and basket design and Simon two-stage model to test a set of drugs (currently 24) on new indications based on molecular diagnostics and an amalgamated algorithm (J. Transl. Med, 2022 and NCT04817956) developed 2020, opened Q2 2021. 24 drugs available from six different companies provide free drugs and per-patient cost;
iii) **Associated projects** for research on statistics, control cohorts in PCM, health economy and reimbursement models, organization, and the regulatory framework with legal and ethical aspects with different funding sources 2021-22;
iv) The **CONNECT** Public-Private Partnership for PCM Implementation discussing and observing the projects with all stakeholders (developed 2020, operative from January 2021;
v) **MATRIX – Norwegian Centre for Clinical Cancer Research** allowing for exploring new PCM diagnostics, trial designs and treatments (application 2021, opened 2022); and
vi) **European projects** by a growing consortium of partners interested in PCM implementation. **PCM4EU** funded by EU4Health under the Europe Beating Cancer plan has 17 partners in 14 countries. Here OUS has co-WP leads in WP2, WP3 and WP4, and the project is about rolling out advanced molecular diagnostics and enabling more countries to practice PCM and run DRUP-like clinical trials (DLCTs). The **PRIME-ROSE** project funded by Horizon Europe under the EU Mission Cancer, has 24 partners from 18 countries, is coordinated by DCM, OUS and with OUS WP leaders in WP2, WP3 and WP7. PRIME-ROSE is about aggregating data from DLCTs, organizing RWE control cohorts and designing expansion cohorts to build evidence faster and create the knowledgebase of what are effective treatments, and the project has a significant position in PCM in Europe. Through current work we aim to further position this European initiative for more funding opportunities, facilitate industry collaboration, and we work to raise more funding for middle-income countries in Europe.

These team efforts to advance implementation of PCM in Norway has so far attracted more than 250 million NOK in public support (including that from the Norwegian Cancer Society to IMPRESS). In addition, comes public reimbursement of testing and private funding in the form of company contributions of free drugs and per patient costs (>> 20 million NOK). InPreD organizes testing (still scaling, soon to run at all six university hospitals) across Norway, with an agreed division of labor in an inclusive competence network (2 WGS centres OUS and HUS Bergen, 6 centres running large gene panels and all pathology depts running smaller gene panels). The IMPRESS clinical trial

include all hospitals that treat cancer patients (17 hospital trusts, 24 sites) and with a lot of competence building (the majority of Norwegian oncologist have referred patients to InPreD and discussed their molecular findings in the national MTB). MATRIX includes 15 hospitals as partners.

Impact: In the first 18 months (Q2 2021 to Q3 2022), we screened more than 600 patients and as we end 2023 and get closer to 3 years of operation, more than 1500 patients have been offered advanced molecular diagnostics in InPreD and have been included in the screening phase of IMPRESS-Norway. More than 27% of the screened patients (>350 end 2023) have been offered inclusion in an IMPRESS trial treatment arm (and an additional 7-8% were offered inclusion in other trials or compassionate use programs). We observe that more than 35% of these have clinical benefit at 16 weeks of treatment. As this develops and capacity scales, we anticipate offering advanced molecular diagnostics to all Norwegian patients with a locally advanced or metastatic cancer (first 2,500 per year still eligible for trial inclusion in a late treatment line of approx. 10,000 per year with advanced cancer, later up to 5,000 per year as we move forward in the lines of treatment). This case may, as it develops, make significant changes in how we diagnose and treat cancer patients in Norway. Drugs with promising results from IMPRESS-Norway can be further explored through risk-sharing agreements with industry and the public health care system (industry partners pay for drugs the first 16 weeks, and the public health care system reimburse after 16 weeks inside the IMPRESS trial for expansion cohorts (as per decision in the joint national decision body for drug reimbursement).

Examples of other PCM trials resulting from the focused underpinning research and PCM implementation efforts (see also DCM, OUS Impact Cases on Underpinning Research and CoE Centre for Cancer Biomedicine and on Immuno-oncology)**:**

Resulting from the **KG Jebsen Colorectal Cancer Research Centre** and two consecutive OUS Strategic Research Area project **SMART Colorectal Cancer** and **TEAM-ACT** focusing on biomarkers and personalized treatment modelling, specific drug vulnerabilities of colorectal cancer subtypes were identified (Clin Cancer Res, 2018, ao) and tumor organoids used to model development of chemoresistance in a personalized manner (Clin Cancer Res, 2020, J Transl Med 2021). This **functional precision oncology method**, is now used in a prospective intervention study of tumor organoid-guided treatment selection for metastatic colorectal cancer, **EVIDENT** (*ex vivo* drug sensitivity testing; ClinicalTrials.gov Identifier: NCT05725200).

MATRIX-RARE is a trial that will run through MATRIX, use the InPreD diagnostic setup and use knowledge from IMPRESS-Norway. It will focus on subgroups of patients with rare hard-to-treat cancers (anaplastic thyroid cancer, salivary gland carcinoma, glioblastoma multiforme, cholangiocarcinoma and small intestine cancers), who benefit from PCM and will initiate treatment in earlier lines of treatment.

5. Sources to corroborate the impact

- Infrastructure for Precision Diagnostics, InPreD
- IMPRESS-Norway trial: https://impress-norway.no and NCT04817956
- CONNECT Public-Private Partnership: https://www.connectnorway.org
- MATRIX – Norwegian Centre for Clinical Cancer Research: https://www.matrix-fkb.no/en/home
- PCM4EU – www.pcm4eu.eu
- PRIME-ROSE – www.prime-rose.eu
- Norwegian Cancer Genomics Consortium, https://kreftgenomikk.no/en/
- Description of MetAction trial (link) and NCT02142036.
- The Explorer, March 24, 2022. *Norway's precision medicine takes aim at cancer.*
- CONNECT-Norway, May 5, 2022. *Norwegian Cancer Precision Medicine Implementation Consortium: Norwegian cancer initiatives receive international attention*.
- GenomeWeb, June 10, 2022: *Norway's Fledgling Precision Oncology Effort Finding Early Success*

Oslo University Hospital and University of Oslo, Division of Cancer Medicine - Case 4

Institution: Oslo University Hospital
Administrative unit: Division of Cancer Medicine
Title of case study: Palliative Care
Period when the underpinning research was undertaken: 2012-2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2022 - 2024
Period when the impact occurred: 2012-2022

5. Summary of the impact (indicative maximum 100 words)

The European Palliative Care Research Centre (PRC) have been expanded internationally. International pain (ICD-11) and cachexia classification systems have been revised and international guidelines have been updated (ESMO and EAPC) under our leadership. An innovative computer based tool for symptom assessment is developed and validated – Eir.

Large scale RCTs and cohort studies are conducted – MENAC, EPCCS, Zopiclone Trial, 2 vs 3 step pain ladder, and HUNT Pain Examination Study. Lancet Oncology Commission on palliative care (PC) was led by PRC. New models of PC (Pallion and Orkdal Study) was developed and tested - and now further developed and implemented in the EU Funded MyPath project (https://mypath-cancercare.eu/).

2. Underpinning research (indicative maximum 500 words)

The European Palliative Care Research Centre (PRC), established in 2009, as a joint venture between Trondheim University Hospital and The Norwegian University of Science and Technology NTNU, and the Department of Oncology, Oslo University Hospital and Institute of Clinical Medicine, University of Oslo. PRC coordinates groups and individual researchers within 26 core collaborating centres across Europe and overseas, approved by the Norwegian Cancer Society.

This research structure has provided us with the opportunity to collaborate nationally and internationally in palliative care and cancer research. This has been fundamental to reach stakeholders and research partners throughout Europe and North America. Hence, the position of PRC as a major research collaborative, nationally and internationally, has solidified in the last decade.

The main research focus is palliative care (PC), encompassing the wider patient-centred care concept. The four main pillars of research are: *Symptom management*; herein: pain, cachexia, psychological distress, sleep, *hard-to–treat-cancers*: pancreatic cancers and brain metastases, *health care services* research and *implementation science research*. In the past 5-6 years we have been incorporated modern implementation science strategies to enhance the impact and sustainability of our research results. Our development of Eir, an innovative digital symptom assessment tool, is a central element in all research activities. The overarching aim is to improve patient clinical care using evidence-based research methods, nationally and internationally, focusing on outputs that enhance the effectiveness of health care interventions to the benefit of patients, caregivers, health care providers and the society.

Professor Stein Kaasa, Head of Department of oncology, and professor at UiO since 2015
Senior researcher Marianne J. Hjermstad, Department of oncology since 2005, and PRC since 2009
Professor Nina Aass, Head of palliative care section and professor at UiO since 2010

Professor/researcher Asta Bye, Department of oncology since 2003, PRC since 2021, and Oslo Metropolitan University since 1992
MD/senior researcher Olav Yri, Department of oncology and PRC since 2017
MD/senior researcher Olav Dajani, Department of oncology and PRC since 2001
PhD candidates/MD Rebecca Rootwelt Winther since 2018 and Astrid Karlsson since 2017
PhD/senior researcher Tonje Lundeby, Department of oncology and PRC since 2015
PhD/researcher Kjersti S. Grotmol, Department of oncology and PRC 2015-2018
Professor Jon H. Loge, Department of oncology and PRC 2015-2020
PhD/researcher Amaia Urrizola, Department of oncology and PRC, since 2022

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6. *ESPEN guidelines on nutrition in cancer patients*. Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, Fearon K, Hütterer E, Isenring E, Kaasa S, Krznaric Z, Laird B, Larsson M, Laviano A, Mühlebach S, Muscaritoli M, Oldervoll L, Ravasco P, Solheim T, Strasser F, de van der Schueren M, Preiser JC.Clin Nutr. 2017 Feb;36(1):11-48. doi: 10.1016/j.clnu.2016.07.015. Epub 2016 Aug 6.PMID: 27637832.

4. Details of the impact (indicative maximum 750 words)

Symptom management. Pain classification, assessment, treatment, and evaluation constitute the main areas of research, and in which we have conducted numerous observational and randomized trials over the years[1]. We have challenged the clinical appropriateness of the traditional 3-step WHO pain ladder for relief of cancer, which generated great interest and discussions in renowned medical journals and cancer pain associations[2]. This has led to better understanding and treatment also in non-cancer populations[3]. Further, our work on pain classification has had an important impact on clinical practice[4]. Supported by EAPC, ESMO and other PC and pain stakeholders, we have advocated the systematic use and implementation of validated pain assessment tools, paper-based and digital. The latter, Eir, is an innovative and dynamic, web-based measure including the

most commonly encountered symptoms by cancer patients. Eir provides immediate real time overview of patients' symptom burden, its development over time, also suggesting treatment recommendations according to evidence-based treatment guidelines.

Other symptoms in our portfolio in which we have been the driving force nationally and internationally, are sleep, psychological distress, cognitive function, and physical function. All of these were part of our national and international trials, such as the EPCCS study (2011-18) and the Zopiclone RCT (2017-22) [5]. The breadth of our research represents an important contribution to the understanding and uptake of validated symptom assessment methods and their importance for patients' well-being and even survival. Taken together, our research results have and will continue to guide the assessment and treatment of these symptoms and give rise to new research.

The multifactorial cancer cachexia syndrome with weight loss, poor dietary intake and progressive loss of skeletal muscle mass remains a clinical challenge as it leads to progressive functional impairment carrying a poor survival prognosis. Our group has contributed substantially in the launching of multiple international assessment and treatment guidelines on cachexia with ESMO and ESPEN to increase the awareness of this syndrome and improve clinical outcomes[6]. Given the devastating outcomes of cachexia, the uptake of these guidelines has been great, with many new trials in its wake. Among these is the ongoing international MENAC-RCT (2015-23) led by OUS. We have also conducted several small scales clinical studies focusing on patients' and carers' experiences in the context of cachexia.

Hard-to–treat-cancers: pancreatic cancers and brain metastases. Pancreatic cancers is one of the few cancers in which the survival prognosis has not improved substantially in the last three deceased. The high symptom burden and rapid functional decline, together with the high prevalence of cachexia, accentuate the need for early implementation of PC at the time of diagnosis, an internationally agreed-upon method to improve patients- care, but not part of routine cancer care. The MENAC study has primarily included patients with pancreatic cancer and lung cancer, Preliminary results indicate that anti-cachexia treatment will be changed internationally based on our results. Further, PRC leads the major work of revising the international guidelines on cachexia classification and treatment, currently ongoing.

Our focus on brain metastases corresponds with all of our areas of research. The incidence increases as more patients live longer with "active disease". Overall, BM implies a short survival time, but with huge variations across diagnostic cancer groups. Our large national research program has revealed a substantial overuse of whole-brain radiotherapy in patients who do not benefit from this, given their short survival at start of treatment. To this end, our recently published results has the potential to revise the current treatment guidelines on brain radiotherapy, to prevent futile treatment in a large cohort of cancer patients with a short survival time. Our results on family issues suggest that an approach actively involving caregivers is essential to optimize patients' and caregivers' wellbeing.

Health care services research. Provision of optimal care to the individual patient at the health care level, has been part of our research focus for decades. This implies avoidance of futile treatment, early implementation of palliative patient-centred care, universal treatment guidelines and predictable treatment trajectories. Our cluster-randomized PALLiON trial (2015-22) investigated the effect of digital symptom assessment, compulsory use of digital patient-reported symptoms in consultations, and a specific patient care pathway on use of chemotherapy at end-of-life. Results paved the route for the MyPath EU project. Based on the BM-project (2017-ongoing), we aim to use the results of the futile radiotherapy to adjust the national treatment guidelines for BM

treatment. The Orkdal project (2013-20) is a unique example of how we combine our research pillars, PC and optimised individual symptom management, cancer treatment, and provision of health care services also outside institutional care. Here we implemented the provision of a standardized care pathway with integrated care to home-dwelling and hospitalized patients in a Norwegian rural region.

Implementation research. Our decades-long research endeavours has made us embark on implementation science strategies to conduct research with sustainable practice changes. Explanations of why health innovations fail are numerous, but mostly related to insufficient planning, and poor anchoring and follow-up from all involved. Related to the BM-project (2017-ongoing), our ongoing goal is to use implementation strategies to prevent futile radiotherapy in daily clinical practice. Following PALLiON, and as part of the ongoing MyPath EU-project (2022-ongoing), we will enhance the implementation of early PC and systematic patient-centred care in all clinical encounters. Notably, PRC has a pivotal role in the ongoing and the forthcoming Joint Action calls from EU (JANE1&JANE2). The aim is to prepare, develop and establish expert networks to improve cancer care, promote patient-centred care and create collaborative actions across disciplines and areas, in line with e.g. EU's Beating Cancer plan. PRC leads the work-package on palliative care, and are involved in 2-3 other.

Taken together, our research endeavours, extensive international network and participation in internationally endorsed evidence-based treatment guidelines resulted in three EU grants and one large national grant in 2022 (MyPath, JANE, EUonQOL, Matrix, all 2022-ongoing)

5. Sources to corroborate the impact (indicative maximum of ten references)

Development of EirV3 – a computer-based tool for patient reported outcome measures in cancer Krogstad H, Brunelli C, Sand K, Andersen E, Garresori H, Halvorsen T, Haukland EC, Jordal F, Kaasa S, Loge JH, Løhre ET, Raj SX, Hjermstad MJ. JCO Clin Cancer Inform. 2017 Nov;1:1-14. doi: 10.1200/CCI.17.00051.

PALLiON – PALLiative care Integrated in ONcology. Study protocol for a Norwegian national cluster randomized control trial with a complex intervention of early integration of palliative care. Hjermstad MJ, Aass N, Andersen S, Brunelli C, Dajani O, Garresori H; Hamre H, Haukland E; Holmberg M; Jordal F; Krogstad H; Lundeby T, Løhre ET; Mjåland S; Nordbø A; Paulsen P; Staff ES; Wester T, Kaasa S Loge JH. Trials. 2020 Apr 2;21(1):303. doi: 10.1186/s13063-020-4224-4.

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Implementing a Standardized Care Pathway Integrating Oncology, Palliative Care and Community Care in a Rural Region of Mid-Norway. Brenne AT, Løhre ET, Knudsen AK, Thronæs M, Lund J, Kongshaug N, Neverdahl MN, Rystad K, Johansen MH, Braseth TI, Kasa S. Oncol Ther. 2021 Dec;9(2):671-693. doi: 10.1007/s40487-021-00176-y. Epub 2021 Nov 3.

Brenne AT, Knudsen AK, Raj SX, Skjelvan L, Lund J, Thronæs M, et al. *Fully Integrated Oncology and Palliative Care Services at a Local Hospital in Mid-Norway: Development and Operation of an Innovative Care Delivery Model*. Pain Ther. 2020;9(1):297-318. DOI: 10.1007/s40122-02

Oslo University Hospital and University of Oslo, Division of Cancer Medicine, Case 5

Institution:	Oslo University Hospital (OUS) and University of Oslo (UiO)
Administrative unit:	Division of Cancer Medicine (DCM)
Title of case study:	Implementing a OUS Comprehensive Cancer Centre (OUS-CCC) – Enhancing the organizational infrastructure for cancer research and cancer care
Period when the underpinning research was undertaken: 2015 (and also w later papers)	
Period when staff involved in the underpinning research were employed by the submitting institution: From 2015-	
Period when the impact occurred: 2015-2022 and beyond	

6. Summary of the impact

Cornerstones of the CCC concept are the integration of research and clinical care, and the translation of research findings into evidence-based practice changes. The designation of OUS as a Comprehensive Cancer Centre (OUS-CCC) (OECI-accredited 2017, re-accredited 2023) mobilized and combine relevant disciplines, and the infrastructure for cancer research was strengthened and further developed. This included starting a pan-cancer research biobank and quality registries for all tumour types and establishing a matrix-organisation and governance structure with a CCC Executive Bord and Research Council with members from all relevant departments and institutes. This new organization modernized our research eco-system by creating space for new initiatives, changed research culture and opened a channel for bottom-up influence on health politics and administration. The CCC structure is increasingly recognised across Europe as a key factor in improving quality, facilitating coordination and/or reducing variation and inequalities in diagnosis, treatment, training/education, and research in cancer care. In recognition of such effects of a CCC organisation, the EU sets out both in the Europe's Beating Cancer Plan and the EU Mission on Cancer to further develop the CCC concept. OUS-CCC is actively involved these processes as a key partner in the Joint Action programs within the EU4Health program for building European Network of CCCs (CraNE) and the EU networks of Expertise on Cancer (JANE).

7. Underpinning research

The integration of research and clinical care, as well as the translation of research findings into evidence-based practice, is a fundamental aspect of the Comprehensive Cancer Centre (CCC) concept (linked papers w. G Sæter OUS-CCC as co-author). In the Nordic countries standardized cancer care pathways were implemented through politically imposed reforms (See analysis in references in pt 3, Mæhle et al, 2020, Mæhle et al 2021a and 2021b and reviewed in Mæhle and Smeland, 2021). This led to focus on standardization and quality assessment and next on organisation in our hospital and in the wider region. The Nordic countries, therefore, looked to the European CCC concept and the OECI Accreditation and Designation programme where Prof. Gunnar Sæter and others from OUS DCM actively participated as assessors (described in Kehrloesser et al, 2021). The designation of OUS-CCC by the OECI in 2017 as the second CCC in the Nordic region (after Helsinki) presented an opportunity to leverage the resources and expertise across the institution and mobilize all relevant disciplines for the advancement of cancer care. OUS has next guided a number of other centres in Sweden and Denmark on their path to accreditation further strengthening Nordic collaboration.

Overall, the CCC concept aims to create a cohesive and interdisciplinary environment where research and clinical care work hand in hand to improve cancer treatment. Through the establishment of infrastructure, governance structures, and collaborative mechanisms, the CCC at OUS is poised to facilitate significant advancements in cancer research and ultimately enhance patient outcomes.

Core points of the insight delivering the impact of a CCC organisation at OUS are:

- Establishing a program for precision oncology (see impact case 3). The early phase of this national program was initiated by the CCC-Executive Board reaching out to all relevant divisions/departments/institutes at OUS and included representatives from three core disciplines; laboratory research, pathology and oncology and all members with high academic competence.
- Strengthening translational research in major tumour groups with access to **biobank** materials from the prospective research biobank combined with registry data. This now includes prostate, gynaecological, breast, colorectal and lung cancer.
- OUS-CCC has a clear ambition to increase the number of patients included in clinical trials and provides support for clinical studies.
- The CCC has established a "dashboard" on cancer-specific activity, extracting data from a data warehouse and enabling monitoring of number of patients, newly referred patients, and newly diagnosed patients in addition to number of patients recruited to clinical trials. The percentage of patients included in clinical intervention studies has increased from 9.5% in 2018 to 12.2% in 2022 strengthening our clinical research. DCM has a continuous focus to increase this further.
- Immune therapy including cell therapy is a focus area for OUS-CCC and exemplifies the importance of integrating laboratory research with clinical research. The core infrastructure for immune/cell therapy are at the Dept of Cancer Immunology at the ICR, the Section for Cell Therapy at Dept of Oncology (including the Advanced Cell Therapy Centre, ACT) and the Phase 1 unit at Dept of Oncology (See impact case 2).

These improvements are based on systematic assessment of experiences, peer-based discussions and accreditation, reports from the CCC Scientific Advisory Board, documented in administrative reports, follow-up meetings with the research groups by the Board and reports and articles in scientific journals. Through the establishment of a CCC, we have also managed to transform the knowledge into operational initiatives and thus delivering the impact. This illustrates how we have created a learning environment in our dynamic way of leading and managing the cancer centre with its care and research activities.

Names of the key researchers and positions held at the adm. unit at the time of the research.

- **Sigbjørn Smeland**, Professor, Director of the Division of Cancer Medicine (DCM) and chair of the CCC Board,
- **Per Magnus Mæhle**, PhD, General Manager of the CCC Executive Board
- **Gunnar Sæter**, Professor, previous Research Director OUS-CCC (2017-2019), OECI Board Member and Accreditation assessor (2016-2023)
- **Åslaug Helland**, Research Director of DCM and of the OUS-CCC. Member of OUS-CCC Executive Board, Chair of the OUS-CCC Research Council
- **Kjetil Taskén**, Professor, Head of the Institute for Cancer Research (2018), Member of the DCM leadership group and of the OUS-CCC Executive Board, Member of the OUS-CCC Research Council
- **Stein Kaasa**, Professor, Head of the Dept of Oncology, Member of the DCM leadership group and of the OUS-CCC Executive Board, Member of the OUS-CCC Research Council
- **Morten Tandberg Eriksen**, Head of Division of Surgery, Inflammation and Transplantation (2017-23), Member of the OUS-CCC Executive Board

3. References to the research

- **Mæhle PM, Small Hanto IK, Smeland S.**: Practicing Integrated Care Pathways in Norwegian Hospitals (2020): Coordination through Industrialized Standardization, Value Chains, and Quality Management or an Organizational Equivalent to Improvised Jazz Standards. Int J Environ Res Public Health. 2020;17(24):9199.

- **Mæhle P.M.,** Hajdarevic, S., Håland, E., Aarhus, R., **Smeland, S**. & Mørk, B.E. (2021a). Exploring the triggering processes of a cancer care reform in three Scandinavian countries. International Journal of Health Planning and Management, 2021-11, Vol.36 (6), p.2231-2247. doi: 10.1002/hpm.3278

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- **Kjetil Taskén, Hege E. G. Russnes,** Eline Aas, Line Bjørge, Egil S. Blix, CONNECT Public–Private Partnership Consortium, Espen Enerly, **Gro L. Fagereng,** Åsmund Flobak, Bjørnar Gilje, Bjørn T. Gjertsen, **Tormod K. Guren**, Jutta Heix, **Eivind Hovig,** Randi Hovland, InPreD-Norway and National Molecular Tumor Board Consortium, IMPRESS-Norway Consortium, Per E. Lønning, **Leonardo A. Meza-Zepeda, Per M. Mæhle**, Hilde L. Nilsen, Steinar Ø. Thoresen, Ketil Widerberg, **Sigbjørn Smeland, Åslaug Helland** (2022): A national precision cancer medicine implementation initiative for Norway, Nature Medicine, 28, pages 885–887 (2022). https://rdcu.be/cM70C

- **Helland, Å., Russnes, H.G., Fagereng, G.L.,** Al-Shibli, K. , Andersson, Y, Berg, T., Bjørge, L., Blix, E., **Bjerkehagen, B., Brabrand, S.,** Cameron, M.G., Dalhaug, A., Dietzel, D., Dønnem, T., Enerly, E.., Flobak, Å., Fluge, S., Gilje, B., Gjertsen, B.T., Grønberg, B.H., Grønås, K., **Guren, T**., Hamre, H., Haug, Å., Heinrich, D., **Hjortland, G.O., Hovig, E.**, Hovland, R., Iversen, A.-C., Janssen, E., **Kyte, J.A.**, von der Lippe Gythfeldt, H., **Lothe, R.**, Lund, J.-Å, **Meza-Zepeda, L.**, Munthe-Kaas, M.C., Nguyen, O.T.D., Niehusmann, P., Nilsen, H., Puco, K., Ree, A.H., Riste, T.B., Semb, K., Steinskog, E.S.S. Stensvold, A., Suhrke, P., Tennfjord, Ø., Tjønnfjord, G.E., Vassbotn, L.J., Aas, E.,, Aasebø, K. Taskén, K., Smeland, S. *Improving public cancer care by implementing precision medicine in Norway: IMPRESS-Norway.* **J. Transl.Med.**, 2022, 20:225, pp 1-11. doi: 10.1186/s12967-022-03432-5 .- *Description of IMPRESS.*

- Kehrloesser S, Oberst S, Westerhuis W, Wendler A, Wind A, Blaauwgeers H, Burrion JB, Nagy P, **Sæter G**, Gustafsson E, De Paoli P, Lovey J, Lombardo C, Philip T, de Valeriola D, Docter M, Boomsma F, Saghatchian M, Svoboda M, Philip I, Monetti F, Hummel H, McVie G, Otter R, van Harten W. Analysing the attributes of Comprehensive Cancer Centres and Cancer Centres across Europe to identify key hallmarks. Mol Oncol. 2021 May;15(5):1277-1288. doi: 10.1002/1878-0261.12950. Epub 2021 Mar 30. PMID: 33734563; PMCID: PMC8096787.

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4. Details of the impact

Following more than 2 years of preparatory work, OUS was designated as a Comprehensive Cancer Centre (OUS-CCC) in April 2017 by the Organisation of European Cancer Institutes (OECI) that operates a European Accreditation and Designation Programme for CCCs. During 2017-21 OUS-CCC worked to improve in areas identified in the accreditation such as molecular pathology, clinical trials and trial infrastructure, clinician time for research, training of cancer nurses, precision cancer medicine and more. Next, the preparation for the re-accreditation process started in 2021 and included revision of the OUS Cancer Strategy (Cancer Strategy 2017-22 and 2022-26 here) and

further focus on areas OUS needed to strengthen such as patient centred care and cancer rehabilitation. Following this effort, OUS-CCC was reaccredited in April 2023.

To ensure effective governance and oversight of the research activities within the CCC, an Executive Board and a Research Council with representatives from all relevant departments and institutes were established. The Research Council is responsible for coordinating research efforts, promoting collaboration, and ensuring high standards of research quality. Furthermore, a Scientific Advisory Board conducts site visits every second year to provide independent evaluation and guidance on the research conducted within the CCC, encompassing various domains such as basic, translational, clinical, patient-centred, and epidemiological research.

The impact of the research and knowledge of this case is delivered by the interaction between knowledge providers and responsible leaders or between researchers producing the knowledge and those transforming and adapting it into practical initiatives and organizational solutions. In addition, these core people have a staff working on the same development at operational, administrative, and political levels in our regional and national health case system, in other cancer centres and on health organisation and policy in the Nordic countries and around Europe.

The knowledge referred to have had an impact on change and improvements processes on several levels of the hospital and healthcare system:
Level 1) Establishment of the Cancer Center with its Cancer Center Board and a cancer centre Research Council in 2016 created an arena facilitating cross-organizational coordination of resources in the hospital and its research environment. This has also resulted in major initiatives enhancing cancer research, like:

- Systematically process of establishing a cancer biobank with a broad consent. This has led to a cancer biobank with biological material collected from 2500-3000 patients annually.
- A national program for Precision cancer medicine (InPred, IMPRESS-Norway, CONNECT, MATRIX) followed by taking a core position in European initiatives on precision cancer medicine (PRIME-ROSE, PCM4EU). Patients with advanced malignancies now have access to advanced molecular diagnostics (>500 genes, TSO500), possible treatment in IMPRESS-Norway (>1500 included patients January 2024, 24 drugs available), and DCM are leading partners in EU-funded projects like PCM4EU and PRIME-ROSE (impact case 3).
- Research initiatives supporting the development of patient centred care (MyPath and MATRIX). The **MyPath** research project will develop a novel digital solution, MyPath, consisting of electronic patient-centred care pathways – custom-made for each individual patient, including real-time communication of symptoms and care preferences (impact case 4).
- Development of a program aiming at developing primary clinical data as a source for creating Real World Evidence (DigiOne). Structured data and transferring the data to OMOP-language, enables systematic quality control of hospital activities, and research collaboration using Real-World-Data.
- Boosting the volume of clinical trials and actively supporting the access of experimental studies for all cancer patients. The establishment of NorTrials-Cancer is part of this effort.

Level 2) The connected cross-organizational collaborative behaviour and attitudes influencing the development of cancer research actively stimulating cross-disciplinary collaboration. This is connected to specific cancer diagnoses and not least across cancer diagnoses for example through workshops and seminars. Most recently diagnosis-specific centres are being established at the new Radium Hospital opening September 2024. Clinical research and closer collaboration with translational research at the Institute for Cancer Research is a main task for these centres.

Level 3) Improved outcome for patients, the bottom-up influence on development of health care and cancer politics and policy implementation. The first is already a reality by increased patient access to advanced experimental studies. The second is a reality through the hospital´s ability to influence the political and administrative initiatives on precision medicine and on the role OUS has achieved in influencing the establishment of a European network of CCCs (CRANE). This aims at taking a coordinating role in the development of cancer research eco-systems in Europe.

Together these impacts of the implementation of the knowledge on the organization of cancer centers in a general university hospital have created a major difference in the speed of development and the strategic capacity both regarding exploiting existing resources in research and on building network and exploring the resources that are available not least on an European stage.

5. Sources to corroborate the impact

- OUS-CCC UiO
- OUS-CCC OUS
- OUS-CCC- Annual Reports 2017-2023: https://www.ous-research.no/home/ous-ccc/Annual-reports
- OUS-CCC Cancer Strategy 2022-26
- CRANE JA: European Network of Comprehensive Cancer Centres
- JANE JA: Networks of Expertise on Cancer
- Infrastructure for Precision Diagnostics, InPreD
- IMPRESS-Norway trial: https://impress-norway.no
- CONNECT Public-Private Partnership: https://www.connectnorway.org
- MATRIX – Norwegian Centre for Clinical Cancer Research: https://www.matrix-fkb.no/en/home
- PCM4EU – www.pcm4eu.eu
- PRIME-ROSE – www.prime-rose.eu
- OUS-CCC participation in DigiOne, https://www.ous-research.no/home/ous-ccc/DigiONE/23892

[Oslo University Hospital, Division of Emergencies and Critical Care] [case number 1]

Institution: Oslo University Hospital
Administrative unit: Division of Emergencies and Critical Care
Title of case study: Evaluation of the Effects of Remdesivir and Hydroxychloroquine on Viral Clearance in COVID-19
Period when the underpinning research was undertaken: March 28 2020 – October 4 2020
Period when staff involved in the underpinning research were employed by the submitting institution: The whole study period
Period when the impact occurred: The impact of this research occurred during and in the aftermath of the NOR-Solidarity trial; from March 2020 and today. **Briefly:** The Nor-Solidarity trial was an independent add-on study to the WHO Solidarity trial that evaluated the effects of hydroxychloroquine (HCQ) and remdesivir compared to standard of care (SoC) in hospitalized COVID-19 patients. The trial engaged 23 hospitals across Norway, representing a collaborative national endeavor aimed at actively participating in a significant global investigation. The NOR-SOLIDARITY trial included biobanking and additional clinical and biochemistry data collection as well as follow-up beyond the WHO Solidarity core protocol. NOR-Solidarity was launched March 28, 2020, and included the first patient to WHO Solidarity. HCQ was removed from the trial June 8th because of lack of evidence confirmed both in the internal WHO interim analyses and in external report from the NHS-based Recovery study in England (PMID: 33031652). Based on the interim results from the WHO Solidarity trial, which excluded clinical benefit from any of the treatment arms, the Executive Committee of the Nor-Solidarity trial decided to stop inclusion to remdesivir arm. This decision was based on an overall low clinical effect globally and a presumed neglectable benefit on the Norwegian patient population. NOR-Solidarity was stopped October 5th 2020.

Summary of the impact

The impact can be delineated into three distinct directions.

1. The data has been valuable for the scientific community, playing a pivotal role in decision-making processes that have informed guidelines and meta-analyses. This in turn has been translated into clinical medical practice.
2. The project has expanded Norwegian researchers' opportunities, giving an entrance to participate and build a pan-European research network. Holding the position as PI for a large pharmaceutical RCT has placed Norway and Oslo University Hospital in key positions.
3. The project has fostered new and extended collaborative initiatives among hospitals in the South-eastern region of Norway.

2. Underpinning research

The main result from the NOR-Solidarity trial was an overall lack of effect of remdesivir and HCQ on the clinical course of patients hospitalized for COVID-19 disease. Specifically, there was no observed effect on oropharyngeal SARS-CoV-2 viral clearance. Thus, the findings questioned the antiviral potential of these drugs in hospitalized COVID-19 patients, and have been instrumental for:

1. A living WHO guideline on drugs for Covid 19, last updated nov 2023 (PMID: 35470203).
2. As the evidence from RCTs of remdesivir in patients treated in hospitals for Covid-19 was conflicting, the WHO Solidarity Trial Consortium was conducted and published in Lancet

(2022): Remdesivir and three other drugs for hospitalised patients with COVID-19: final results of the WHO Solidarity randomised trial and updated meta-analyses.

3. In April 2020 key persons in the NOR-Solidarity Steering Committee were invited to a meeting with researchers from the French National Institute of Health and Medical Research (INSERM), immediately leading to close collaboration on a proposal to EU-Horizon 2020. In June 2020, our proposal, titled *European Research and Preparedness Network for Pandemics and Emerging Infectious Diseases – EU-RESPONSE* (Proposal number: 101015736), was awarded a grant of 15.7 million euros. Oslo University Hospital (OUH) co-leaded the work building a new multinational European Adaptive Platform Trial – the EU-SolidAct. This is a flexible platform, providing a modular trial network enabling most, if not all, European hospitals to participate at their preferred level of commitment. In the short-term this project focused on COVID-19, however, the long-term objectives are to build a platform trial network on emerging infectious diseases in general.
4. OUH was appointed as PI for the first trial (Bari-SolidAct) testing the efficacy of baricitinib in hospitalized SARS-CoV-2 patients (PMID: 36627655). The establishment of this study highlighted the imperative for an efficient pharmacovigilance system in multi-country clinical trials, addressing challenges related to local legislation. Notably, it pioneered a *Voluntary Harmonization Procedure*, that enabled coordinated and uniform legislation across multiple European countries.
5. New and extended collaborative initiatives among hospitals in the south-eastern region of Norway; The multicentre community acquired pneumonia and trauma induced ARDS (**CAPTAIN**) study is an ongoing multicentre observational and exploratory study, collecting sequential clinical, physiological, radiological, and immunological data aiming to investigate the phenotypic heterogeneity in ARDS, triggered by community acquired pneumonia (CAP) and trauma. The data collection provides vital clinical and epidemiological insights, delivering the first holistic view of Norwegians affected by CAP- and trauma-induced ARDS.

K**ey researchers and positions during the projects:**

- **Andreas Barratt-Due, MD, PhD:** Consultant and assistant section leader of Department of Anesthesia and Intensive Care Medicine, Oslo University Hospital (OUH)
- **Pål Aukrust, PhD prof:** Consultant and Head of Department of infectious Diseases, OUH
- **Marius Trøseid, PhD prof:** Consultant at Department of infectious Diseases, OUH
- **Inge Olsen, PhD:** Researcher and biostatistician at Dept. of Research Support for Clinical trials, OUH
- **Katherina Nezvalova Henriksen**, **PhD**, Clinical Pharmacist, OUH
- **Yazdan Yazdanpanah, PhD prof:** Director of the Immunology, Inflammation, Infectiology, and Microbiology Institute (I3M) at INSERM, France
- **Domique Costagliola, PhD:** Senior researcher with on epidemiology, clinical research in infectious diseases and biostatistics, INSERM, France
- **Alpha Diallo, MD:** Drug safety specialist, co-morbidities, drug-induced adverse events, INSERM, France

3. References to the research

- Repurposed Antiviral Drugs for Covid-19 - Interim WHO Solidarity Trial Results; **NEJM 2021, PMID: 33264556**
- Evaluation of the Effects of Remdesivir and Hydroxychloroquine on Viral Clearance in COVID-19; **Ann Int Med 2021, PMID: 34251903**
- Respiratory dysfunction three months after severe COVID-19 is associated with gut microbiota alterations**. J Intern Med, 2022 PMID: 35212063**

- Accelerating clinical trial implementation in the context of the COVID-19 pandemic: challenges, lessons learned and recommendations from DisCoVeRy and the EU-SolidAct EU response group; **Clin Microbiol Infect 2022, PMID:34763056**
- Assessing the Evidence on remdesivir; **Lancet Infect Dis 2021, PMID: 34838222**

4. Details of the impact

The execution of NOR-Solidarity trial has been of paramount significance, unlocking opportunities that would not have been attainable otherwise. The study yielded scientifically results that stand independently, while concurrently serving as crucial data for subsequent knowledge production. Our research has allowed for a better understanding of COVID-19's pathology, leading to the development of new treatment options and therapeutic approaches. The outcomes from the global WHO Solidarity have undeniably played an important role in formulating evidence-based guidelines for the treatment of SARS-CoV-2 infected patients, which are decisive for today's clinical practice. The knowledge gained from this research will have implications beyond COVID-19 and potentially inform the treatment of other viral diseases.

Our research adheres to national aims on the preparedness for future pandemics: The research and knowledge gained during the COVID-19 pandemic will help society be better prepared for future infectious disease outbreaks. This includes improved early detection methods and the development of effective antiviral drugs.

<u>International collaboration beyond the COVID-19 pandemic</u>

The execution of NOR-Solidarity was a project that initiated collaboration across countries in Europe. Clinicians and researcher involved in NOR-Solidarity became integral contributors to a broader body of research, assuming key positions in the development of a pan-European research platform. Except from the successful NHS-based Recovery study in England, other European countries needed a research platform for rapid and coordinated investigation of new candidate drugs during ongoing pandemics. EU-SolidAct is an Adaptive Platform Trial master protocol developed for evaluating drug interventions in hospitalized subjects with COVID-19. While this master protocol is developed for therapeutic interventions in hospitalized patients, it could also form the basis for trial protocols on other interventions and/or in non-hospitalized populations. The protocol is, additionally, developed to facilitate a joint European response to the challenge of evaluating interventions during future epidemics. The work with the master protocol started in May 2020, whereas the first specific protocol executed was Bari-SolidAct (OUH - OUS-research.no). The project encountered several hurdles, including those related to pharmacovigilance, resulting in delayed commencement of the study (May 2021). Still, the project has addressed several key challenges, established infrastructure, and a research network across Europe that will continue to benefit in the future. Key persons from the NOR-Solidarity in this process have been Marius Trøseid, Inge Olsen and Katherina Nezvalova Henriksen.

<u>Investment in Research and Development:</u> The unprecedented global collaboration and funding put towards COVID-19 research have highlighted the importance of research and development in tackling public health crises. The execution of NOR-Solidarity has engaged national and international governments and organizations to increase funding for research and development efforts across various fields, leading to advancements in the healthcare sector. This, in turn, will foster economic growth and competitiveness in the long run.

<u>National collaboration</u>

The execution of NOR-Solidarity was a project that initiated collaboration across hospitals within Norway. The establishment of this national collaborative network serves as a major impact of the NOR-Solidarity project. The various ICUs and infectious disease departments became closer, and as

a direct result of this, the CAPTAIN study was launched. The completion of this study will have important collaborative impact and great utility for future clinical practice and research in the region**.** From the NOR-Solidarity, Andreas Barratt-Due, has been a key person establishing this. The study started in 2022.

Impact on clinical practice

In addition to the establishment of a national network, the NOR-Solidarity has been a project with impact on improving clinical practice. Among others the development of 'A living WHO guideline on drugs for covid-19 PMID: 35470203 has had an impact on clinical practice.

Impact on society

Knowing that our national health care system was very early involved in the battle of managing the Covid-19 pandemic, and that we prepare for future pandemics is of the utmost importance for society's safety.

Impact on economy

Research on COVID-19 has played a crucial role in the development of effective vaccines and treatments. Our contribution is the knowledge gained on SARS-CoV-2 virus clearance, that will aid in controlling the spread of the virus, allowing economies to reopen and recover.
The unique global collaboration and funding put towards COVID-19 research have highlighted the importance of research and development (R&D) in tackling public health crises. Governments and organizations all over the world are likely to increase funding for R&D efforts, leading to advancements in healthcare. This, in turn, will foster economic growth and competitiveness in the long run.

In summary, our research has contributed to the knowledge on COVID-19 in general and will have a transformative impact on national healthcare systems. Such as informing strategies for preparedness, treatment protocols and methods, diagnostic tools, and professional collaboration. These outcomes will strengthen healthcare systems and improve their ability to address future health challenges. Overall, the long-term impact of COVID-19 research will not only contribute to overcoming the current pandemic but also strengthen society's resilience against future health challenges.

6. **Sources to corroborate the impact**

- New clinical guidelines: A living WHO guideline on drugs for covid-19 PMID: 35470203
- The publication *'Remdesivir and three other drugs for hospitalised patients with COVID-19: final results of the WHO Solidarity randomised trial and updated meta-analyses*', **Lancet** 2022 https://doi.org/10.1016/ S0140-6736(22)00519-0, ***refers to*** Barratt-Due A et al, (2021) *Evaluation of the Effects of Remdesivir and Hydroxychloroquine on Viral Clearance in COVID-19 : A Randomized Trial, Ann Intern Med*, PMID 34251903
- Participating in building a multinational European Adaptive Platform Trial focusing on emerging infectious diseases in general, and by receiving grant: **EU-RESPONSE** (Proposal number: 101015736)

[Oslo University Hospital, Division of Emergencies and Critical Care] [case number 2]

Institution: Oslo University Hospital
Administrative unit: Division of Emergencies and Critical Care
Title of case study: Symptom burden and follow-up during and after intensive care treatment to improve mental and physical long term outcome in patients and their family.
Period when the underpinning research was undertaken: 2009-2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2014
Period when the impact occurred: 2012-2022

1. Summary of the impact

Through our research the last decade, we have documented mental and physical disorder after intensive care unit (ICU) discharge in several patients and their families. This can be better discovered through an outpatient follow-up clinic which was established in 2022. Three months after ICU discharge, ICU-survivors and their closest relative receive examinations and therapeutic consultations to evaluate their physical and mental status. Depending on their needs, they are further helped through fast-track referrals to rehabilitation centres and/or local or central specialists. Additionally, our recently introduced Comfort Bundle and diaries for patients focus on improving long-term outcomes after ICU treatment.

2. Underpinning research

We have previously (prior to 2012) documented through increasing focus on symptom burden and multiple symptoms among ICU patients, the presence of the Post-intensive care syndrome (PICS). PICS consist of physical and mental health problems that are present during the ICU stay and persist after critical illness and discharge from the ICU. Although not being ICU patients, our early research in symptom burden and multiple symptoms was also investigated in another group of critically ill patients; patients with severe pulmonary disease. We documented that 48% of them had major psychological and physical symptoms (1). They were also younger, more often women, and reported worse disease-specific quality of life scores compared to the patients with less symptoms.

In a randomized controlled trial (RCT) from 2020 with general ICU patients, we documented that approximately 1/3 of discharged ICU patients experienced clinically relevant post-traumatic stress symptoms (PTSS) both early after ICU discharge, and after one year (2,3). Both having a delusional memory from the ICU and being younger were variables associated with more PTSS.

PICS can also be present in family members of ICU patients. In an observational study focusing on family caregivers of ICU patients, we also documented that 54% of them reported high PTSS levels when the patient was admitted to and treated in the ICU, which decreased during the first six months after discharge, however still present in several (4). The family caregivers experienced a median of nine (range 0-24) different symptoms during the ICU stay, and psychological symptoms were most common (5).

In an effort to prevent and reduce symptom burden leading to PICS, we have recently developed a Comfort Bundle (a wall-hung bedside whiteboard) to inspire and remind nurses to systematically plan and promote comfort to the ICU patients (6). Following a pilot test and implementation in two ICUs at OUS, further research to evaluate its usability is ongoing in different ICUs at three hospitals in Oslo.

Finally, the use of nurse written diaries during the intensive care stay, have shown that diary writing was meaningful not only for patients receiving the diary, but also for the nurses in managing care The ICU survivors receive the diary at the ICU follow-up consultation, and might also impact on reducing long term symptom burden. This will be further explored through our research, and symptoms of PICS is the main outcome in two large ongoing observational studies, led by members of the research team.

Key researchers and positions during the project period:

Tone Rustøen, RN, PhD, professor UiO and leader of the nursing research group at Division of Emergencies and Critical Care, OUS and NORSMAN network.
Kristin Hofsø, Intensive care nurse (CCN), PhD, associate professor, the chair of the follow-up clinic and main supervisor for 4 PhD students on symptom management research in ICU patients.
Kirsti Tøien, CCN, PhD. 50% research and 50% at the follow-up clinic, main supervisor for two PhD students.
Helene Berntzen, CCN, PhD, nurse in Research and professional development, main supervisor for one PhD student.
Åse Valsø, CCN, PhD, associate professor, nurse in Research and professional development.
Hanne Birgit Alfheim, CCN, PhD, Department of Anesthesia and Intensive Care, Vestre Viken Hospital Trust, Bærum Hospital. Supervisor for two PhD students on symptom management research in adult and pediatric ICU patients.
Kjetil Sunde, MD, PhD, professor, Department of Anesthesiology and Intensive Care Medicine, OUS and Institute of Clinical Medicine, UiO.

3. References to the research

1. Christensen VL, Rustøen T, Cooper BA, Miaskowski C, Henriksen AH, Bentsen SB, Holm AM. Distinct symptom experiences in subgroups of patients with COPD. Int J Chron Obstruct Pulmon Dis. 2016 Aug 2;11:1801-9. doi: 10.2147/COPD.S105299. 2016.
2. Valsø Å, Rustøen T, Småstuen MC, Ekeberg Ø, Skogstad L, Schou-Bredal I, Myhren H, Sunde K, Tøien K. Effect of Nurse-Led Consultations on Post-Traumatic Stress and Sense of Coherence in Discharged ICU Patients With Clinically Relevant Post-Traumatic Stress Symptoms-A Randomized Controlled Trial. Crit Care Med. 2020 Dec;48(12):e1218-e1225. doi: 10.1097/CCM.0000000000004628.
3. Valsø Å, Rustøen T, Skogstad L, Schou-Bredal I, Ekeberg Ø, Småstuen MC, Myhren H, Sunde K, Tøien K. Post-traumatic stress symptoms and sense of coherence in proximity to intensive care unit discharge. Nurs Crit Care. 2020 Mar;25(2):117-125. doi: 10.1111/nicc.12466.
4. Alfheim HB, Hofsø K, Småstuen MC, Tøien K, Rosseland LA, Rustøen T. Post-traumatic stress symptoms in family caregivers of intensive care unit patients: A longitudinal study. Intensive Crit Care Nurs. 2019 Feb;50:5-10. doi: 10.1016/j.iccn.2018.05.007. Epub 2018 Jun 21.
5. Alfheim HB, Rosseland LA, Hofsø K, Småstuen MC, Rustøen T. Multiple Symptoms in Family Caregivers of Intensive Care Unit Patients. J Pain Symptom Manage. 2018 Feb;55(2):387-394. doi: 10.1016/j.jpainsymman.2017.08.018. *Epub 2017 Aug 31.*
6. Berntzen H, Storsveen AM, Bjørk IT, Wøien H, "Please mind the gap": A secondary analysis of discomfort and comfort in intensive care. *Journal of Clinical Nursing,* 2020:00:1-14. doi:10.1111/jocn.15260

4. Details of the impact

Through our research the last 10-15 years, we, among others, have documented that long term mental and physical disorder after ICU discharge is frequent in both patients (called PICS) and their

families (called PICS-F)(2-6). In an RCT in 523 patients evaluating the effect on PTSS through nurse led consultations on PTSS early after ICU discharge that started in 2013, no effects were relieved within the first year after ICU discharge (2). Low sense of coherence, pain, and previous psychiatric problems were associated with increased level of PTSS after one year. With the establishment of the ICU follow-up clinic in 2022, it was our intention to gain focus on mental and physical function three months after ICU discharge, since the majority of these patients, and families, are left on their own to manage daily life after critical illness. The ICU follow-up clinic is multi-professional and consists of both screening for commonly reported health challenges, as well as therapeutic consultations by a physical therapist, and ICU nurse and -physician. This consultation is broader than the nurse-led consultations (2), more targeted towards physical and mental function, and also including the family. In a sub-study from the RCT, we also found that pain was present in nearly 70% of patients early after ICU discharge, and that pain intensity was still at a moderate level after one year. High PTSS, female gender, shorter ICU stay, and more traumatic ICU memories were significantly associated with higher worst pain intensity after one year (2). However, as already stated, not only the patients are affected by ICU treatment. In a study on family caregivers of 211 ICU patients between 2012 and 2018, we showed that the family caregivers experienced a high number of symptoms, most often psychological symptoms (4). Lower levels of hope, being younger, having more comorbidities and being on sick leave were also associated with higher PTSS levels. Further studies in the same sample also showed that the family members experienced multiple symptoms (median of nine symptoms) (5). Younger age, being a spouse of an ICU patient, and having more comorbidities were significantly associated with the number of symptoms. Thus, the situation after ICU discharge is complex. Depending on their needs, the patients are further helped through fast-track referrals to rehabilitation centres and/or local or central specialists. With the presence and inclusion of the family member, their common problems thereby gain focus and can help them in problem solving together.

Based on our previous research, we have also introduced new strategies in the ICU with the intention to improve long term outcome after the ICU stay. With the Comfort Bundle, developed by the research group in 2021, we aim to inspire and remind nurses to systematically plan and promote comfort to the ICU patients (6). It includes a whiteboard that displays the individualized comfort measures and promotes involvement and communication with other healthcare personnel, patients, and relatives about matters important to the individual patient. They documented a gap between ICU patients' comfort needs and nurses' achievements in fulfilling these.

One study regarding the use of nurse written diaries started in 2019 in ICUs have had media attention that has led to increased focus on the follow-up of ICU-survivors and the use of ICU-diaries (see 5. Sources to corroborate the impact**,** 7,8). Nationally, a network of units that use ICU-diaries is established. Our results also shows that diaries may serve other purposes than helping patients to understand their critical illness trajectory. In cases of a poor prognosis, nurses adapted their writing to comfort the family rather than informing the patient.

Our research has received both internal and external funding. Norwegian Symptom Management Network (NORSMAN) was established in 2016 and funded by South-Eastern Norway Region Health Authority and refunded for three more years in 2019. NORSMAN is a regional network for research and innovation to reduce symptom burden and improve quality of life in patients with various disorders. As many of the researchers and PhD students involved also have clinical positions in ICUs, the results of our research impacts on the care provided. Many of the studies are about patients while in the ICU, as well as their outcomes after ICU discharge and the rehabilitation of these patients. We collaborate close with user participants, mostly former ICU patients. Several studies also include the family caregivers.

5. Sources to corroborate the impact (indicative maximum of ten references)

1. OUH - Nursing Research Group (ous-research.no)
2. Norwegian Symptom Management Network (NORSMAN) - Oslo universitetssykehus HF (oslo-universitetssykehus.no)
3. Rikshospitalet har etablert ny klinikk for pasienter som har vært innlagt på intensivavdelingen - VG Temadag Gøteborg 2023 (nofi.info)
4. Pårørende på intensivavdelinger i Norge før og under covid-19-pandemien (sykepleien.no) DOI: 10.4220/Sykepleienf.2023.91979
5. Self-reported symptoms experienced by intensive care unit patients: a prospective observational multicenter study. Intensive Care Med. 2023 Nov;49(11):1370-1382. doi: 10.1007/s00134-023-07219-0.
6. Experiences of family members during COVID-19 patients critical illness. https://doi.org/10.1002/nop2.1734
   Use of diary:
7. DOI: 10.1016/j.aucc.2023.02.002
8. https://radio.nrk.no/podkast/ekko_-_et_aktuelt_samfunnsprogram/l_e1dfd268-2f73-4dde-9fd2-682f739ddea6?utm_source=nrkradio&utm_medium=delelenke-ios&utm_content=podcast:l_e1dfd268-2f73-4dde-9fd2-682f739ddea6

[Oslo University Hospital, Division of Emergencies and Critical Care] [case number 3]

Institution: Oslo University Hospital
Administrative unit: Division of Emergencies and Critical Care
Title of case study: Causes and consequences of individual differences in pain sensitivity
Period when the underpinning research was undertaken: 2005-2018
Period when staff involved in the underpinning research were employed by the submitting institution: 2004-now
Period when the impact occurred:2012-now

1. Summary of the impact

Individual differences in pain sensitivity and clinical pain are now studied as part of the concept of "personalized medicine." This has focused on risk factors that can explain the large variability in health outcomes during the lifespan and following identical diseases, injuries, and operations. These differences in acute and chronic pain outcomes have a major impact on health expenses, amounting to 4% of GDP. Furthermore, this allowed us to address gender inequalities and specific women's health issues. Our results have led to a political demand to increase both competence and capacity to treat chronic pain.

2. Underpinning research

Our research group started studying individual differences in pain in 2004, when we first focused on and described the large interindividual variation in clinical pain and pain sensitivity (Rosseland 2004; Nielsen 2005; Romundstad 2006). At this time, most researchers were busy averaging results from RCTs in meta-analysis, believing that the mean results would be the answer to everybody. We believe that studying individual differences is important. We received National Research Council (NRC) and Health South-East (> 10 million NOK) support to sample data as part of the Tromsø study.

Research by our group established the genetic and environmental contributions to the enormous interindividual variation with twin research (Nielsen, 2008). This has impacted researchers to study individual risk factors and has motivated large consortiums like PAIN OUT (from 2012) The consequences for the individuals and for society have been studied further first of all in large epidemiological studies as part of the next waves of the Tromsø study. The Tromsø Pain study (Tromsø6 2007-2008), the youth study FitFutures (2011-2012), and Tromsø7 (2015-2016) are by far the world's largest studies where pain sensitivity and pain tolerance were tested. By combining this with other available data, we have shown important risk factors for acute pain and chronic pain. This has had a major societal impact. Chronic pain is now considered a major contributor to the burden of disease worldwide (Global Burden of Disease Project). We recently published health economy calculations, showing that the cost of chronic pain in Norway amounts to 4% of the gross domestic product (GDP), which has led to a political focus on this patient group.

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Key researchers

- Audun Stubhaug, professor, MD Ph.D, head of department

- Christopher Sivert Nielsen, Ph.D researcher, psychologist, and professor, National Institute of Public Health with a 20% position at dept of Pain Management and Research, OUS

- Leiv Arne Rosseland, professor MD, Ph.D., head of the department for research and development, OUS.

- These researchers have been active during all the years since 2004 with many collaborators

3. References to the research

Rosseland LA, Stubhaug A. Gender is a confounding factor in pain trials: women report more pain than men after arthroscopic surgery. Pain. 2004;112:248-253.
doi: 10.1016/j.pain.2004.08.028. PMID: 15561379.

Nielsen CS, Price DD, Vassend O, Stubhaug A, Harris JR. Characterizing individual differences in heat-pain sensitivity. Pain. 2005;119:65-74.
doi: 10.1016/j.pain.2005.09.018. PMID: 16298065.

Romundstad L, Breivik H, Roald H, Skolleborg K, Romundstad PR, Stubhaug A. Chronic pain and sensory changes after augmentation mammoplasty: long term effects of preincisional administration of methylprednisolone. Pain. 2006;124:92-9.
doi: 10.1016/j.pain.2006.03.020. PMID: 16650580.

Nielsen CS, Stubhaug A, Price DD, Vassend O, Czajkowski N, Harris JR. Individual differences in pain sensitivity: genetic and environmental contributions. Pain. 2008;136:21-9.
doi: 10.1016/j.pain.2007.06.008. PMID: 17692462.

4. Details of the impact (indicative maximum 750 words)

Our studies on individual variations in pain sensitivity have gained worldwide interest and have been leading in this field for several years. Our vision contrasts with others in our field who believed the answer to important health questions was to obtain results for a medium person in a systematic review.

Our vision of individual aspects has now been accepted as the leading guide for pain researchers. The main topic of the European Federation of IASP Chapters (EFIC) 2023 conference was “personalized pain treatment". Individual differences in pain physiology and interference are major research topics in the field.

The publications listed above underline this.

5. Sources to corroborate the impact

Oslo University Hospital and University of Oslo (OUS and UiO)

Division of Surgery, Inflammatory Diseases and Transplantation (KIT)

Case number 1

Institution: Oslo University Hospital
Administrative unit: Division of Surgery, Inflammation Medicine and Transplantation
Title of case study: Liver transplantation as a treatment option in non-resectable colorectal liver metastases
Period when the underpinning research was undertaken: 2005 →
Period when staff involved in the underpinning research were employed by the submitting institution: 2005 →
Period when the impact occurred: 2018 →

1. Summary of the impact

Colorectal cancer (CRC) is a leading cause of mortality in the Western world, and a large proportion of patients develop non-resectable liver metastases (CRLM). The expected 5-year survival on palliative chemotherapy is around 10%. CRLM has until recently been considered an absolute contraindication for liver transplantation. This research program has demonstrated that post-transplant survival outcomes comparable to conventional liver transplant indications may be obtained by applying stringent selection criteria. Several transplant centers worldwide have taken up the concept with ongoing trials. International professional societies have included separate sections for transplant oncology in their programs, and international consensus guidelines have been published.

2. Underpinning research

The research program has progressed stepwise, following the IDEAL guidelines for surgical innovation and research.
A pilot "proof of concept" study was started in 2005, and CRLM patients with diversity in tumor load, treatment regimens, and response to treatment were included. The study was published in 2013 and demonstrated that an estimated 5-year overall survival of 60% could be obtained. Maximal tumor diameter, elevated carcinoembryonic antigen level, no response to chemotherapy, and short interval from diagnosis to transplant were predictive factors for inferior post-transplant survival. They were used to calculate the "Oslo-Score" for stratifying transplant candidates according to risk. However, disease-free survival in the cohort was short, and most patients developed recurrence, which mainly manifested as lung metastases. This is distinctly different from that observed after chemotherapy or liver resection. Most lung lesions could be treated by curative intent resection. Moreover, when compared to a control group, the growth rate of lung metastases in the immunosuppressed liver transplanted cohort was not different, contradicting the existing assumption that the immunosuppression used in liver transplant for CRLM would lead to accelerated tumor growth.

A sequel study started in 2012 and aimed to restrict inclusion to avoid the negative predictive factors identified in the pilot study. the first outcomes were published in 2020, and all patients

displayed an Oslo-Score of 0-1. The estimated 5-year survival was 83%, fully comparable to liver transplantation for conventional indications.
PET/CT with ^{18}FDG is commonly used to rule out extrahepatic disease in CRLM patients. We have demonstrated that the metabolic tumor volume (MTV) defined as the enhancement volume > 40% of standardized maximal uptake volume (SUV_{max}) on pre-transplant PET/CT is highly predictive of long-term survival after liver transplant for CRLM with a cutoff value of 70 cm^3. MTV < 0 cm^3 also predicts long-term survival after lung resection for recurrence and may act as a surrogate marker of "tumor biology" in selecting CRLM transplant candidates.
The scarcity of liver grafts for transplantation is a significant limitation for the wider implementation of liver transplantation for malignant disease. In 2015, our group published a novel surgical concept to expand the donor pool. The RAPID concept is a two-stage procedure that combines partial liver resection, liver transplantation of small partial split liver grafts from a deceased or a living donor, and modulation of graft portal inflow to induce fast liver regeneration. The second stage with final hepatectomy is usually possible after 2-3 weeks. More European centers have adopted this concept, and the RAPID technique has been the subject of two international consensus conferences.

Key researchers:

- Svein Dueland MD PhD, Initiator of the research group and leader 2015-2022, →
- Aksel Foss MD PhD, Initiator of the research group and leader 2005-2015, left in 2015
- Pål-Dag Line MD PhD. Initiator of the research group, leader 2022 →
- Morten Hagness MD PhD, joined 2006, dissertation 2013, group member →
- Harald Grut MD PhD, joined 2015, dissertation 2019, Post-doctoral researcher →
- Tor Magnus Smedman, joined 2017, dissertation 2023, Post-doctoral researcher →
- Trygve Syversveen MD PhD, joined 2015, group member →
- Jon Magnus Solheim, joined 2015, PhD student 2019 →

3. References to the research

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4. Details of the impact

Turning an absolute contraindication into a possible indication for selected patients in a field where scarcity of liver grafts is a worldwide issue requires broad and consistent scientific evidence with international impact over time. Moreover, since transplant recipients, in general, have an increased incidence of de-novo malignancies, it has been postulated that immunosuppression in patients transplanted for metastatic cancer may lead to uncontrollable proliferation of occult micrometastasis.

The pilot SECA-I trial by Hagness et al. in 2013 was published in Annals of Surgery, the highest-impact surgical journal at the time. It was the first controlled prospective trial on liver transplantation for CRLM and sparked significant international interest for two main reasons:

- A substantial treatment benefit was obtained compared to palliative chemotherapy, far beyond what could be expected.
- Predictive factors relevant to improved patient selection were identified

Although a 60% 5-year survival is a good outcome for patients with an expected survival rate of about 10%, it is still a lower rate than required for routine allocation of liver grafts. The Oslo score, derived from this study, was therefore paramount for designing the inclusion criteria in the subsequent SECA-II trial published in Annals of Surgery by Dueland et al. in 2020.

From 2015 and onwards, our group ran several sub-protocols elucidating the impact of immunosuppression on lung metastases, the impact of metabolic tumor volume derived from PET/CT for stratifying patients with short and long survival probabílity as well as the effect on other negative predictive factors like primary tumor sidedness and nodal status, KRAS/BRAF mutation status has on survival outcomes. The collective research effort led to our group getting invited to the annual and biannual conferences of the International Liver Transplant Society (ILTS) and the International Hepato-Pancreato-Biliary Association (IHPBA) from 2016 and onwards to present our studies and/or hold state-of-the-art lectures. Before this, liver transplant for malignancy was mainly limited to hepatocellular carcinoma (HCC) and a few cases of hilar cholangiocarcinoma.

With the broadening of the field that this research program initiated, the term “Transplant Oncology” has been applied to describe transplant for malignancy, signifying a broader multidisciplinary management of patients with non-resectable liver tumors. In 2019, we were invited as a contributor to the ILTS Consensus Conference on Transplant Oncology in Rotterdam and contributed to one of the proceeding papers.
In 2021, the IHPBA decided to publish international consensus guidelines for liver transplantation in non-resectable CRLM in Lancet Gastroenterology and Hepatology. We were invited to contribute, and the guidelines are primarily based on the collective research efforts of the Transplant Oncology Research group at Oslo University Hospital.

The RAPID technique can improve the availability of liver grafts from deceased donors by providing the left lateral sector split graft as a surplus liver. It may also allow living donation between adults with a much lower risk, similar to pediatric liver transplantation, which is standard of care practice worldwide, including in Norway. Together with 5 other European centers, we have demonstrated the technical feasibility and safety of the RAPID procedure, and it has been the main topic of one monothematic conference of the International Society for Liver Surgeons. In October 2023, The 5.

Congress of advanced hepatobiliary surgery of the ISLS devoted a one-day international consensus conference on RAPID according to the Danish Model, where the proceedings are currently in press. Multiple trials have since 2015 been started on liver transplantation for CRLM.

Our research group has helped multiple centers to start transplant programs for CRLM, including Cleveland Clinic, the University of Rochester NY, Stockholm, Gothenburg, Copenhagen, and the National Protocol of the NHS in the UK.

Lastly, we have been invited to contribute to the latest revisions of surgical textbooks and comprehensive monographs on the updated treatment of colorectal liver metastases, indicating that what was once considered a contraindication is gradually becoming part of the standard of care.
The United Network for Organ Sharing has assigned an expert committee where we have participated as experts to work on allocation policies, including MELD exception points, for liver transplantation of CRLM in the US (dr. Shimul Shah (shahsu@ucmail.uc.edu), personal communication.

5. Sources to corroborate the impact (group members in **Bold**)

1. Hibi T, Rela M, Eason J, **Line PD,** Fung J, Sakamoto S, Selzner N, Man NK, Ghobrial RM, Sapisochin G. Liver Transplantation for Colorectal and Neuroendocrine Liver Metastases and Hepatoblastoma. Working Group Report from the ILTS Transplant Oncology Consensus Conference. Transplantation. 2020 Jun;104(6):1131-1135. doi: 10.1097/TP.0000000000003118.

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Oslo University Hospital and University of Oslo (OUS and UiO)

Division of Surgery, Inflammatory Diseases and Transplantation (KIT)

Case number 2

Institution: Oslo University Hospital (OUS) and University of Oslo (UIO)
Administrative unit: Division of Surgery, Inflammatory Diseases and Transplantation (KIT)
Title of case study: Covid-19: – identifying predisposing factors and vaccine side effects that changed treatment guidelines and vaccine policies
Period when the underpinning research was undertaken: 15.02-2020 -31.12.22
Period when staff involved in the underpinning research were employed by the submitting institution: Before, during and after the period.
Period when the impact occurred: 15.02.2020 – 31.12.22

1. Summary of the impact

The COVID-19 pandemic was an enormous challenge for the infected patients and their relatives, the health care system and the whole society. The pandemic was also a major scientific challenge for the research community, and the Translational Research Group (at our Research Institute for Internal Medicine) in KIT took this challenge. We established a nationwide RCT with biobanking from 20 March 2020. In parallel, extensive studies were carried out to map immunopathogenic mechanisms in COVID, pioneering genetic exploration to identify predisposing factors were performed, and later in the pandemic, our research elucidated the underlying mechanisms for the severe side effects of one of the SARS-CoV-2 vaccines within weeks after these adverse effects were reported. This research had instant clinical and societal impact.

2. Underpinning research

Our Translational research group was heavily involved in COVID-related research even at the start of the pandemic. Two weeks after the shut-down in Norway, members of our research group initiated a RCT (Norwegian Medical Agency 20/04950-23)) in Norway including researchers from 23 Norwegian hospitals (Nor-Solidarity), testing out anti-viral drugs as part of the WHO-Solidarity trial. The Nor-Solidarity trial was one of the first to show that the tested medications (i.e., remdesivir and hydroxychloroquine) had no effects on viral load and markers of inflammation in hospitalized patients. Later, we played a major role in testing out immunomodulation agents in hospitalized COVID-19 patients by leading a pan-European platform trial (EU-Solid Act, EU CTIS-number 2022-500385-99-00), paving the way for up-coming studies in emerging pandemics. In contrast to most other RCTs at the time, we organized extended biobanking in these trials including not only plasma/serum but also peripheral blood mononuclear cells and whole blood. The use of this and other biobanks resulted in several publications in relation to immunopathogenic mechanisms in hospitalized COVID-19 patients. These studies suggested a role of extensive activation of the complement system as part of the innate immunity, persistent T cell activation and T cell exhaustion, interaction between immune activation and extracellular matrix remodeling in relation to pulmonary remodeling, increased cellular senescence/accelerated aging and altered DNA repair mechanisms as well as the possible role of gut-microbiota related mediators in the pathogenesis of severe COVID-19 disease. Some of these studies have pointed out potential novel targets for therapy in severe COVID-19 as well as possible mechanisms for long-COVID symptomatology showing persistent immune activation and immune exhaustion even three and 12 months after hospitalization.

In parallel with these studies, another subunit of the research group published as early as June 2020 a groundbreaking article in New England Journal of Medicine on genetic susceptibility to severe

COVID-19 pointing among others to a potential involvement of the ABO blood group. In a follow-up study they showed that the major genetic COVID-19 risk locus is common and has moderate to large effects on COVID-19 outcomes, including mortality, and these effects were age dependent such that the magnitude of risk increases in younger individuals.

In 2021, members of our group, together with other researchers at the Research Institute of Internal Medicine and Department of Hematology (OUS) was the first to report a rare but severe side effect of one of the vaccines that was used against SARS-CoV-2 (AstraZeneca), referred to as vaccine-induced immune thrombotic thrombocytopenia. Follow-up studies from our research group demonstrated that mechanisms leading to this massive thromboembolism, involved formation of antibodies against platelet-factor 4 and formation of neutrophil extracellular traps. Overall, the COVID-19 pandemic showed the ability of our research group to rapidly shift focus by using our expertise in inflammation, metabolism, genetic and thromboembolic research, using a translation approach by combining advance laboratory and clinical research, to contribute to resolve one of the largest health challenges in this decade, involving researchers from a wide range of disciplines across the Institute, OUS, Norway and other countries.

KEY RESEARCHERS

Date: 1.2.2019 – 31.12.2022

- **Prof. Tom Hemming Karlsen**, Senior consultant, Head of Research, KIT, UiO and OUS
- **Prof. Marius Trøseid,** Senior consultant and professor, KIT, UiO and OUS
- **Prof. Johannes Hov**, Senior consultant and professor, KIT, UiO and OUS
- **Prof. Pål Aukrust**, Senior consultant and professor, KIT, UiO and OUS
- **Dr. Tuva B Dahl**, Senior Researcher, KIT, OUS
- **PhD student** Sarah Murphy, MSc, KIT, OUS
- **Prof. Thor Ueland**, KIT, UiO and OUS
- **Prof Pål Andre Holme**, senior consultant, Research institute of Medicine (RIIM), and Dep. Of Hematology Cancer Clinic, UIO and OUS
- **Dr. Annika Michelsen**, Senior Researcher, KIT, UiO
- **Prof. Bente Halvorsen**, Head of Research Institute of Internal Medicine, KIT, UiO and OUS

Key contextual information about the area of research

The pandemic was a reality in the beginning of 2020 and in particular in March 2020 after the Sars-CoV-2 virus had hit worldwide. There was an immediate and huge need of more knowledge of the SARS-Cov2 virus infection and its ravage of human health. KIT did in accordance with OUS and UiO a rapid consolidation of the research forces involving both OUS and UIO employees. This move gave powerful cross-boundaries expertise, ready to underpin Covid-19 disease and testing repurposed drugs (clinical intervention trials). This demonstrates the ability of researchers to shift focus and use their expertise on a huge challenge for the health-care system and the whole society in Norway and in the rest of the world. On this background, the research activity in KIT increased during this period despite problem with delivery of equipment and lab consumables and restriction of activity to avoid spreading of the virus. This period of research also illustrates the ability to rapidly move from idea stage to new knowledge when this is urgently needed. Thus, whereas the treatment of severe Covid-19 in the start of the pandemic was based on rumors, our research contributed to the use of science-based treatment modalities. Moreover, whereas the immunopathogenic mechanisms in the start of the pandemic was not well understood or simplified ("cytokine storm"), our research contributed to a better understanding of these mechanism that involved immune exhaustion and accelerated aging as well as genetic factors. Our research was also able to rapidly elucidate the mechanisms leading to the severe side effects of one of the SARS-CoV-2 vaccine.

3. References to the research

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Grimsrud, (…..77 authors) ….Jesus M Banales, Johannes R Hov, Trine Folseraas, Luca Valenti, Andre Franke, Tom H Karlsen ***Title: Genomewide Association Study of Severe Covid-19 with Respiratory Failure***, **Year:** 2020, **Journal ref:** N Engl J Med. 2020 Oct 15;383(16):1522-1534. doi:10.1056/NEJMoa2020283. Epub 2020 Jun 17. **Link:** Genomewide Association Study of Severe Covid-19 with Respiratory Failure | NEJM **Citations:** 1249 (Scopus. 05.01.2024)

B) Authors: Nina H Schultz, Ingvild H Sørvoll, Annika E Michelsen, Ludvig A Munthe, Fridtjof Lund-Johansen, Maria T Ahlen, Markus Wiedmann, Anne-Hege Aamodt, Thor H Skattør, Geir E Tjønnfjord, Pål A Holme ***Title: Thrombosis and Thrombocytopenia after ChAdOx1 nCoV-19 Vaccination***, **Year:** 2021, **Journal ref:** N Engl J Med. 2021 Jun 3;384(22):2124-2130. doi: 10.1056/NEJMoa2104882. Epub 2021 Apr 9., **Link:** Thrombosis and Thrombocytopenia after ChAdOx1 nCoV-19 Vaccination | NEJM **Citations:** 995 (Scopus. 05.01.2024)

C) Authors: Holm S, Kared H, Michelsen AE, Kong XY, Dahl TB, Schultz NH, Nyman TA, Fladeby C, Seljeflot I, Ueland T, Stensland M, Mjaaland S, Goll GL, Nissen-Meyer LS, Aukrust P, Skagen K, Gregersen I, Skjelland M, Holme PA, Munthe LA, Halvorsen B. ***Title: Immune complexes, innate immunity, and NETosis in ChAdOx1 vaccine-induced thrombocytopenia***, **Year:** 2021 **Journal ref:** European Heart Journal, Volume 42, Issue 39, 14 October 2021, Pages 4064–4072, https://doi.org/10.1093/eurheartj/ehab506 **Link:** Immune complexes, innate immunity, and NETosis in ChAdOx1 vaccine-induced thrombocytopenia | European Heart Journal | Oxford Academic (oup.com) **Citations:** 38 (Scopus. 05.01.2024)

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F) Authors: Anders Tveita, Sarah Louise Murphy, Jan Cato Holter, Anders Benjamin Kildal, Annika E Michelsen, Tøri Vigeland Lerum, Mari Kaarbø, Lars Heggelund, Aleksander Rygh Holten, Ane-Kristine Finbråten, Karl Erik Müller, Alexander Mathiessen, Simen Bøe, Børre Fevang, Beathe Kiland Granerud, Kristian Tonby, Andreas Lind, Susanne Gjeruldsen Dudman, Katerina Nezvalova Henriksen, Fredrik Müller, Ole Henning Skjønsberg, Marius Trøseid, Andreas Barratt-Due, Anne Ma Dyrhol-Riise, Pål Aukrust, Bente Halvorsen, Tuva Børresdatter Dahl, Thor Ueland, NOR-SOLIDARITY Consortium and the Norwegian SARS-CoV-2 Study Group Investigators ***Title: High Circulating Levels of the Homeostatic Chemokines CCL19 and CCL21 Predict Mortality and Disease Severity in COVID-19*** **Year:** 2022 **Journal ref:** J Infect Dis. 2022 Dec 13;226(12):2150-2160. doi: 10.1093/infdis/jiac313. **Link:** High Circulating Levels of the Homeostatic Chemokines CCL19 and CCL21 Predict Mortality and Disease Severity in COVID-19 | The Journal of Infectious Diseases | Oxford Academic (oup.com) **Citations:** 10 (Scopus. 05.01.2024)

4. Details of the impact

- The Nor-Solidarity trial contributed to the change in the treatment modalities of severe COVID-19 disease in Norway and in other countries.
- Our data on persistent immune activation following acute SARS-CoV-2 paved the way for the understanding of the mechanisms of the condition that later has been named long-COVID.

- Our data on the genetic factors that could pre-dispose to COVID-19/severe COVID-19 resulted in similar studies in other research groups.
- Members of our research group rapidly characterized the immunopathogenic mechanisms leading to the severe side effects of the Astra ZenecaSARS-CoV-2 vaccine.
- All these results were published in high-ranked Scientific Journal, and researchers from our group were also active in media.

Wider body of research and its contributions

- The Nor Solidarity trial was part of an international study (WHO Solidarity) that included researchers from several countries throughout the world.
- The Nor Solidarity trial included a close collaboration with 23 hospitals in Norway strongly influencing the treatment modalities of hospitalized COVID-19 patients.
- The Nor Solidarity trial including sub-studies on immunopathogenic mechanisms has resulted in strong research network that will be/are used in relation to other challenges for the health care system and the society such severe influenza, management of patients at intensive care units in more general term, forthcoming pandemics and post-infectious conditions.
- Our studies on COVID-19 have accelerated the process of research collaboration across the disciplines bringing together strong researchers from various clinical disciplines (e.g., infectious diseases, intensive care treatment, pulmonary disorders, cardiology, neurology, haematology) with researcher focusing on basic molecular mechanism (e.g., researcher within the field of immunology, virology, cancer, metabolism, genetic, genome stability).
- Our research group have established a strong a large network in relation to genetic studies in various disorders that were used and expanded during the pandemic illustrating the potential to obtain important results within a short time frame in a complicated area of research.
- Our research has played a major role in characterization the mechanisms that leaded to the severe side effects of Astra Zeneca SARS-CoV-2 vaccine that also could of relevance for certain other types of vaccines.

Details of the beneficiaries

- Our studies have influenced WHO and their guidelines of management of COVID-19
- Our studies have influenced the management of COVID-19 in all hospital in Norway.
- Through our commination in the media, our research has contributed to a better understanding of COVID-19 in the general population in Norway.
- Through our research and clinical network in Norway and Europe, our studies have contributed to a better understanding on how to organize similar large studies in Norway and beyond.

Details of the nature of the impact

- Our studies have been a major contributor to the guidelines of treatment option in severe COVID-19 in Norway, Europa and in the recommendation from WHO.
- Our studies have resulted in the establishing of a scientific and clinical consortium to rapidly meet the challenges in forthcoming pandemics (EU-SolidAct EU response group).
- Our research has establish translational research collaboration across the disciplines that rapidly could perform advanced in depth studies on immunopathogenic mechanisms in emerging diseases like COVID-19.
- Our research resulted in a rapid elucidating of the mechanisms leading to the severe side effects of the Astra Zeneca vaccine that resulted in the stop of this vaccine in Norway followed by Denmark and some other nations.

In total, this had important impact both clinically, academically and societal.

Extent of the impact.

- Our publications from Nor Solidarity and WHO solidarity during 2021-22 illustrate the shift in clinical guidelines (PMID: 34251903, PMID: 34411368)
- Members from our research group have played a major role in establishing and leading the EU-SolidAct/EU Response consortium (PMID: 34763056, PMID: 3631)
- Our research has contributed to a better understanding of the immunopathogenic mechanisms of severe COVID-19 resulting a several important publications (PMID: 35876699, PMID: 35982589, PMID: 35984738, PMID: 36514358, PMID: 34853380, PMID: 36216188, PMID: 35212063).
- Our data on the side effects of the Astra Zeneca vaccine were published in very high-ranked journals (PMID: 34405870, PMID: 33835768)
- Our data on the role of genetic in COVID-19 has received much attention in the research community (PMID: 32558485, PMID: 34597274, PMID: 35410380)

Dates of impacts occurred.

Norway (and several other European countries) paused the use of AZ vaccine on March 11th, 2020, due to reports from Denmark and other European countries of adverse effects possibly from receiving the vaccine. Reference: https://www.theguardian.com/society/2021/mar/11/denmark-pauses-astrazeneca-vaccines-to-investigate-blood-clot-reports and COVID-19 Vaccine AstraZeneca: PRAC investigating cases of thromboembolic events - vaccine's benefits currently still outweigh risks - Update | European Medicines Agency (europa.eu).

- Hydroxycloroquine was stopped as part of standard of care of severe COVID-19 patients' summer 2020
- Remdesivir was restricted to less severe cased during 2022. The clinical and basic research network in Norway was established during 2020 and have expanded since then.

5. Sources to corroborate the impact

Clinical trials / Interventions

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Human Genetics

2. COVID-19 Host Genetics InitiativeMapping the human genetic architecture of COVID-19 Meta-Analysis Nature2021 Dec;600(7889):472-477. doi: 10.1038/s41586-021-03767-x. Epub 2021 Jul 8. PMID: 34237774
3. A second update on mapping the human genetic architecture of COVID-19.COVID-19 Host Genetics Initiative.Nature. 2023 Sep;621(7977):E7-E26. doi: 10.1038/s41586-023-06355-3. Epub 2023 Sep 6. PMID: 37674002
4. Understanding COVID-19 through genome-wide association studies. Nat Genet. 2022 Apr;54(4):368-369. doi: 10.1038/s41588-021-00985-x.PMID: 35410380

Vaccine

5. Nature; How could a COVID vaccine cause blood clots? Scientists race to investigate (nature.com) <https://www.nature.com/articles/d41586-021-00940-0> PMID: 338466075
6. N Engl J Med 2021 Jun 3;384(22):2092-2101. Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 Vaccination. PMID: 33835769
7. JCI Journal of Clinical Investigation <javascript:void(0)> Open AccessVolume 131, Issue 11June 2021 Article number e151092 PMID: 33945504
8. Journal of Thrombosis and Haemostasis <javascript:void(0)> Open AccessVolume 19, Issue 6, Pages 1585 - 1588June 2021 PMID: 34018298
9. Nature Communications NETosis and thrombosis in vaccine-induced immune thrombotic thrombocytopenia | Nature Communications <https://www.nature.com/articles/s41467-022-32946-1> PMID: 36064843
10. Editorial in EHJ European Heart Journal, Volume 42, Issue 39, 14 October 2021, Pages 4073–4076, https://doi.org/10.1093/eurheartj/ehab585. Published: 21 September 2021 PMID: 34545405

Oslo University Hospital and University of Oslo (OUS and UiO)

Division of Surgery, Inflammatory Diseases and Transplantation (KIT)

Case number 3

Institution: Oslo University Hospital and University of Oslo
Administrative unit: Division of Surgery, Inflammatory Diseases and Transplantation (KIT)
Title of case study: Colorectal Cancer Screening – From Clinical Trials to Population Screening
Period when the underpinning research was undertaken: 2000-2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2003-2022
Period when the impact occurred: 2017-2022

1. Summary of the impact

This case illustrates long-term, strategic clinical testing from small feasibility studies to large, population-based clinical trials using different diagnostic tests involving several 100,000 individuals, which lead to nationwide implementation of preventive services against colorectal cancer, one of the most common cancers in the Western World.

The impact of the case is in population health, prevention of disease, personal wellbeing, prioritization of health services, (health) economy, and equality.

2. Underpinning research

The preparatory groundwork for the implementation research for colorectal cancer screening in Norway and the Western world was laid in the early 2000s with the establishment of a rigorous clinical trial and technology science program to develop, refine, test and later implement high-quality endoscopic services which could be used to test screening tools and strategies.

The Environment responsible for this case study started at Telemark Hospital in the late 1990's, continued at Oslo University Hospital from 2003, and is since 2012 organized in the Clinical Effectiveness research group at Oslo University Hospital (in KIT) and the University of Oslo under the leadership of prof. Mette Kalager and Prof. Michael Bretthauer

Examples of early feasibility studies and preparations were randomized trials for carbon dioxide insufflation to replace air as standard gas for gastrointestinal endoscopy (ambient room air was standard around the World at the time). CO2 is now standard for most endoscopic procedures in large parts of the World, thanks to the research group.

The next phase was the implementation and execution of several large-scale randomized trials of screening for colorectal cancer, first in Norway and later in collaboration with other countries, such as:

- The NORCCAP trial, a flexible sigmoidoscopy screening trial that involves 100,000 individuals in Norway in the early 2000s.

- The NordICC trial, a colonoscopy screening trial with 95,000 individuals in Norway, Poland, Sweden and the Netherlands.

- The EPoS trials, a portfolio of 3 clinical trials with altogether 21,000 individuals to test the best surveillance after screening for patients with polyps, in Norway, Spain, Sweden, Denmark, Poland, Austria and the Netherlands.

- The assessment in clinical trials of AI-driven improvements of colonoscopy as a colorectal cancer screening tool, i.e. EndoBRAIN.

Finally, all the results cumulated into a governmental decision in 2018 to start colorectal cancer screening in Norway. The program started in 2022 and will be rolled out into the whole country within 2025.

Key researchers involved:

- Michael Bretthauer, professor UiO, Senior physician and Head of Clinical research unit, OUS.
- Mette Kalager, professor UiO and senior researcher OUS.
- Magnus Løberg, assoc. professor UiO and senior researcher OUS
- Øyvind Holme, assoc. professor UiO and researcher OUS
- Lise M. Helsingen, assoc. Professor UiO and researcher OUS

(All key researchers are still employed in the administrative unit, KIT)

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4. Details of the impact

The research consisted of a series of early-stage, mid-stage and late-stage clinical epidemiology studies and clinical trials, which in a sequential manner explored the best evidence for colorectal cancer prevention over a period of 15 years. The research was supported and underpinned by worldwide collaboration, the generation of clinical practice guidelines and close collaboration with political decision makers towards implementing best evidence preventive services.
Proper, sound and transparent dissemination of the research on every step of the way was achieved by engaging actively in media contributions, op-eds and opinion contributions in oral and written media sources and outlets in Norway and internationally.

The nature and extent of the impact is on the whole Norwegian society by offering screening to all 55-year olds since 2022 based on our research.

The beneficiaries of the research are the Norwegian public at large. The nature of the impact is reduced cases of cancer. The impact occurs as we speak.

5. Sources to corroborate the impact

- **The Norwegian Colorectal Cancer Screening Program: ColorectalScreen Norway (kreftregisteret.no)** – Website for the screening program, implemented nationally in 2022 in all hospital regions in Norway in cooperation with Cancer Registry of Norway.

- **Further information about the underpinning research projects, key researchers, etc.: https://www.med.uio.no/helsam/english/research/groups/clinical-effectiveness/index.html**

Oslo University Hospital and University of Oslo (OUS and UiO)

Division of Surgery, Inflammatory Diseases and Transplantation (KIT)

Case number 4

Institution: Oslo University hospital (OUS) and University of Oslo (UiO)
Administrative unit: Division of Surgery, Inflammatory Diseases and Transplantation (KIT)
Title of case study: Systemic sclerosis: clinical management and disease awareness
Period when the underpinning research was undertaken: 2012-2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2012-2022
Period when the impact occurred: 2015-2022 (and still ongoing)

1. Summary of the impact

Systemic sclerosis (SSc) is a rare, heterogeneous, and complex disease with female predominance and peak age at onset around 50 years. While pathogenesis of SSc is poorly understood, it involves immune-mediated inflammation driving progressive tissue fibrosis and vasculopathy in multiple organs, including skin (scleroderma), lungs, heart, and gastro-intestinal tract (GIT). Effects of existing therapies are limited; largely explaining why SSc has a high disease burden and excess mortality, with interstitial lung disease (ILD) as major cause of death.

From 2012, the OUS/UiO SSc team (from 2022 the NOR-FIORD group, as detailed in Section 3), have conducted trans-disciplinary research having the long-term aim of improving clinical SSc management. While acknowledging that the societal impact of this research may be subject to interpretation, we posit its effects in two pivotal domains:

(I) ***Impact on components of the clinical management continuum provided by the Norwegian specialist health services for SSc patients from diagnosis and throughout their journey.***

Our research has identified shortcomings in the SSc management and provided data on how to address some of them, with potentially wide-reaching impact. A key example is the management of SSc-ILD, where our results showed dependency on high resolution computed tomography (HRCT) imaging for early ILD. Based on these results, a 2020 European consensus argued for universal lung HRCT screening at time of SSc diagnosis, which is now implemented in many countries. In section 3, we discuss impact of research from our team regarding clinical management of pulmonary hypertension. We also discuss impact on GIT involvement, where we set up the first ever early phase randomized clinical trial, providing access to novel therapy for SSc patients in Norway.

(II) ***Impact on the awareness and knowledge level of SSc among stakeholders, including patients, their next of kin, and the public.***

Outlined in section 2, we have contributed research results providing new, unbiased knowledge on incidence, clinical characteristics, specific organ involvements, disease trajectories and risk factors for poor outcome of SSc in Norway. To facilitate integration of these research insights with already existing information on SSc, reach out to stakeholders and disseminate the new knowledge, we applied a set of strategies, described in section 3.

2. Underpinning research

In 2012, the newly established OUH SSc team published the first ever SSc study from Norway. Since then, we have strived to develop innovative, novel, and robust clinical research, focusing on long-term projects with translational aspects. We prioritize research that *addresses unmet clinical needs* in SSc, *fills knowledge gap*s and has immediate and/or long-term *impact on clinical disease management*. Our approaches include observational and interventional studies. Below, we present the parts of this research underpinning the impact summarized in section 1 above:

A. Population-based observational studies

In a major **national-level project** set up in **c**ollaboration with all the other Depts, of Rheumatology in the country, we identified and characterized in detail every single SSc patient resident in Norway from 1999-2012 (n=815) and followed the entire cohort prospectively. Being the only nationwide population-based study ever conducted in SSc, this project provided unique, robust, and unbiased knowledge on SSc incidence, phenotypic spectre, natural history, mortality rates and mortality risk factors (Section 3; ***refs 3 and 4)***. A major goal of the project was to provide detailed prospective data on major organ afflictions, with particular focus on ILD (***ref*** 3) and pulmonary hypertension (PH) (***ref 4***). Underscoring scientific impact, the ILD results were published in the #1 lung medicine journal (***ref 3***), with an accompanying Editorial (Section 5, ref 5.6).

B. Registry based observational studies

Complementing the epidemiology approach, we have through 2012-2022 consecutively included consenting SSc-patients seen at OUH in a prospective observational registry with comprehensive data collection and accompanying biobank (by 2022, >800 unique SSc cases were in the registry). We have used the registry as basis for multiple prospective inter-disciplinary projects involving national and international collaborators. Typically, we include multiple time points and assess multi-parameter data from (A) routine clinical and immunological evaluations (B) protocol organ function studies, like pulmonary function tests (PFT), right heart catheterization (RHC) and echocardiography, (C) advanced tissue imaging, and (D) analyses of candidate liquid biomarkers (derived from collaborative translational studies, like ref 5.4). Among insights obtained by this approach, we highlight work showing importance of lung HRCT in ILD (***ref 1***), work on detrimental mortality risk from SSc heart affliction (***ref 2***) and work indicating predictive ability of novel biomarkers in SSc-PH (ref 5.4). In addition to the OUH registry work, we have taken a leading role in the European Scleroderma Trial and Research (EUSTAR) network, which holds a registry with data on >25 000 SSc cases from >250 SSc expert centres worldwide. Among our EUSTAR cohort projects, we highlight work suggesting that ILD progression in SSc is relapsing rather than relentless progressive, a finding with major implications for clinical management (***ref 5***).

C. **Controlled interventional studies**.

Our observational studies reinforced the notion that GIT dysfunction in SSc was highly common, often severe, and associated with poor outcome (***ref 4***). In collaboration with the University of California in Los Angeles (UCLA) in USA, we identified altered gut microbiota in SSc, possibly representing modifiable environmental risk (ref 5.4). Hence, in 2017, we set up a pioneering controlled pilot trial where we explored safety and effects of standardized faecal microbiota transplantation (FMT) in SSc-patients with severe GIT symptoms (***ref 6***). This study was the first ever to test FMT in any rheumatic disease. Motivated by positive signals from the pilot, we proceeded and were in 2018 able to fund ReSScue, a phase II trial on FMT (by a standardized faecal bacterial culture; ACHIM) in patients with SSc and GIT symptoms. We conducted the trial during the SARS-CoV2 pandemic, and the results are in pipeline (ref 5.9). In 2022, we were able to fund a new controlled full-scale trial, this time on ILD management in SSc, randomizing patients to home monitoring or fixed interval hospital visits (the Nor-mILDer trial).

Key researchers involved:

All the underpinning research described above was led and coordinated by the OUS/UiO SSc team, (within the thematic research group for rheumatology, dermatology and infectious diseases in KIT). The SSc team was originally part of the then Rheumatology sub-group but became the Nor-FIORD group in 2022. While the size and organization of the SSc team have changed, the four people who founded it are still going strong. They are professor **Øyvind Molberg**, who initially led the team and supervised the first PhD students, including **Anna-Maria Hoffmann-Vold**. After completing her PhD Anna was first post-Doc, and from 2018 she led the team, gaining wide international recognition (ref 5.7) The last two original members are **Øyvind Midtvedt**, Senior Consultant and leading clinical expert on SSc, and **Torhild Garen**, who runs the SSc registry. By the end of 2022, the team had grown to 14 members, with 10 being externally funded. In Norway, main collaborators are the nationwide SSc network and a range of OUS researchers in radiology,

lung medicine, cardiology, immunology, and pathology. Among many international collaborators, the UCLA in USA and the University of Zurich, Switzerland are the most important.

3. References to the research, in chronological order, with OUH SSc team underlined

1. Hoffmann-Vold AM, Aaløkken T, Lund MB, Garen T, Midtvedt Ø, Brunborg C, Gran J, Molberg Ø. ***Predictive value of serial high-resolution computed tomography analyses and concurrent lung function tests in systemic sclerosis***/Arthritis Rheumatol/2015/doi: 10.1002/art.39166.
2. Tennøe AH, Murbræch K, Andreassen JC, Fretheim H, Garen T, Gude E, Andreassen A, Aakhus S, Molberg Ø, Hoffmann-Vold AM. ***Left Ventricular Diastolic Dysfunction Predicts Mortality in Patients With Systemic Sclerosis****/J Am Coll Cardiol/2018/doi: 10.1016/j.jacc.2018.07.068*
3. Hoffmann-Vold AM, Fretheim H, Halse AK, Seip M, Bitter H, Wallenius M, Garen T, Salberg A, Brunborg C, Midtvedt Ø, Lund MB, Aaløkken TM, Molberg Ø. ***Tracking Impact of Interstitial Lung Disease in Systemic Sclerosis in a Complete Nationwide Cohort***/Am J Respir Crit Care Med/2019/10.1164/rccm.201903-0486OC.
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5. Hoffmann-Vold AM, Allanore Y, Alves M, Brunborg C, Airó P, Ananieva LP, Czirják L, Guiducci S, Hachulla E, Li M, Mihai C, Riemekasten G, Sfikakis PP, Kowal-Bielecka O, Riccardi A, Distler O; EUSTAR collaborators. ***Progressive interstitial lung disease in patients with SSc-associated ILD in the EUSTAR database***/Ann Rheum Dis/2021/doi: 10.1136/annrheumdis-2020-217455.
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4. Details of the impact

Our research activities on SSc have made distinct and material contributions to the field and have had clinical, academic, and societal impact, as summarized in Section 1, and detailed below:

(I) ***Impact on components of the clinical management continuum provided by the Norwegian specialist health services for SSc patients from diagnosis and throughout their journey***.

Data from our national SSc cohort study showed that all SSc patients in Norway were diagnosed and followed by rheumatologists at public hospitals (**ref 4**). This means that rheumatologists organize all parts of the clinical management chain, including diagnostic work up, patient education, therapy assessment and disease monitoring. Hence, to do SSc research with impact, a good, trustful relation to the rheumatologists in practice is critical. Hence, from the time we began with the national study in 2015, we have actively pursued all opportunities to connect with the clinicians, be it at their own hospitals or at meetings. On these occasions, we have shown and contextualized new research data, but also emphasized the importance of integrating new knowledge in patient education, to facilitate access to accurate and trustworthy disease information at the level of the individual SSc patient.

In 2018, we established a national SSc research network, which included participants from all the rheumatology departments in Norway. We believe this network, among other things, is an indicator of impact from our research activities. Additionally, we have been senior authors on the national SSc management guidelines, which first came in 2020 (ref 5.7).

Regarding impact from research on the clinical management chain, we highlight three specific areas where our results have had clear implications for the patients: (A) evaluation of ILD, (BI) evaluation of PH and (C) treatment of severe GIT symptoms. Notably, out research has also provided data with impact on a range of other clinical management tasks, for example the impact of SSc-related dysfunction of the heart (***ref 2***), time-course of scleroderma and digital ulcers, risk stratification from SSc-specific autoantibodies and other circulating biomarkers (***refs 3, 4***, 5.3. and 5.4), but these have not, to date, had the same clear effects on clinical practice.

A. Evaluation of ILD: In 2012, the role of lung HRCT in SSc-ILD was not clear (ref 5.5). To address this, we conducted a pioneering study in 2015 where we assessed concurrent PFT and lung HRCT data from baseline and follow-up in a large SSc cohort from our registry (ref 1). We made three novel observations. First, patients with no ILD changes by HRCT at baseline never developed ILD. This suggested excellent negative predictive value of HRCT for ILD and indicated that ILD appeared early in SSc. Second, patients with ILD on HRCT often had PFT values within the normal range, suggesting that the common practice of screening for SSc-ILD by PFT was not appropriate. Third, a high proportion of the ILD cases progressed from baseline to follow-up, but the progression rate did not correlate with the baseline PFT value, indicating that screening by PFT also missed progressive ILD cases, with lost opportunities for treatment. The results from the national population cohort confirmed and extended all these findings and added unbiased incidence data showing that nearly 50% of the SSc population had ILD on HRCT. Key take home messages were that HRCT was indispensable for detection of SSc-ILD,that ILD was highly prevalent, and present from the early stages of the disease. Importantly, we did not identify any baseline parameters that predicted presence or progression of ILD. Primarily based on these results, a European expert group on ILD issued a consensus statement in 2020 where they argued for implementation of universal screening for ILD by HRCT in SSc (ref 5.1) This view was confirmed in a recent SSc review in the Lancet (ref 5.2). Many European countries, including Norway (ref 5.7) have implemented screening.

B. Evaluation of PH. In the nationwide population-based cohort study, we found regional differences in the cumulative incidence of PH, corresponding to differences in RHC referral rates. Importantly, we also found that patients who were found to have high probability of PH by echocardiography and risk factor analyses, but had not performed RHC, had mortality rates as high as those with established PH, indicating missed opportunities for PH-specific treatment (**ref 3**). These data highlighted the need for higher clinical PH awareness, more widespread use of PH detection tools and prompt referral to RHC as part of clinical management. Unpublished data indicate uptake of this practice among rheumatologists across the country.

C. Treatment of severe GIT symptoms. As outlined in section 2, we were in 2018 able to provide funding for a national randomized controlled early phase multi-centre trial on safety and efficacy of an intervention aiming to improve lower GIT symptoms in SSc (ref 5.9). The study was organized by our SSc research team, with study sites at four University hospitals, in Oslo, Bergen, Trondheim and Tromsø. Completed in 2022, this was the first ever trial targeting the GIT in SSc, and the first trial in rheumatology to apply standard FMT. While trial results are in pipeline, it was an advance in clinical management that we were able to provide equal opportunities for novel therapies to SSc patients from the whole country.

(II) ***Impact on the awareness and knowledge level of SSc among stakeholders, including patients, their next of kin, and the public.***

Up to 2012, no reliable estimates existed on the size and characteristics of the SSc population in Norway, and we had no data on the natural history or outcome of the disease. Accordingly, when patients and other stakeholders sought information about SSc, we told them about work done by others, mostly originating from tertiary referral centre cohorts. In hindsight, this information was most often not accurate.

In fact, when we compared clinical characteristics, the natural history, and outcomes in our complete, population based SSc cohort to cohorts from other countries, we found differences of major clinical importance. Prime examples include: (I) Higher prevalence of ILD in Norway, but our patients with ILD had more limited and less progressive disease. (II) In Norway, patients had more limited skin changes (scleroderma). (III) We found higher prevalence of GIT involvement in Norway, with GIT-related symptoms increasing over time (***refs 3 and 4***). While case selection in the other cohorts may have contributed to some of the observed differences, the major effects were likely from background genetics and environmental exposures.

Realizing that existing disease information was inadequate, it became a priority to adapt and disseminate new knowledge from our studies to all stakeholders in Norway, starting with the SSc patients and their families. We set up different strategies for reaching out to patients and next of kin at group level and at individual level.
As patient information at individual-level is an integral part of clinical management, we describe our strategy for individual outreach above in the section on management. To reach out to stakeholders at group level, we established contact with the national patient organization for rheumatic diseases (NRF). In close collaboration with them, we set up a research dialogue seminar for patients with SSc and other systemic rheumatic diseases in Oslo in 2014. This was a success, and we have since then co-organized an annual seminar, with more than 300 patients on site, and live streaming. Moreover, we have been given ample opportunities to reach out via NRF's social media platforms and we have given several adapted clinical lectures on SSc at local and regional meetings organized by NRF.
At OUS, we have had the opportunity to disseminate information at group-level by lecturing at the three-day inter-disciplinary SSc courses the hospital organizes three times every year. Through these courses, we have had the opportunity to convey information to, and participate in discussions with, nearly 300 SSc patients and their next of kin.
Incidentally, awareness on SSc in Norway peaked when a highly profiled celebrity went public about her severe SSc and the autologous stem cell therapy she received (in the Netherlands). In this period, national media used us as experts, providing rich opportunities to convey adapted SSc research data to the public. As a corollary, shortly after the media coverage started, we received a long-awaited approval to do the first autologous stem cell therapy on SSc in Norway.
While impact from the described research education activities is expected, there is a paucity of evidence as we have not, at any time point, studied health literacy in the SSc population.

5. Sources to corroborate the impact

5.1 The identification and management of interstitial lung disease in SSc: evidence-based European consensus statements. A.-M. Hoffmann-Vold, T. M. Maher, E. E. Philpot, A. Ashrafzadeh, R. Barake, S. Barsotti, et al. The Lancet Rheumatology 2020 DOI: 10.1016/S2665-9913(19)30144-4
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5.6 Keane MP. The Fibrosis Burden of Systemic Sclerosis. Am J Respir Crit Care Med. 2019 doi: 10.1164/rccm.201907-1438ED.
5.7 (in Norwegian) Systemisk sklerose; Anbefalinger for likeverdig diagnostikk, behandling og oppfølging av pasienter i Norge.
5.8 Anna-Maria Hoffmann-Vold: building bridges in systemic sclerosis (INSIGHTS|PROFILE**.** J. Morgan, The Lancet Rheumatology 2022. DOI: 10.1016/S2665-9913(22)00262-4
5.9 Hoffmann-Vold AM, Fretheim HH, Sarna VK, Barua I, Carstens MN, Distler O, Khanna D, Volkmann ER, Midtvedt Ø, Didriksen H, Dhainaut A, Halse AK, Bakland G, Pesonen M, Olsen I, Molberg Ø. Safety and efficacy of faecal microbiota transplantation by Anaerobic Cultivated Human Intestinal Microbiome (ACHIM) in patients with SSc: study protocol for the randomised controlled phase II ReSScue trial/BMJ Open/2021/doi: 10.1136/bmjopen-2020-048541.

Oslo University Hospital and University of Oslo (OUS and UiO)

Division of Surgery, Inflammatory Diseases and Transplantation (KIT)

Case number 5

Institution: Oslo University Hospital (OUS) and University of Oslo (UiO)
Administrative unit: Division of Surgery, Inflammatory Diseases and Transplantation (KIT)
Title of case study: Kidney transplantation – improved selection, survival and quality of life
Period when the underpinning research was undertaken: 1998 - 2022
Period when staff involved in the underpinning research were employed by the submitting institution: 1992-2022
Period when the impact occurred: 2007-2022

1. Summary of the impact

Clinical research performed by the group over the last decades has focused on an overall improvement in patient long-term outcomes. Together this will have impact on the following:

- **Clinic**: new and improved procedures and services, e.g. more accurate renal function assessments from more easily obtainable finger-prick samples.
- **Health & Quality of Life**: Better individualised drug treatment result in longer patient- and graft-survival and longer time with a higher quality of life compared with dialysis.
- **Economy**: Longer kidney graft-survival will 1) reduce the need for dialysis with substantial lower costs for society (annual saving US$ 80.000 per patient), 2) reduce the shortage of organs available for transplantation and 3) increase patients ability to work.
- **Environment**: Dialysis has a bigger footprint on nature (e.g. wastewater, one-time use plastic products). Also, moving towards more finger-prick based drug monitoring (10 µL blood instead of mL:s) where samples are obtained by the patient at home reduce organic solvent use in the laboratory and reduce travel to hospital.

2. Underpinning research

Clinical research performed by the group over the last decades have focused on an overall improvement in patient outcomes. Our strategy has been to focus on *the right drug to the right patient at the right level.* The hypothesis is that optimally individualised drug choice and dosing will improve graft- and patient-survival and minimizing adverse effects. Relevant to this impact case it all started with the ELITE-Symphony study of minimization of immunosuppressive therapy, a landmark study in kidney transplantation.

Right drug to the right patient: It is always a question in transplant medicine when new drugs become available if they interact with the immunosuppressive drugs that kidney transplants need for the rest of their lives. The group have performed numerous such interaction studies. However, it is also important to investigate if such novel drugs show the same effect in transplants, e.g. due to one well-functioning kidney but overall reduced renal function, denervated kidney etc. One such well cited contribution from the group is the pilot study of empagliflozin (SGLT2-inhibitor) effects in kidney transplants [4]. The study showed that empagliflozin works as expected and is well tolerated in kidney transplants (Midtvedt, Hartmann, Åsberg & Jenssen, 2016-2019). Based on these results, our group has now started a large (n=330) 3-year randomized clinical trial to investigate renal protection-effects of SGLT2-inhibitors on transplant kidney function. An intervention that may prolong graft survival significantly.

Individualized dosing of immunosuppressive drugs: Based on rich high-quality pharmacokinetic data obtained from several clinical studies on tacrolimus performed at our centre, a population pharmacokinetic model has been developed. Bayesian estimates based on this population model are implemented in a clinical computer tool for individualized dosing of tacrolimus. In a prospective, randomized clinical trial we did a head-to-head comparison of tacrolimus target achievement between the computer tool and experienced transplant physicians in the early posttransplant phase [6]. The computer tool showed significant better target achievement. Later studies within the period embracing this Impact Case have taken this application further to also include total systemic drug dose-interval exposure ($AUC_{0\text{-}tau}$) targeted monitoring utilizing finger-prick sampling by the patients themselves, at home (Åsberg & Midtvedt, 2012-2015).

Immunosuppression and viral infections: Infections is a general problem after transplantation due to the immunosuppressive therapy. The most troublesome viral infection after kidney transplantation is mediated by cytomegalovirus (CMV). In 2005 our group performed an investigator-initiated, international, multicentre study on oral (compared with intravenous) treatment of CMV disease in solid organ transplants (The VICTOR-study). Study idea, management, centralized study biobank and primary endpoint analyses (quantitative PCR DNAemia) were all done by our centre. The primary endpoint results were published before the period of this Impact Case but many of the secondary endpoint publications, e.g. impact of immunosuppressive load on CMV viral loads, were produced within the period, all summed up in a *Lessons-learned*-paper [5]. The results have had a big impact on current international guidelines on *management of CMV in transplantation* (Åsberg & Hartmann).

Post-transplant diabetes mellitus (PTDM): Diabetes is common after kidney transplantation. Our group has in the Impact Case period been acknowledged internationally for showing: 1) That PTDM is a major risk factor for death in kidney transplant recipients. 2) That the diagnostic criterion HbA1c is largely invalid the first year after transplantation. 3) That PTDM is mediated not only by decreased insulin release, but also increased glucagon release [2]. 4) That central obesity rather than peripheral obesity predisposes to PTDM. Therefore, two of our review papers published in Nature Rev Nephrol and Nature Rev Endocrinol, respectively, have been widely cited, and we have been instrumental in the two most recent international guideline meetings (2013 and 2022). We are currently member of the EU-funded DOKI (Diabetes-Obesity-Kidney) project. (Hartmann, Åsberg, Reisæter & Jenssen, 2012-2015).

Health Related Quality of Life (HRQoL): The Question-65 study investigates changes in HRQoL in transplant recipients over 65 years, from the time before to long-term after transplantation. The overall finding is that transplantation is associated with a sustained improvement in HRQoL [3]. Comorbidity modulates however this effect and frail patients do not necessarily see the same improvement as patients with low comorbidity burden. This is an important finding for our transplant program that do not have an upper age cut-off for transplant candidates, why these findings potentially can fine tune the evaluation of patients that will benefit from a kidney transplant in an even better way (Midtvedt, Reisæter & Heldal, 2014-2022).

Better determination of outcome endpoints: Renal function assessed by glomerular filtration rate (GFR) is a main endpoint in kidney transplantation. GFR can be *estimated* with different formulas based on for example plasma creatinine but to get an accurate GFR *measurement* the elimination of exogenous administered substances like iohexol (X-ray contrast substance) needs to be determined. We have improved the old iohexol *measured* GFR method by using population pharmacokinetic modelling and Bayesian estimates [1]. The new method (mgfr.no) is more accurate, especially at low GFR levels, and can be carried out in all patients within 5 hours, as opposed to up to 24 hours with the old method, also in patients with low renal function (Åsberg &

Hartmann, 2016-2020).

Key researchers involved

- Professor Trond Jenssen, consultant in nephrology (1997-present), OUS and UiO
- Professor Anders Hartmann, consultant in nephrology (1986-2018), OUS and UiO
- Dr. Anna Varberg Reisæter, consultant in nephrology (1989-2023), OUS and UiO
- Dr. Karsten Midtvedt, consultant in nephrology (1993-present), OUS
- Professor Anders Åsberg, Head of laboratory (2013-present), OUS and UiO
- Associate professor Kristian Heldal, consultant in nephrology (2019-present), OUS and UiO

(And multiple other researchers and research support staff over the years)

3. References to the research

Peer reviewed journal publications

In total 53 original articles in relation to the present Impact Case, including:

1. Åsberg A, Bjerre A, Almaas R, Luis-Lima S, Robertsen I, Porrini E, Schwartz G, Hartmann A, Bergan S. *Measured GFR by utilizing population pharmacokinetic methods to determine iohexol clearance*. KI Reports 2020; 5(2), 189-198. doi: 10.1016/j.ekir.2019.11.012.
2. Halden TAS, Egeland EJ, Åsberg A, Hartmann A, Midtvedt K, Khiabani HZ, Holst JJ, Knop FK, Hornum M, Feldt-Rasmussen B, Jenssen T. *GLP-1 restores altered insulin and glucagon secretion in post-transplantation diabetes mellitus*. Diabetes Care 2016; 39(4): 617-24. doi: 10.2337/dc15-2383.
3. Tsarpali V, Midtvedt K, Lønning K, Bernklev T, Lippe NV, Reisæter AV, Brunborg C, Heldal K. Health-Related *Quality of Life in Older Kidney Transplant Recipients: A National Cohort Study of Short- and Longer-Term Outcomes*. Kidney Med. 2021 Jul 22;3(6):974-983.e1. doi: 10.1016/j.xkme.2021.05.007.
4. Halden TAS, Kvitne KE, Midtvedt K, Rajakumar L, Robertsen I, Brox J, Bollerslev J, Hartmann A, Åsberg A, Jensen T. *Efficacy and Safety of Empagliflozin in Renal Transplant Recipients with Post-Transplant Diabetes Mellitus*. Diabetes Care 2019; 42(6): 1067-1074. doi: 10.2337/dc19-0093.
5. Åsberg A, Humar A, Rollag H, Jardine AG, Kumar D, Aukrust P, Ueland T, Bignamini AA, Hartmann A. Lessons learned from a randomized study of oral valganciclovir versus parenteral ganciclovir treatment of CMV-disease in solid organ transplant patients - The VICTOR trial. Clin Inf Dis 2016; 62(9): 1154-1160. doi: 10.1093/cid/ciw084.
6. Størset E, Åsberg A, Skauby M, Neely M, Bergan S, Bremer S, Midtvedt K. *Improved tacrolimus target concentration achievement using computerized dosing in renal transplant recipients - a prospective, randomized study*. Transplantation 2015; 99(10): 2158-2166. doi: 10.1097/TP.0000000000000708.

Peer reviewed grants

US$ 10,480,000 peer reviewed and US$ 3,100,000 industry funding in the period 2012-2022, including:

- Health region South-East: US$ 6,300,000
- Scandiatransplant: US$ 230,000
- Norwegian Research Council: US$ 2,900,000
- EU Research Council: US$ 550,000
- Coalition for Epidemic Preparedness Innovations (CEPI): US$ 500,000

- Pharma Industry: US$ 3,100,000

4. Details of the impact

The ELITE-Symphony study [A] set the premises of modern immunosuppressive therapy in the field of kidney transplantation, using lower doses of the drugs that generally are associated with significant side-effects, such as nephrotoxicity, post-transplant diabetes mellitus, infection and cancer. In order to keep the immunosuppressive therapy safe for all patients, i.e. assuring that they are not under immunosuppressed, close monitoring of each patients dosing is necessary. Current international guidelines underline the importance of utilizing advanced computer tools and taking AUC-targeted drug monitoring into clinical practice (impact in 2019) [B]. Our data has been central for the development of these guidelines and is based on a tight methodological cooperation between our group and other top centres in the world within this field of research (Limoges, France and Los Angeles, USA).

Taking other variables into consideration in the choice of immunosuppressive and other types of drug therapy in this population is also important and the impact of this need to be investigated. Our research on interaction between new drugs and immunosuppressive therapy is important for an overall safe drug therapy and have laid the ground for the use of novel therapeutics in the field of kidney transplantation (impact between 2012-2022). This will in the end prolong graft-survival and therefore keep more patient away from dialysis treatment which is good for HRQoL and in addition much more cost-effective [C, D]. For example, our pilot study with SGLT2-inhibitor treatment in kidney transplants [4] has paved the way towards as large prospective, randomized, placebo-controlled kidney protective study at our centre (impact in 2022 [E]. If the hypothesis holds true, graft-survival will be prolonged significantly. This possible outcome will provide a significant improvement for both the individual patient experiencing better QoL and longer time in good health and for the society by keeping the financial burden lower allowing more patients to get a good kidney replacement therapy, i.e. kidney transplantation before dialysis.

The VICTOR-study was a close collaboration between top centres within the field of transplant infection disease around the world (Toronto, Glasgow, Minneapolis, Milan, Lausanne). In the VICTOR-study we showed for example that CMV disease can be treated with oral drugs as compared with the need of intravenous therapy that was the gold standard before these results were available (impact in 2010 and onwards) [F]. Intravenous therapy requires in most cases hospitalization of patients which is expensive and in many cases impact negatively on the QoL of the patient. Among the secondary endpoint results from the VICTOR-study, we could for example show a correlation between immunosuppressive load and treatment efficacy of CMV therapy [G]. This further underline the importance of keeping the immunosuppressive therapy as low as possible and this can be done in a safer manner with the novel computer tools developed by our group (impact from 2010 and onwards).

Important impacts on Economy and QoL can be achieved by more precise diagnostic tools. Our research has improved both the diagnosis of PTDM, an important risk factor for patient survival (impact from 2015 and onwards) [H]. With better diagnostic tools proper intervention may be applied at an earlier stage and long-term outcomes will as a result improve. The improved and more patient friendly new method for determine measured GFR based on iohexol serum clearance (mgfr.no) is important for collection of accurate endpoint data in prospective clinical trials. It has also brought us a tight international collaboration, also on PTDM, with Professor Porrini (Tenerife). Together we now validate the improved measured GFR method in different populations with impaired renal function, also using a finger-prick method for obtaining the necessary iohexol blood concentrations (see below).

Limiting the number of patients receiving dialysis treatment will save the environment from a significant impact that large volumes of one-time equipment, wastewater etc. represent (impact

from 2012 and onwards). Our research has also been in the forefront in the field of transplantation regarding development of finger-prick, micro sampling by the patient themselves (at home). This has so far been applied for drug monitoring [I] and is now available in clinical practice at our centre (impact from 2021 and onwards) [J]. This saves the environment from excessive use of organic solvents in the laboratory. In addition, it is a more patient friendly alternative than venepuncture, both since it is less painful, smaller blood volume and patients can take the samples themselves in their own home. Samples are sent to the laboratory by standard mail service, saving both resources at the hospital and limit the number of visits (travel) to the hospital. The impact of our research is better QoL and reduced negative impact on the environment (impact from 2021 and onwards).

5. Sources to corroborate the impact

A. Ekberg H et al. Reduced exposure to calcineurin inhibitors in renal transplantation. N Engl J Med. 2007 Dec 20;357(25):2562-75. doi: 10.1056/NEJMoa067411.

B. Brunet M et al. Therapeutic Drug Monitoring of Tacrolimus-Personalized Therapy: Second Consensus Report. Ther Drug Monit. 2019 Jun;41(3):261-307. doi: 10.1097/FTD.0000000000000640.

C. Zhang Y et al. Healthcare costs after kidney transplantation compared to dialysis based on propensity score methods and real world longitudinal register data from Sweden. Sci Rep. 2023 Jul 3;13(1):10730. doi: 10.1038/s41598-023-37814-6.

D. Heldal K et al. Kidney transplantation: an attractive and cost-effective alternative for older patients? A cost-utility study.Clin Kidney J. 2019 Feb 28;12(6):888-894. doi: 10.1093/ckj/sfz018.

E. Heerspink HJL et al. Effect of dapagliflozin on the rate of decline in kidney function in patients with chronic kidney disease with and without type 2 diabetes: a prespecified analysis from the DAPA-CKD trial. Lancet Diabetes Endocrinol. 2021 Nov;9(11):743-754. doi: 10.1016/S2213-8587(21)00242-4.

F. Åsberg A et al. Oral valganciclovir is noninferior to intravenous ganciclovir for the treatment of cytomegalovirus disease in solid organ transplant recipients. Am J Transplant. 2007 Sep;7(9):2106-13. doi: 10.1111/j.1600-6143.2007.01910.x.

G. Åsberg A et al. Effects of the intensity of immunosuppressive therapy on outcome of treatment for CMV disease in organ transplant recipients. Am J Transplant. 2010 Aug;10(8):1881-8. doi: 10.1111/j.1600-6143.2010.03114.x.

H. Hjelmesaeth J et al. The impact of early-diagnosed new-onset post-transplantation diabetes mellitus on survival and major cardiac events. Kidney Int. 2006 Feb;69(3):588-95. doi: 10.1038/sj.ki.5000116.

I. Vethe NT et al. Tacrolimus Can Be Reliably Measured With Volumetric Absorptive Capillary Microsampling Throughout the Dose Interval in Renal Transplant Recipients. Ther Drug Monit. 2019 Oct;41(5):607-614. doi: 10.1097/FTD.0000000000000655.

J. Vethe NT et al. Clinical performance of volumetric finger-prick sampling for the monitoring of tacrolimus, creatinine and haemoglobin in kidney transplant recipients. Br J Clin Pharmacol. 2023 Aug 3. doi: 10.1111/bcp.15870.

Oslo University Hospital, and the Faculty of Medicine, University of Oslo; Division of Gynaecology and Obstetrics

case number#1

Institution: Oslo University Hospital, and the Faculty of Medicine, University of Oslo; OUS and UiO, Klinmed
Administrative unit: Division of Gynaecology and Obstetrics, DivObstGyn
Title of case study: Saving lives by improving mother's care; A study of the numbers, causes and contributing factors of maternal deaths
Period when the underpinning research was undertaken: 2010-2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2006-2022
Period when the impact occurred: 2012-2022

1. Summary of the impact

The impact of the current study is reducing the number of maternal deaths in Norway by making pregnancy safer.

A detailed scrutiny of all maternal deaths since 1995 showed that preeclampsia was the leading cause of death with one to two deaths yearly. These deaths occurred among young and previously healthy women. Along with the current research and after implementation of new national guidelines for the management of women with severe preeclampsia, such deaths were prevented. After 2012, no death from preeclampsia has occurred in Norway.

2. Underpinning research

Through establishment of a valid reporting system and audit assessment of maternal deaths in 2010, we report on the cause of death and the quality of care during 1995 and onwards.

The definition of a maternal death is the death of a woman while pregnant or within 6 weeks after delivery. Hence, we cannot count such deaths automatically from any registration source. As an example, the Medical Birth Registry of Norway has incomplete registration of numbers of maternal deaths.
An increasing load of evidence from all over Europe indicated that maternal deaths are seriously underreported, also in developed countries like the Scandinavian.

Through registry linkage and direct reporting from hospitals all over the country, we established a valid reporting system of maternal deaths, which count all deaths, also the indirect deaths. Indirect maternal deaths includes deaths caused by pre-existing maternal disease. Experienced senior clinicians from different health regions in Norway (Pål Øian (The Arctic University of Norway), Ferenc Macsali (Haukeland University Hospital), Liv Ellingsen (Oslo University Hospital), Siri Vangen (Oslo University Hospital), Lill Trine Nyfløt (Oslo University Hospital) and Anne Flem Jacobsen (Oslo University Hospital)) took part in the audit group. The audit group scrutinised each case to classify the cause of death and the quality of care by using a modified UK-based form, the Confidential Enquiry into Maternal and Child Health form (CEMACH), continued by the Maternal, Newborn and Infant Clinical Outcome Review Program (MBRRACE_UK).

Through systematic audit assessment, the audit group concluded that improvements to care could have made a difference to the outcome in 14 out of 16 maternal deaths from preeclampsia.

3. References to the research (names in bold are DivObstGyn affiliated researchers)

1) Maternal deaths from hypertensive disorders: lessons learnt. **Nyfløt LT**, **Ellingsen L**, **Yli BM, Øian P, Vangen** S. Acta Obstet Gynecol Scand. 2018 Aug;97(8):976-987. doi: 10.1111/aogs.13357. Epub 2018 May 8.PMID: 29663318

2) Maternal deaths in Norway 2005-2009. **Vangen S**, Ellingsen L, Andersgaard AB, **Jacobsen AF, Lorentzen B, Nyfløt LT**, Rygh AB, Skulstad SM, Tappert C, **Øian P.**Tidsskr Nor Laegeforen. 2014 Apr 29;134(8):836-9. doi: 10.4045/tidsskr.13.0203.

3) Norwegian national guideline in obstetrics. Hypertensive pregnancy complications Hypertensive svangerskapskomplikasjoner og eklampsi (legeforeningen.no) **Annetine Staff** et al. 2020. The Norwegian Medical Association. This Chapter also includes patient information, both in Norwegian and in English, also guiding future health follow-up among survivors of preeclampsia.

4) Hvorfor dør kvinner av graviditet i dag? Report (Why do mothers die of pregnancy today?) **Lill Trine Nyfløt, Liv Ellingsen, Siri Vangen**. modredodsrapport_2021_web.pdf (oslo-universitetssykehus.no)

5) Article/interview, VG: **Færre dødsfall blant gravide og nybakte mødre i Norge**. (Fewer deaths among pregnant and new mothers in Norway) **Trine Nyfløt**, 2022.

4. Details of the impact

Before this study was undertaken no evidence of the numbers and causes of maternal deaths existed in Norway. A similar situation was found in the other Nordic countries. Then the Nordic Maternal Collaboration was founded in 2010 based on request from Birgit Bødker, chief obstetrician in Nordsjællands Hospital, Denmark. Denmark had already set up a reporting system of maternal deaths based on registry linkages. The same year a similar reporting system was set up in Norway in collaboration with The Medical Birth Registry and senior obstetricians around the country. The Medical Birth Registry of Norway is linking the Birth Registry with the Cause of death registry routinely in January every year. The file is sent to the project leader for further analyses and audit assessments. In addition, to secure a complete registration, cases are reported directly from the hospitals.

Retrospective analyses from 1995 showed that preeclampsia was by far the most important cause of death. Furthermore, the finding that improvement to care could have made a difference to the outcome in the large majority of these deaths showed the need for revision of the guideline for the management of women with preeclampsia. Blood pressure treatment, stabilization before a caesarean section, and timely induction of birth, were crucial issues for prevention of further deaths from preeclampsia. In addition, this message was disseminated at internal meetings, and national and international meetings. In particular, the senior obstetrician Liv Ellingsen at Rikshospitalet, Oslo University Hospital took a major role in disseminating the results at every occasion. This process took place during 2012 -2022. Since 2012, there has been no maternal death from preeclampsia in Norway.

We believe the participation of senior obstetricians in the audit group being active at the obstetric departments around the country and their participation in updating clinical guidelines is crucial for the eradication of maternal deaths from preeclampsia in Norway.

In 2016, the study "Saving lives by improving mother's care" was awarded three full years postdoctoral from South-East Health Region Authority (Totally 3 147 000, a 20 % position expands the study period to 1928). The postdoctoral candidate will continue monitoring trends, causes and risk factors for maternal deaths. In particular, the project aims to go into details of maternal sepsis and suicides. The candidate also leads the Nordic collaboration. A joint Nordic data file from 2005 and onward is available for analyses.

A report with clinical advice based on the audit assessments of the cases is published every three on the research centre's home page.

5. Sources to corroborate the impact (names in bold are DivObstGyn affiliated members)

1) Maternal mortality in eight European countries with enhanced surveillance systems: descriptive population based study. Diguisto C, Saucedo M, Kallianidis A, Bloemenkamp K, Bødker B, Buoncristiano M, Donati S, Gissler M, Johansen M, Knight M, Korbel M, Kristufkova A, **Nyflot LT**, Deneux-Tharaux C.BMJ. 2022 Nov 16;379:e070621. doi: 10.1136/bmj-2022-070621

2) The impact of cardiovascular diseases on **maternal deaths** in the Nordic countries. **Nyfløt LT,** Johansen M, Mulic-Lutvica A, Gissler M, Bødker B, Bremme K, **Ellingsen L**, **Vangen S.** Acta Obstet Gynecol Scand. 2021 Jul;100(7):1273-1279. doi: 10.1111/aogs.14104. Epub 2021 Feb 21.PMID: 33524162

3) **Maternal deaths** in the Nordic countries. **Vangen S**, Bødker B, Ellingsen L, Saltvedt S, Gissler M, Geirsson RT, Nyfløt LT.Acta Obstet Gynecol Scand. 2017 Sep;96(9):1112-1119. doi: 10.1111/aogs.13172. Epub 2017 Jul 7.PMID: 28542709

4) Maternal deaths from hypertensive disorders: lessons learnt. **Nyfløt LT, Ellingsen L, Yli BM, Øian P, Vangen S**. Acta Obstet Gynecol Scand. 2018 Aug;97(8):976-987. doi: 10.1111/aogs.13357. Epub 2018 May 8.PMID: 29663318

5) Maternal deaths in Norway 2005-2009. **Vangen S, Ellingsen L,** Andersgaard AB, **Jacobsen AF, Lorentzen B, Nyfløt LT**, Rygh AB, Skulstad SM, Tappert C, **Øian P.**Tidsskr Nor Laegeforen. 2014 Apr 29;134(8):836-9. doi: 10.4045/tidsskr.13.0203.

6) National Guidelines in Obstetrics. Hypertensive pregnancy complications. Hypertensive svangerskapskomplikasjoner og eklampsi (legeforeningen.no). **Annetine Staff** et al. 2020, The Norwegian Medical Association.

7) Hvorfor dør kvinner av graviditet i dag? (Why do mothers die of pregnancy today?) modredodsrapport_2021_web.pdf (oslo-universitetssykehus.no)

8) Article/interview, VG: Færre dødsfall blant gravide og nybakte mødre i Norge. (Fewer deaths among pregnant and new mothers in Norway) **Trine Nyfløt**, 2022.

University of Oslo (UiO)/Oslo University Hospital (OUS), Division of Mental Health and Addiction (DMHA)
Case number: 1

Institution: UiO/OUS
Administrative unit: DMHA
Title of case study: Defining the outcome of psychotic disorders
Period when the underpinning research was undertaken: 2012-2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2012-2022
Period when the impact occurred: 2016 -

1. Summary of the impact (indicative maximum 100 words)

Psychotic disorders are lifelong relapsing-remitting disorders with a negative impact on quality of life and increased risks of disability and premature death. To what extent the disorders are neurodegenerative/progressive and when adverse developments occur is unclear. The current research (NORMENT Centre aim 4) has shown that the long-term outcomes of first-treatment patients are better than assumed, with few indications of neuroprogression, and that clinical trajectories in the first year of treatment are highly indicative of long-term outcomes. This also makes the initial treatment phase a critical window for intervention. The findings considerably impact how we meet and inform new patients with these disorders, and give directions for the subsequent phases of research.

2. Underpinning research (indicative maximum 500 words)

In the preceding period, our research group had been instrumental in showing that early interventions for psychotic disorders had a significant impact on short- and long-term outcomes. To what extent psychotic disorders by nature were a) relatively stable neurodevelopmental disorders, where prompt interventions lead to "more benign illness trajectories from the start of treatment," or b) to what extent prompt treatments were "stopping neuroprogressive processes" in an inherently neurodegenerative disorder were not known. This difference is not just of academic interest but significantly impacts how we understand psychotic illnesses, focus treatment efforts, and motivate patients to engage in treatments. Our main hypothesis was that a) differences in illness severity between first- and multi-episode patients were based on the enrichment of treatment unresponsive patients in multi-episode samples rather than illness progression, and b) following from this that first-episode samples were the most relevant samples to investigate not only for predictors of outcome but also treatment effects. To achieve this, we established a comprehensively characterized (genetics, environmental risks, illness history, clinical symptoms, cognitive functioning, and brain imaging) first-treatment sample recruited consecutively from the catchment-area-based services in the larger Oslo region, followed up after one and ten years. All participants gave consent to registry linkage. The findings can be summarized as follows:

1) There were significant MRI differences between patients and healthy controls but no signs of progressive brain change over the first year, as suggested by earlier studies.
2) There were significant differences between patients and healthy controls, but improvement rather than progression in cognitive functioning over the first year.
3) Negative symptoms are seen as core psychopathologies in schizophrenia spectrum disorders. We found small improvements in negative symptoms over the first year of treatment, with primarily stable levels from there to the ten-year follow-up.
4) Patients with stable high negative symptoms had more cognitive dysfunctions

5) Symptom developments were influenced by childhood adverse events and cannabis use.
6) The chances of full recovery in the long term were higher than often assumed and may be a treatment goal for a subset of patients.
7) General cognitive functioning fell from premorbid levels to the start of treatment in both schizophrenia and bipolar I disorder but improved from this level to ten-year follow-up.

The research was ongoing throughout the ten-year period, but the long-term follow-ups were delayed due to corona lockdowns. Results concerning the course of positive psychotic symptoms, mood symptoms, and brain structures are presented at scientific conferences but are currently unpublished. Analyses of predictors of course trajectories are ongoing. The preliminary results are in line with the following conclusion:

I. Clinical symptoms, cognitive function and MRI findings do not support the idea of neuroprogression in the majority of schizophrenia spectrum - and bipolar disorders
II. The majority of patients are without continuous and severe symptoms after 10 years of treatment and the chances of full recovery is high, especially in bipolar disorders.
III. The main prediction analyses are not completed, but given the small effect sizes for associations to clinical symptoms in cross-sectional studies, we do not expect that current biomarkers (including polygenic risk scores) will have significant influence.

Professor Ingrid Melle (clinical): 2012-2022
Professor Ingrid Agartz (imaging): 2012-2022.
Professor Ketil Sundet (cognition): 2012-2018
Senior scientist, later Associate professor Torill Ueland (cognition): 2012-2022
Senior scientist, later Professor Trine Vik Lagerberg (clinical): 2013-2022
Senior scientist, later Professor Unn Haukvik (imaging): 2015-2022
Senior scientist Carmen Simonsen (recovery): 2013-2022
Associate professor Nils Eiel Steen (biomarkers): 2013-2022

3. References to the research (indicative maximum of six references)

1) Haukvik UK, Hartberg CB, Nerland S, Jørgensen KN, Lange EH, Simonsen C, Nesvåg R, Dale AM, Andreassen OA, Melle I, Agartz I. No progressive brain changes during a 1-year follow-up of patients with first-episode psychosis. Psychol Med. 2016 Feb;46(3):589-98. doi: 10.1017/S003329171500210X. Epub 2015 Nov 3. PMID: 26526001.
2) Demmo C, Lagerberg TV, Kvitland LR, Aminoff SR, Hellvin T, Simonsen C, Haatveit B, Andreassen OA, Melle I, Ueland T. Neurocognitive functioning, clinical course and functional outcome in first-treatment bipolar I disorder patients with and without clinical relapse: A 1-year follow-up study. Bipolar Disord. 2018 May;20(3):228-237. doi: 10.1111/bdi.12569. Epub 2017 Nov 9. PMID: 29121444.
3) Lyngstad SH, Gardsjord ES, Engen MJ, Haatveit B, Ihler HM, Wedervang-Resell K, Simonsen C, Melle I, Færden A. Trajectory and early predictors of apathy development in first-episode psychosis and healthy controls: a 10-year follow-up study. Eur Arch Psychiatry Clin Neurosci. 2020 Sep;270(6):709-722. doi: 10.1007/s00406-020-01112-3. Epub 2020 Mar 4. PMID: 32130475; PMCID: PMC7423800.
4) Engen MJ, Vaskinn A, Melle I, Færden A, Lyngstad SH, Flaaten CB, Widing LH, Wold KF, Åsbø G, Haatveit B, Simonsen C, Ueland T. Cognitive and Global Functioning in Patients With First-Episode Psychosis Stratified by Level of Negative Symptoms. A 10-Year Follow-Up Study. Front Psychiatry. 2022 Mar 25;13:841057. doi: 10.3389/fpsyt.2022.841057. PMID: 35401286; PMCID: PMC8990888.
5) Åsbø G, Ueland T, Haatveit B, Bjella T, Flaaten CB, Wold KF, Widing L, Engen MJ, Lyngstad SH, Gardsjord E, Romm KL, Melle I, Simonsen C. The Time is Ripe for a Consensus Definition of Clinical Recovery in First-episode Psychosis: Suggestions Based on a 10-Year Follow-up Study. Schizophr Bull. 2022 Jun 21;48(4):839-849. doi: 10.1093/schbul/sbac035. PMID: 35419608; PMCID: PMC9212094.
6) Flaaten CB, Melle I, Gardsjord E, Bjella T, Engen MJ, Vaskinn A, Åsbø G, Wold KF, Widing L, Lyngstad SH, Haatveit B, Simonsen C, Ueland T. Course of intellectual functioning in schizophrenia

and bipolar disorder: a 10-year follow-up study. Psychol Med. 2023 Apr;53(6):2662-2670. doi: 10.1017/S0033291721004645. Epub 2022 Mar 8. PMID: 35256030; PMCID: PMC10123835. Published online by Cambridge University Press: 08 March 2022

4. Details of the impact (indicative maximum 750 words)

The significance of early intervention in schizophrenia spectrum disorders was established in the 2000s. Follow-ups of the initial early intervention cohorts provide indications of a high prevalence of positive outcomes in the long run which played a critical role in prompting the establishment of early psychosis services. Due to the limited availability of long-term prospective studies on this group, our replication provides important confirmation. Our research in addition emphasizes the importance of the first treatment response for long-term outcomes and address the characteristics of clinical recovery. While the first finding has obvious implications for study designs, for both studies of prediction biomarkers and for intervention studies, there has been limited discussion of the ramifications.

The primary impact of the research, however, relates to the long-term prospective study of bipolar I disorder. This is the first study of its kind, and its findings clearly contradict the idea of bipolar I disorder as neuroprogressive. This has sparked interest and debate, and have clear relevance for our understanding and treatment of bipolar I disorder. The neuroprogression hypothesis states that the disorder develops in stages of increasing severity, and that a relapse drives new relapses and increased cognitive dysfunction. While there is no doubt that relapses are harmful and may cluster, the idea that these are intrinsic to the disorder has been determinative for treatment priorities. The notion that the disorder develops with increasing severity may also increase hopelessness in a clinical disorder with high levels of depression and suicidal behavior.

5. Sources to corroborate the impact (indicative maximum of ten references)

What does it mean to recover from psychosis (APA blogs). https://www.psychiatry.org/news-room/apa-blogs/new-study-looks-at-what-it-means-to-recover-from-m (May 21. 2022).

Samamé C. What do psychiatrists do with hypotheses proven false? The case of neuroprogression in bipolar disorders. Psychol Med. 2023 Nov 10:1-2. doi: 10.1017/S0033291723003318. Epub ahead of print. PMID: 37947198.

Dols A, Schouws S, Orhan M, Beunders A. Shifting from prevention of the next episode to optimizing inter-episodic functioning Commentary on "The neuroprogression hypothesis in bipolar disorders: Time for apologies?". Bipolar Disord. 2023 Dec;25(8):696-697. doi: 10.1111/bdi.13394. Epub 2023 Nov 20. PMID: 37984974.

University of Oslo (UiO)/Oslo University Hospital (OUS), Division of Mental Health and Addiction (DMHA)
Case number: 2

Institution: UiO/OUS
Administrative unit: DMHA
Title of case study: Brain connectome development and mental illness
Period when the underpinning research was undertaken: 2014-2019
Period when staff involved in the underpinning research were employed by the submitting institution: 2014-2019
Period when the impact occurred: 2017-2022

3. Summary of the impact (indicative maximum 100 words)

Our research provided important new insight into the development of brain networks in youths, and its vulnerability to disorder. We have gained a better understanding of normal brain development and the diverging patterns this may take in some children who develop mental illness. This work is therefore an important step toward the identification of robust biomarkers that will enable us to detect signs of reduced mental health in the developing brain before the outbreak of severe symptoms.

2. Underpinning research (indicative maximum 500 words)

The brains of children and adolescents are highly plastic, which allows for an enormous potential for learning and development in this period, however, in some children this plasticity comes at a cost. In an alerting report, the World Health Organization attributed about one third of all years lived-with-disability worldwide to neuropsychiatric conditions and it is increasingly recognized that many severe mental disorders originate in neurodevelopment, likely long before the outbreak of severe symptoms and subsequent diagnosis. To date, little is known why the brain of those children and adolescents is vulnerable to mental illness. Biomarkers that allow for an early detection are urgently needed to reduce the duration of untreated illness and facilitate early support.

In this work, we studied the development of brain networks in a large US cohort of 797 individuals aged 8-22 using functional magnetic resonance imaging of the brain. We revealed that during neurodevelopment the connections of the human brain evolve into a unique pattern that – like a fingerprint – renders us distinct from one another. Maturation was particularly profound during adolescence, supporting that puberty is a sensitive period in which the brain undergoes tremendous changes, yielding stable and individualized brain networks in early adulthood. Importantly, individuals with pre-clinical signs of mental illness displayed a delayed maturation in their fingerprinting pattern. We found that brain connections in those individuals were less stable across different tasks and contexts and were less individualized. Consequently, less distinct network fingerprints were associated with higher level of symptom burden. This has triggered a number of follow up studies and sparked exciting new questions that we and other labs are currently pursuing.

The work was conducted by NORMENT researchers Kaufmann, Alnæs, Doan, Brandt, Andreassen and Westlye. It built on results from various prior studies on the brain functional connectome that NORMENT researchers have performed since the establishment of the centre in 2013 (e.g., Brandt et al. 2015, Schizophrenia Bulletin; Kaufmann et al. 2015, Schizophrenia Bulletin; Skåtun et al. 2015, Schizophrenia Bulletin; Kaufmann et al. 2016, NeuroImage). Following publication of the findings in the leading neuroscience outlet (Kaufmann et al. 2017, Nature Neuroscience), several follow-up studies have been conducted at NORMENT (e.g., Kaufmann et al. 2018; JAMA Psychiatry). Furthermore, the Research Council of Norway has funded a Young

Research Talents project that follows up the findings with new dedicated studies on the identification of signs of mental illness in the developing human brain (project LifespanHealth).

3. References to the research (indicative maximum of six references)

Main reference:

- Kaufmann, T., Alnæs, D., Doan, N.T., Brandt, C.L., Andreassen, O.A., Westlye, L.T. (2017). Delayed stabilization and individualization in connectome development are related to psychiatric disorders. Nature Neuroscience. https://www.nature.com/articles/nn.4511

Related work by NORMENT authors:

- Kaufmann, T., Alnæs, D., Brandt, C.L., Bettella, F., Djurovic, S., Andreassen, O.A., Westlye, L.T. (2018). Stability of the Brain Functional Connectome Fingerprint in Individuals With Schizophrenia. JAMA Psychiatry. https://jamanetwork.com/journals/jamapsychiatry/fullarticle/2680567
- Kaufmann, T., Alnæs, D., Brandt, C.L., Doan, N.T., Kauppi, K., Bettella, F., Lagerberg, T.V., Berg, A.O., Djurovic, S., Agartz, I., Melle, I.S., Ueland, T., Andreassen, O.A., Westlye, L.T. (2017). Task modulations and clinical manifestations in the brain functional connectome in 1615 fMRI datasets. NeuroImage. https://www.ncbi.nlm.nih.gov/pubmed/27916665
- Skåtun, K.C., Kaufmann, T., Doan, N.T., Alnæs, D., Cordova-Palomera, A., Jönsson, E.G., Fatouros-Bergman, H., Flyckt, L., KASP, Melle, I., Andreassen, O.A., Agartz, I., Westlye, L.T. (2016). Consistent Functional Connectivity Alterations in Schizophrenia Spectrum Disorder: A Multisite Study. Schizophrenia Bulletin. https://academic.oup.com/schizophreniabulletin/article/43/4/914/2548978
- Brandt, C.L., Kaufmann, T., Agartz, I., Hugdahl, K., Jensen, J., Ueland, T., Haatveit, B., Skåtun, K.C., Doan, N.T., Melle, I., Andreassen, O.A., Westlye, L.T. (2015). Cognitive Effort and Schizophrenia Modulate Large-Scale Functional Brain Connectivity. Schizophrenia Bulletin. https://academic.oup.com/schizophreniabulletin/article/41/6/1360/2526022
- Kaufmann, T., Skåtun, K.C., Alnæs, D., Doan, N.T., Duff, E.P., Tønnesen, S., Roussos, E., Ueland, T., Aminoff, S.R., Lagerberg, T.V., Agartz, I., Melle, I., Smith, S.M., Andreassen, O.A., Westlye, L.T. (2015). Disintegration of Sensorimotor Brain Networks in Schizophrenia. Schizophrenia Bulletin. https://academic.oup.com/schizophreniabulletin/article/41/6/1326/2526034

4. Details of the impact (indicative maximum 750 words)

Improving our understanding of the pathophysiology of severe mental illness is key in their treatment and prevention. Over the past decades, it has become increasingly clear that these disorders originate in neurodevelopment, yet we lack sensitive methods to detect abnormalities in brain development early. Because the disorders are typically diagnosed in early adulthood when severe symptoms manifest, it is likely that the period of untreated illness spans several (neurodevelopmental) years. Discovering biomarkers that allow us to trace patterns of abnormal brain development are therefore among the key challenges that the field is facing.

Researchers at NORMENT have illustrated that the brain develops into a fingerprint-like pattern in youths and found that deviations from this neurodevelopmental trajectory are indicative of pre-clinical signs of mental illness. This is an important first step toward the development of biomarkers.

Consequently, the findings have received marked attention in the community as for example indicated by a highlighting commentary by UCLA Professor Adriana Galvan in the News and Views section of Nature Neuroscience, the high number of citations the paper has already received in the 2.5 years since publication, and the reception of the prestigious Excellent Paper in Neuroscience Award 2018.

The research has triggered new questions that have been followed up at NORMENT, for example how the interplay between environmental and genetic risk factors influences the individualization of the brain during childhood and adolescence. We hope that future research building on this study will lead to the identification of robust biomarkers that will enable us to

detect signs of reduced mental health in the developing brain before the outbreak of severe symptoms.

5. Sources to corroborate the impact (indicative maximum of ten references)

Kaufmann et al. 2017, Nature Neuroscience

- was highlighted by Nature Neuroscience with a commentary in the *New and Views* section of their April 2017 issue: https://www.nature.com/articles/nn.4530
- was awarded the ERA-NET NEURON Excellent Paper in Neuroscience Award 2018 (3000€). https://www.neuron-eranet.eu/en/881.php
- was awarded the Best Publication Award 2017 by Oslo University Hospital (50k NOK). https://www.ous-research.no/home/ous/News/17883
- has been cited 220 times (Google Scholar). With an *Altmetric* score of 153, it is in the 98th percentile of all papers tracked by *Altmetric* of similar age in all journals . https://www.nature.com/articles/nn.4511/metrics
- was outlined in the Research News of the University of Oslo https://www.med.uio.no/klinmed/english/research/news-and-events/news/2018/the-brain%E2%80%99s-fingerprint-reveals-early-signs-of-men.html
- led to funding of a Young Research Talent grant to the first author of the study that largely builds on the findings of this study and follows up the research toward the discovery of biomarkers for the early detection of signs of mental illness in the developing brain (Project 276082 LifespanHealth). https://prosjektbanken.forskningsradet.no/#/project/NFR/276082

University of Oslo (UiO)/Oslo University Hospital (OUS), Division of Mental Health and Addiction (DMHA)
Case number: 3

Institution: UiO/OUS
Administrative unit: DMHA
Title of case study: Cardiovascular comorbidity in mental illness
Period when the underpinning research was undertaken: 2013-2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2014-2019
Period when the impact occurred: 2014-2019

4. **Summary of the impact** (indicative maximum 100 words)

The life expectancy in patients with severe mental disorders (schizophrenia and bipolar disorder) are reduced by 10-20 years. A major cause of the excessive deaths is comorbid cardiovascular disease (CVD). We have documented levels and patterns of change of cardiovascular risk factors in schizophrenia and bipolar disorder during the recent years. We have performed a series of studies of cardiovascular comorbidity in severe mental disorders during more than 15 years. This research has been a basis for targeted interventions in the clinics aiming to reduce the cardiovascular comorbidity and mortality in these patients.

2. Underpinning research (indicative maximum 500 words)

Patients with severe mental disorders have significantly higher mortality than the general population from unnatural causes (suicide, homicide or accidents); however, there largest cause of increased mortality is natural causes (somatic conditions) such as CVD. Persons who have been hospitalized for a psychotic disorder have a two to three-fold increased risk of dying from CVD, and the gap in life expectancy between severe mental disorders and the rest of the population is increasing.

Cardiovascular risk and mechanisms in severe mental disorders have been focused by the research group of NORMENT for several years. We have demonstrated that certain antipsychotic agents (especially clozapine) stimulate cellular lipid biosynthesis and the existence of lipid dysregulations during antipsychotic treatment independent of body mass index. We have also identified lipid dysregulations related to antidepressant medication. Our researchers have contributed to identifying broad genetic overlap between severe mental disorders and cardiovascular risk factors, and corroborated the cardiovascular link by demonstrating relationships between lipid profiles and clinical traits.

A good example is the study "Cardiovascular risk remains high in schizophrenia with modest improvements in bipolar disorder during past decade". Here we investigated the potential preconditions for the cardiovascular mortality in this patient group, documenting broadly increased cardiovascular risk factors in schizophrenia and bipolar disorder compared to the general population. There was no decrease in cardiovascular risk factors in patients with schizophrenia during the past decade and only a small-moderate degree decreases in patients with bipolar disorder. The study was based on a collaboration between the Precision Psychiatry research group and the Mechanisms of Psychopathology research group at NORMENT.

The study is part of a series of studies related to cardiovascular risk and mechanisms such as Andreassen et al. (2013), Ringen et al. (2014), Quintana et al. (2016), Fjukstad et al. (2016), Gohar et al. (2019). Recently, we have also documented biological/genetic underpinnings of these traits, reflecting the close relationship between cardiovascular and mental disease (Mørch et al. 2019, Bahrami et al. 2020; Torgersen 2021, Rødevand et al. 2021, 2023). These NORMENT studies are

part of the basis for cardiovascular preventive interventional initiatives in mental health clinics in Norway.

3. References to the research (indicative maximum of six references)

- Ringen et al. Increased mortality in schizophrenia due to cardiovascular disease - a non-systematic review of epidemiology, possible causes, and interventions Front Psychiatry 2014, 4: 137
- Rodevand L, Steen NE, Elvsashagen T, et al. Cardiovascular risk remains high in schizophrenia with modest improvements in bipolar disorder during past decade. Acta Psychiatr Scand Apr 2019;139(4):348-360.
- Andreassen OA, Djurovic S, Thompson WK, et al. Improved detection of common variants associated with schizophrenia by leveraging pleiotropy with cardiovascular-disease risk factors. Am J Hum Genet Feb 7 2013;92(2):197-209.
- Morch RH, Dieset I, Faerden A, et al. Inflammatory markers are altered in severe mental disorders independent of comorbid cardiometabolic disease risk factors - inflammatory markers and immune activation in severe mental disorders. Psychol Med 2019:49;10, 1749-57.
- Bahrami S, Steen NE, et al. Shared genetic loci between body mass index and major psychiatric disorders: A genome-wide association study, JAMA Psychiatry 2020 77(5):503-512.
- Rødevand L, Rahman Z, Hindley GFL et al., Characterizing the Shared Genetic Underpinnings of Schizophrenia and Cardiovascular Disease Risk Factors. Am J Psychiatry 2023;180(11):815-826.

4. Details of the impact (indicative maximum 750 words).

The research group has for several years been doing research of cardiovascular risk factors and comorbidity in severe mental disorders. The group has been a major national force in focusing the comorbidity in severe mental disorders as exemplified by a range of high impact publications in international journals encompassing national and international collaborations including the Psychiatric Genomics Consortium with 38 participating countries.

In addition to contributing to awareness among clinicians both nationally and internationally as exemplified by publishing review articles in core journals (Ringen et al. 2014), the research has manifested in a program at the Division of Mental Health and Addiction, Oslo University Hospital (OUS) called “Hjertefrisk” (“Healthy heart”) initiated in spring 2017. The Hjertefrisk algorithm is a tool for health professionals to identify and monitor increased risk of diabetes and CVD in people with severe mental illness. The form defines appropriate monitoring measures during antipsychotic medication, and the complete Hjertefrisk algorithm is available in one page including characteristics of patients at risk and appropriate interventions. The program is implemented in the Division at OUS with a catchment area of about 500 000 individuals as well as in several other hospitals, forming a national multicentre project. This project is a major contribution towards adequate treatment of the cardiovascular risk at a national level in people with severe mental disorders, aiming to decrease the excessive mortality.

The research has also led to a series of projects of high intensive aerobic training (HIT), benefitting these patient groups in Trondheim and Vestfold. Moreover, patients at OUS have had the possibility to attend a naturalistic interventional study applying motivational techniques to reduce cardiometabolic risk.

Based on the cardiovascular research initiatives, the NORMENT researchers have been successful in achieving a prestigious EU H2020 grant as the coordinator of the project “CoMorMent – predicting comorbid cardiovascular disease in individuals with mental disorder by decoding disease mechanisms”. CoMorMent is a collaboration between eight countries.

Further, the research in CVD comorbidity led to a large grant from the RCN; CVD-MENT, that investigates clinical interventions (RCT of physical exercise) to reduce the CVD risk in patients with severe mental disorders.

Finally, we recently initiated a clinical trial, STABIL-NOR, a randomized double blind RCT with GLP agonist semaglutide to reduce weight gain in people with schizophrenia (Norwegian Multi-site study including Haukeland Univ Hospital, Oslo Univ Hospital, Stavanger Univ Hospital, St Olavs University Hospital). This will lead to better CVD health for patients, and increase the awareness of these problems in the clinic.

5. Sources to corroborate the impact (indicative maximum of ten references)

- The "Hjertefrisk" project:
  1) https://oslo-universitetssykehus.no/avdelinger/klinikk-psykisk-helse-og-avhengighet/hjertefrisk-hjelpemiddel-for-oppfolging-og-tiltak-hos-pasienter-med-psykiske-lidelser-eller-rusmiddelproblemer-i-kardiometabolsk-risikogruppe
  2) https://www.med.uio.no/norment/forskning/samarbeid/hjertefrisk/

Led to several new projects to target CVD comorbidity in mental disorders:

- Olav Thon Foundation: CVD-Mental disorder comorbidity project: https://www.med.uio.no/norment/forskning/aktuelt/aktuelle-saker/2016/stotte-fra-olav-thon-stiftelsen.html

- RCN: CVD-Ment project https://prosjektbanken.forskningsradet.no/en/project/FORISS/326813?Kilde=FORISS&distribution=Ar&chart=bar&calcType=funding&Sprak=no&sortBy=date&sortOrder=desc&resultCount=30&offset=270&LTP.1=LTP2+Fornyelse+i+offentlig+sektor

- EU: H2020 CoMorMent project https://www.comorment.uio.no/ https://prosjektbanken.forskningsradet.no/project/EU/847776

Dissemination activities:

- https://www.med.uio.no/norment/forskning/aktuelt/aktuelle-saker/2015/hjerte-karsykdom-og-psykisk-lidelse.html
- Genetics of mental illness and weight. Forskning.no 2020.
- https://www.nettavisen.no/ensomhet/psykisk-helse/helt-alene/f/5-95-832311
- Schizophrenia and physical exercise. Aftenposten 2020
- Shared genetics of schizophrenia and comorbid CVD The Mental Elf 2023

University of Oslo (UiO)/Oslo University Hospital (OUS), Division of Mental Health and Addiction (DMHA)

Case number: 4

Institution: UiO/OUS
Administrative unit: DMHA
Title of case study: DBT research and impact in Norwegian mental health care
Period when the underpinning research was undertaken: 2013 to date
Period when staff involved in the underpinning research were employed by the submitting institution: 2008 to date
Period when the impact occurred: 2013 to date

5. Summary of the impact

This case study outlines the impact of the NSSF's efforts to improve the knowledge base and disseminate knowledge in the use of Dialectical Behaviour Therapy (DBT) in Norway and internationally. DBT was originally developed to treat adult patients with recurrent suicidality, self-harming behaviour and borderline personality disorder (BPD) and later adapted for the use with adolescents. NSSFs research activities in DBT has primarily focussed on establishing the efficacy and effectiveness of DBT when used with adolescents. The NSSF has played a pivotal role in the treatment of these conditions in Norway across several domains. Firstly, by initiating and coordinating the implementation of DBT across different settings in the public healthcare system, focusing treatment efforts and cooperation at a national level. Secondly, by expanding the application of DBT to new settings, as well as in promoting innovative approaches to patient-feedback, treatment evaluation and clinical research.

2. Underpinning research (indicative maximum 500 words)

Dialectical Behaviour Therapy (DBT) was originally developed by Marsha M. Linehan to treat suicidal and self-harming women with Borderline Personality Disorder (BPD). BPD is associated with frequent hospitalizations, long-term psychosocial sequelae, and increased risk of suicide and early death (Temes et al., 2019). DBT is currently empirically supported by more than 40 randomized trials. The model has proven effective in treating a number of mental illnesses tied to severe emotion regulation problems, as well as in treating complex and serious conditions such as BPD with comorbid post-traumatic symptoms. Effect studies have shown that DBT significantly reduces suicidal behaviour, self-harm, need for admission at emergency wards or emergency rooms, therapy dropout rates, drug abuse, anger and depression, as well as improves general functioning for social and global goals. No other treatment method has such comprehensive evidence for its effectiveness in use for people with BPD, a population that is generally recognized as being hard to treat.

It was, however, not until our group in 2014 published the first randomized controlled study (RCT) on a substantially shortened version of this treatment adapted for suicidal adolescents (DBT-A) that evidence emerged in support of its effectiveness (Mehlum et al, 2014), cost-effectiveness (Haga et al, 2018) and long-term sustained benefits (Mehlum et al, 2016, 2019, Dibaj et al, 2023) in this age segment. In fact, prior to the publication of our initial RCT, no psychosocial or psychopharmacological intervention had demonstrated effectiveness in the treatment of suicidal and self-harming behaviour in adolescents. Our RCT demonstrated that DBT is an effective intervention to reduce self-harm, suicidal ideation, and depression in adolescents with repetitive self-harming behaviour (Mehlum et al, 2014). Our findings have later been replicated by several randomized trials in the US (McKauley et al, 2018, Goldstein et al, 2023) and Spain (Santamarina-Perez et al, 2020).

Longitudinal studies are crucial in determining the longer-term effect of therapy on symptom remission. There is a gap in the research literature concerning the potential effects of DBT in the years after initial treatment. Furthermore, there is a lack of follow-up studies assessing outcomes for individuals that have been struggling in adolescence during their transition to young adulthood. Addressing this gap, our group conducted assessments at one-, three- and twelve years follow-up post treatment completion. Follow-up investigations revealed that DBT is associated with a stronger long-term reduction in self-harm and a more rapid recovery in the aforementioned symptoms compared to treatment as usual (Mehlum et al, 2016, 2019). DBT was also associated with long-term improvements in emotion regulation (Dibaj et al., 2023), a factor which has been identified as key to increased resilience in the face of adversity. Future quantitative and qualitative publications are underway, assessing the diagnostic and psychosocial outcomes more than ten years after the initial RCT. Clinical longitudinal studies of this duration is rare, but especially important to identify characteristics of individuals at heightened risk for enduring impairment. Early identification of vulnerable adolescents ensures that the appropriate level of care can be initiated as early as needed during development. Shifting maladaptive developmental trajectories for high-risk youth can potentially save patients years lost to mental illness, and reduce the long-term burden on the mental health system and society at large. Our study has shown that DBT is one of a select few programs to be effective in this regard.

3. References to the research (indicative maximum of six references)

Mehlum L., Tormoen A.J., Ramberg M., Haga E., Diep L.M., Laberg S., Larsson B.S., Stanley B.H., Miller A.L., Sund A.M., & Groholt B. (2014). Dialectical behavior therapy for adolescents with repeated suicidal and self-harming behavior: A randomized trial. *Journal of the American Academy of Child and Adolescent Psychiatry*, *53*(10), 1082–1091. https://doi.org/10.1016/j.jaac.2014.07.003

Mehlum L., Ramberg M., Tormoen A.J., Haga E., Diep L.M., Stanley B.H., Miller A.L., Sund A.M., & Groholt B. (2016). Dialectical Behavior Therapy Compared with Enhanced Usual Care for Adolescents with Repeated Suicidal and Self-Harming Behavior: Outcomes over a One-Year Follow-

Up. *Journal of the American Academy of Child and Adolescent Psychiatry*, *55*(4), 295–300. https://doi.org/10.1016/j.jaac.2016.01.005

Mehlum, L., Ramleth, R., Tørmoen, A. J., Haga, E., Diep, L. M., Stanley, B. H., Miller, A. L., Larsson, B., Sund, A. M., & Grøholt, B. (2019). Long term effectiveness of dialectical behavior therapy versus enhanced usual care for adolescents with self-harming and suicidal behavior. *Journal of Child Psychology and Psychiatry*, *60*(10), 1112–1122. https://doi.org/10.1111/jcpp.13077

Dibaj, I. S., Tørmoen, A. J., Klungsøyr, O., Haga, E., & Mehlum, L. (2023). Trajectories and Predictors of Change in Emotion Dysregulation and Deliberate Self-Harm Amongst Adolescents with Borderline Features. *Clinical Child Psychology and Psychiatry*, *0*(0), 1–17. https://doi.org/10.1177/13591045231177374

Haga, E., Aas, E., Grøholt, B., Tørmoen, A. J., & Mehlum, L. (2018). Cost-effectiveness of dialectical behaviour therapy vs. Enhanced usual care in the treatment of adolescents with self-harm. *Child and Adolescent Psychiatry and Mental Health*, *12*(22), 1-11. https://doi.org/10.1186/s13034-018-0227-2

4. **Details of the impact** (indicative maximum 750 words)

The pioneering clinical research on DBT conducted by the NSSF has been of great importance to the implementation of this treatment in Norway and internationally. In the years following the initial RCT, our centre has operated the national training program for DBT therapists in Norway. The educational program is one of the few worldwide that is directly certified by the Linehan Institute as an independent international collaborator. Thus, our centre has had a solid role as the only provider of the intensive training and supervision in DBT in Norway. The training program is continually informed by insights provided by the RCT findings and follow-up studies, ensuring high quality and up-to date education and training. So far, NSSF has trained more than 600 DBT therapists and helped establish DBT programmes in more than 50 clinical units in adult and child and adolescent mental health across all regions of the country and in every hospital trust (see www.dbt.no <http://www.dbt.no>). No other country in the world has covered to the same extent the population's need for this kind of treatment.

The NSSF continues to provide clinical consultation and mentorship to a substantial proportion of these units and offers update trainings at regular intervals. Recently the centre launched a group based, digital discussion series called DBT-Chats. DBT-Chats provide an online meeting place for clinical consultations and a chance to get professional input from expert DBT-teachers. NSSF also makes resources available in the form of tools for self-evaluation in assessing quality and adherence to DBT principles, video resources explaining central skills in DBT and material to be used in DBT sessions. The centre has organized several advanced courses in the application of DBT

for different psychiatric disorders as well as a Mindfulness retreat, providing clinicians with the opportunity to enhance their skills as DBT therapists. NSSF is also responsible for organizing the biennial national conference in DBT; so far, seven conferences have taken place.

Throughout the years, the NSSF has widely disseminated knowledge on the treatment method through publications in national journals (Alfheim et al, 2015, Mehlum et al, 2015a, 2015b, Haga et al, 2015, Dymbe et al, 2020) and at professional meetings and webinars. To support continued clinical DBT research the centre has established a network for collaborating clinical units who wish to use a common protocol to evaluate their own patients at baseline, midway in the treatment and at end-of-treatment and 6 months follow-up. This network serves two broad purposes: 1) to increase and maintain quality of care on an ongoing basis in participating units and 2) to more effectively collect data for clinical research purposes. So far, eight clinical units in Norway have become members of the network and the first foreign clinical unit (in Denmark) has signed up for participation. The NSSF manages and funds data collection, data storage and data analysis, through use of digital tablets in remote access to the TSD-server at the University of Oslo. The preliminary findings from the network have already been presented at international conferences.

The NSSF continues to play an important role in coordinating research- and treatment efforts, and played an important part in establishing The Norwegian Association for Dialectical Behavioural Therapy (DBT). The centre also maintains strong collaborations on DBT related research internationally. The head of NSSF, Professor Lars Mehlum, was one of the founders of the recently established World DBT Association (WDBTA) and its Scientific Committee and helps organize scientific meetings in many different countries.

Over the last decade DBT has become a highly valued and relevant treatment method for a wide range of patients with recurrent suicidal and self-harming behaviour in Norway. You can find DBT units in Child and Adolescent Mental Health Services, in adult psychiatric outpatient settings and in the Substance Misuse Services. In the last few years, implementation of DBT has transcended the boundaries of specialized mental health services, so that child welfare services have now started to use adapted versions of the treatment in close collaboration with the NSSF. The model is being used in both specialized institutions for adolescents with behavioural and emotional problems as well as in community programmes, and has so far been shown to have good feasibility and acceptability (Espenes et al., 2023). In our most recent project, the NSSF aids the Directorate of Child Welfare to adapt DBT to existing Multisystemic treatment programmes in local communities, strengthening the system in its effort to deliver appropriate care to young people with complex challenges.

Our investigative efforts has shown DBT to be a cost-effective, flexible and efficacious framework for treatment. The DBT community in Norway is growing, and provides clinicians with a platform for valuable professional exchange, learning and support. In surveys conducted by Norwegian health authorities among hospital managers and clinicians, these have repeatedly mentioned the importance of DBT and the increasing availability of this treatment all over the country. Improving access to essential and evidence-based treatment for patient groups at a high risk of suicide

contributes to the national selective suicide preventative efforts. At the same time, thousands of patients and their families have received effective treatment, improving quality of life at an individual level.

5. Sources to corroborate the impact (indicative maximum of ten references)

Division Director Benedicte Thorsen-Dahl, , Division of Mental Health, Sykehuset Innlandet Hospital Trust, Gjøvik, Norway

Section Leade Gjertrud Kvalstad, St Olavs Hospital, Trondheim, Norway

Professor Michaela Swales, Bangor University, United Kingdom

Vice-president for Institute services and Director of CE/CME Tony Dubose, Behavior Tech Institute, Seattle, USA

Senior adviser Karin Gravbrøt, Norwegian Directorate of Health, Division of Mental Health and Addiction, Oslo, Norway

University of Oslo (UiO)/Oslo University Hospital (OUS), Division of Mental Health and Addiction (DMHA)

Case number: 5

Institution: UiO/OUS
Administrative unit: DMHA
Title of case study: Norwegian OMT – from high threshold to low threshold treatment; saving lives
Period when the underpinning research was undertaken: 2012-2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2012-2022
Period when the impact occurred: 2012-2022

1. Summary of the impact (indicative maximum 100 words)

A primary focus of the Norwegian Centre for Addiction Research (SERAF)'s research involves improving treatment and outcomes among people with opioid use disorders. For nearly two decades, SERAF's ongoing research has played a crucial role in improving opioid maintenance treatment (OMT) for over 8,300 patients, and the program saves more than 100 lives from overdose deaths annually. Since its implementation in 1998, the Norwegian OMT program has been transformed, largely attributed to the extensive body of high-quality research evidence produced at SERAF within the local context. Today, the OMT program is one of the most accessible and high-quality OMT programs internationally with skilled staff and high retention rates. The program is founded on national treatment guidelines, which have been informed by SERAF's research. SERAF's research dissemination efforts are targeted at OMT clinic leaders, decision makers, and a growing international audience. SERAF's research often involves the stakeholder perspectives, and the patient advocacy organization "proLARNett" has been involved in the development of our research and dissemination.

2. Underpinning research (indicative maximum 500 words)

In 1998, Norway began offering OMT nationally. The initial program was restrictive, high-threshold and had a limited capacity. At the time, Norway was a country with high and rising overdose death rates. In 2001, the annual number of overdose deaths was above 400, primarily due to heroin overdose. From the start of the program, the Directorate of Health allocated funding to the University of Oslo to establish a small research unit that was given the duty of monitoring the development of the OMT program. In 2008, the research council in Norway (RCN) provided SERAF with what ultimately became a 10-year centre grant to develop and expand the research base for addiction treatment. SERAF has one research group, that focuses on opioids, OMT and overdose prevention. This group produces the annual National OMT Status Report, which is based on national data collection from all OMT clinics. The report provides a rich descriptive summary of how the program is developing with a focus on regional differences. In addition, together with the Oslo University Hospital, SERAF has been instrumental in leading biannual OMT clinic leader network meetings. In these meetings, the annual OMT report is discussed in conjunction with new national and international research, with the aim of developing the program, as well as of reducing geographical variations in OMT in Norway. These meetings include the participation of patient advocacy organizations, such as proLARNett.

At SERAF, we have established national-level cohort data on patients in OMT, linking it with high-quality national health registries. The national OMT-cohort includes data on all patients receiving

treatment and has formed the basis for a number of publications in high-ranking journals which focus on various aspects of treatment. In 2008, SERAF published its first data linkage paper, which specifically examined mortality rates, including those caused by overdose. Since then, the national OMT cohort dataset has been linked with various registries and has been part of several PhD projects, master's theses, and published papers. The research has focused not only on mortality, but also on additional outcomes related to OMT, including crime, physical health and mental health.

Our research has had a profound impact on describing the outcomes and benefits of the OMT program. This includes providing evidence that engagement in OMT reduces overdose mortality, decreases crime rates, minimizes acute health care incidents, and mitigates other negative health outcomes. Additionally, SERAF has had a research project that focused on pregnancy and motherhood among OMT patients, resulting in 4 PhD thesis, and multiple published papers. Again, SERAF's research has been forming the evidence base for our national treatment guidelines for mothers in OMT.

Our initial research showed that being in OMT provided risk reduction (e.g., in terms of overdose), while risk remained high for patients who were outside of or leaving treatment. Our results consequently led to the understanding that the national program needed to expand to reach as many people with treatment need as possible. Furthermore, the initial stringent treatment regulations, which included expelling patients for non-compliance, were reconsidered based on our research which demonstrated an increased risk for expelled patients. Our research results were communicated to the national government, via the Directorate of Health, as well as within the clinic leader network. As a result, the practice of expelling patients ceased almost entirely. In addition, enhanced access to treatment, including reducing the barriers to treatment, has become the focus of the Norwegian OMT program, including specific low-threshold OMT programs in the larger cities.

In recent years Norway's OMT program has become one of Europe's most comprehensive programs, covering around 80% of the target population. Additionally, SERAF's research has shown that when compared internationally, the program has a high retention rate of 75% or more 12 months after treatment initiation. Also, OMT reduces overdose mortality to about 20% of the levels seen among those outside of treatment. In addition, it was found to reduce crime and physical comorbidity by more than 50% for patients. An important finding highlighted by SERAF's research, is that the induction phase (defined as the first four weeks of treatment), typically identified as a high-risk period internationally, does not result in elevated risk in Norway.

Showing that OMT reduces overdose deaths and other negative outcomes resulted in the program's transformation from high threshold to more liberal. We have followed the program's evolution regularly through monitoring of research results, and twice-yearly communication directly to clinic leadership, which has impacted clinical development rapidly. This research and practice feedback loop results in a swift transformation, liberalisation, and expansion of the program. Recent SERAF research shows that the OMT program in Norway results in more than 100 lives saved from overdose death each year.

Names of the key researchers involved were as follows.

-Helge Waal, SERAF, 1995-2010, (retired at 70 years of age), but still active in research, Professor and past centre leader
-Thomas Clausen, SERAF, 2006-current, Researcher, Professor and current centre leader
-Anne Bukten, SERAF, 2008-current, PhD student, postdoctoral research fellow and senior researcher
-Marianne Riksheim, SERAF,- (2012-current) PhD student (statistician) and researcher
-Svetlana Skurtveit, SERAF (2008-current) (20% position) Professor

The 2008-2018 centre grant from RCN allowed for SERAF to invest time and researchers in a spectrum of OMT-related activities and in creating national cohort data as a foundation for the linkage studies. The RCN grant made the National OMT cohort named "NorComt" possible to establish, which has resulted in three PhD theses, and multiple publications, and later with registry linkages. The project has evolved into the AgeSUD project at SERAF, which focuses on ageing and old age in OMT, as OMT patients in Norway have reduced overdose mortality, thus the cohort ages. When the RCN program started, OMT internationally was often based on rather restrictive clinical guidelines, or guidelines did not exist. Few countries had access to countrywide national datasets, which made the research from Norway pioneering, in terms of both being nationally representative and covering a countries treatment response, and in fostering rapid transformation of the program on a national basis.

3. References to the research (indicative maximum of six references)

Clausen, Thomas; Anchersen, Katinka & Waal, Helge (2008). Mortality prior to, during and after opioid maintenance treatment (OMT): A national prospective cross-registry study. Drug and Alcohol Dependence. ISSN 0376-8716. 94. doi: 10.1016/j.drugalcdep.2007.11.003.

Bukten, Anne; Skurtveit, Svetlana; Gossop, Michael; Waal, Helge; Stangeland, Per Ingolf & Havnes, Ingrid Amalia [Vis alle 7 forfattere av denne artikkelen] (2012). Engagement with opioid maintenance treatment and reductions in crime: a longitudinal national cohort study. Addiction. ISSN 0965-2140. 107(2), s. 393–399. doi: 10.1111/j.1360-0443.2011.03637.x.

Bukten, Anne; Stavseth, Marianne Riksheim; Skurtveit, Svetlana; Tverdal, Aage; Strang, John & Clausen, Thomas (2017). High risk of overdose death following release from prison: variations in mortality during a 15-year observation period. Addiction. ISSN 0965-2140. 112(8), s. 1432–1439. doi: 10.1111/add.13803.

Bukten, Anne; Stavseth, Marianne Riksheim & Clausen, Thomas (2019). From restrictive to more liberal: variations in mortality among patients in opioid maintenance treatment over a 12-year period. BMC Health Services Research. ISSN 1472-6963. 19(1). doi: 10.1186/s12913-019-4382-9.

Røgeberg, Ole; Bergsvik, Daniel & Clausen, Thomas (2021). Opioid overdose deaths and the expansion of opioid agonist treatment: a population-based prospective cohort study. Addiction. ISSN 0965-2140. s. 1–9. doi: 10.1111/add.15739.

Medved, David; Clausen, Thomas; Bukten, Anne; Bjørnestad, Ronny & Muller, Ashley Elizabeth (2020). Large and non-specific somatic disease burdens among ageing, long-term opioid maintenance treatment patients. Substance Abuse Treatment, Prevention, and Policy. ISSN 1747-597X. 15, s. 1–9. doi: 10.1186/s13011-020-00311-4.

4. Details of the impact (indicative maximum 750 words)

SERAF has provided government authorities and the national clinic leader network with updated and locally relevant research to understand and improve the Norwegian OMT program. The research underpinning it has been published internationally in leading peer reviewed journals. Hence, it has also

been important to the development of the evidence base for OMT internationally. SERAF's research has been included in published meta-analyses and cited in international clinical recommendations.

Initially, Norway had a strict OMT program from which patients could be expelled if they used drugs while in treatment because of the belief that only a persistent motivation for rehabilitation and a drug-free life could lead to success within OMT. Our research, however, has shown that patients who were denied continued treatment were at risk of negative outcomes. SERAF argued that the practice of expelling patients was causing death, including overdose deaths.

Similarly, the initial phases of the OMT program were characterized by limited capacity and waitlists for treatment entry. As the national OMT dataset included information about pre-treatment periods, we were able to study OMT in a pre, during, and after perspective, and could then document for policy makers and clinicians that waiting for OMT was potentially lethal. Treatment capacity had to be increased, and waitlists reduced to a minimum. This led to a shift in the clinical practice, and a SERAF staff member was part of the group that developed the first clinical guidelines issued in 2010.

In this process, the research results from SERAF were used to support the idea that as many as possible from the target group needed to be given access to long-term treatment. From 2010 and onwards very few patients have been expelled. The number of OMT patients has increased annually and currently are believed to include more than 80% of those in need, with virtually no waitlist. The OMT program now includes two tracks: one for those aiming for rehabilitation and a drug free life, constituting about 70% of the population; and a low-threshold harm reduction track including about 30% of the OMT patient population whose treatment goals do not include complete abstinence.

When comparing OMT outcomes internationally, such as mortality, the results show that OMT in Norway manages to provide treatment in a safe manner. This is likely related to the existence of speciality in addiction medicine, and the formal integration of OMT in the secondary healthcare system. Medical specialist doctors provide OMT in collaboration with primary care doctors, further strengthening its effectiveness. SERAF's staff members have been involved in advocating for and later establishing the new medical speciality, and our staff members have been among the first clinical mentors and teachers at the training courses for addiction specialists. SERAF also provides evidence-based teaching for medical students at the University of Oslo. Again, SERAF's research has been put into practice and efficiently reached clinicians with relevant, locally based evidence. Decision makers and clinicians may be more likely to embrace and adhere to our findings when they align with their local and clinical experience.

Thus, the Norwegian OMT program, which initially was criticized for being too limited, too strict, and too rigid, has become a wide-reaching, high-quality program, with a great life-saving potential. The ongoing research has allowed ongoing monitoring and the provision of the results back to the medical staff providing the program, making it a dynamic program which is constantly evolving. In 2022, a revised version of the clinical guidelines (originating from 2010) was released. Essential components of the evidence-base cited in the revised guidelines were derived from SERAF's research.
In two papers we studied regional differences in OMT in Norway. The findings were promptly disseminated with the clinic leader network, leading to rapid adjustments in clinical practice and fostering a more standardized treatment approach on a national level.

The success of the OMT program has contributed to a significant reduction in premature mortality due to overdose deaths. As a result, this has led to a rapid aging of the OMT population. Currently, more than 40% of the OMT population is aged 50 years or older. This is a sign of successful treatment, but it also leads to new clinical challenges, such as an increase in somatic morbidity and premature mortality from physical causes among OMT patients. This shift has moved some of SERAF's research focus to a project investigating ageing in OMT with the goal to further improve health and longevity

among OMT patients. Evidence points towards the importance of focusing on lifestyle-related disorders, and of supporting beneficial lifestyles such as non-smoking, low alcohol consumption, physical activity, and healthy diets among OMT patients. Additionally, the provision of treatment such as hepatitis C treatment has been emphasised as important for OMT patients.

SERAF has received funding from the Directorate of Health, as a centre from RCN, and received in grants for researcher-driven projects. This funding, in addition to being university-based, provides us with the opportunity to impact training by incorporating our local high-standard evidence into teaching. Moreover, it provides us with a platform to engage with decision-makers in the Directorate of Health and involvement in the development of clinical guidelines, together with stakeholders in the field. In addition, we have been participants in the twice-yearly clinical leadership network in OMT, giving us direct access to the clinics providing OMT. All of these advantages combined have put SERAF in a position not only to perform important research, but also to impact decisions and the development of the national OMT program into one of Europe's best quality OMT programs. One of SERAF's advantages has been that our projects have taken a "national" approach in data collection, hence giving us opportunity to present nationally relevant results. Also, our collaboration both with clinical staff, service-user organisations, and stakeholders has resulted in the research being directly clinically relevant and over time adapting to and evolving onto new topics and research needs.

Norway has developed two national treatment guidelines involving OMT: the general guidelines and the specific guidelines for pregnancy and motherhood in OMT. SERAF's research has served as an important evidence base for both. Furthermore, the lifesaving potential of OMTs has contributed to the ageing of the OMT cohort and a decline in heroin overdoses nationally. Instead, prescription opioids are a dominant cause of overdose deaths nationally since 2016 and onwards. Hence, one of SERAF's current and future research focus is how to prevent overdoses among opioid users who use opioids as pain treatment, illustrating some of SERAF's research with dynamic shift in focus and approach as the local context evolves over time.

5. Sources to corroborate the impact (indicative maximum of ten references)

Espen Freng Directorate of Health; Espen.Freng@helsedir.no

Martin Blindheim; Directorate of Health; Martin.Ingvald.Blindheim@helsedir.no

Jens J. Guslund; Directorate of Health; Jens.J.Guslund@helsedir.no

Gitte Huus; Ministry of Health, Norway; gitte.huus@hod.dep.no

John Strang; King's College, London: john.strang@kcl.ac.uk

Department of Ophthalmology, Oslo University Hospital [Impact case 1]

Institution: Department of Ophthalmology, Division for Head, neck and reconstructive surgery
Administrative unit: Oslo University hospital/ University of Oslo
Title of case study: LUCAS impact case study
Period when the underpinning research was undertaken: 2008-2015
Period when staff involved in the underpinning research were employed by the submitting institution: 2008-2015
Period when the impact occurred: 2013 and ongoing

1. Summary of the impact

The LUcentis Compared to Avastin Study (LUCAS) was a randomized controlled trial treating exudative AMD (nAMD) with Lucentis (ranibizumab) versus Avastin (bevacizumab) following an "inject and extend" protocol. The study showed that an off-label treatment of nAMD with the cheaper drug Avastin was equally effective and safe as Lucentis. It also showed that treatment intensity could be individualised. This has led to significant cost savings in ophthalmology internationally.

2. Underpinning research

Neovascular age-related macular degeneration (nAMD) has been the most common cause of serious visual loss and blindness in the elderly population in Western countries. There was no effective treatment until anti-VEGF drugs became available. Avastin was approved for cancer treatment but was introduced as an intravitreal treatment for nAMD by Professor Philip J. Rosenfeld in 2005. In 2007, Lucentis was approved for intravitreal treatment for nAMD but at a much higher cost than Avastin. Because of the high cost of Lucentis and a very large patient group with a chronic disease that required repeated intravitreal injections for an extended period, there was a great need to perform a randomised controlled trial comparing Avastin and Lucentis. LUCAS (Lucentis Compared to Avastin Study) was designed and performed without any contribution from the pharmacy industry and financed by the Ullevål University Hospital. The study was the first randomized, multicentre prospective trial designed with the treat and extend treatment modality, which maximises cost-effectiveness. 432 patients with previously untreated nAMD were included from 10 sites in Norway and randomized to either Avastin or Lucentis and followed up for two years. The results showed that both drugs improved vision equally, the number of injections were similar between the drugs, the treatment was safe, and interval between injections could be extended from 4 up to 12 weeks.

Main responsible persons at OUH/UiO:

- Dr. Karina Berg MD, PhD, Dept. Ophthalmology, Oslo University Hospital
- Professor Ragnheidur Bragadottir, Dept. of Ophthalmology, Oslo University Hospital and University of Oslo
- Professor dr. Terje Pedersen, Institute of clinical medicine, University of Oslo
- Leif Sandvik, Research leader in statistics, Oslo university Hospital

References to the research:

1. Berg K, Pedersen T R, Sandvik L, Bragadóttir R. Comparison of Ranibizumab and Bevacizumab for Neovascular Age-Related macular degeneration According to LUCAS Treat-and-Extend Protocol. Ophthalmology 2015; 122: 146-152.
2. Berg K, Hadzalic E, Gjertsen I, Forsaa V, Berger LH, Kinge B, Henschien H, Fossen K, Markovic S, Pedersen TR, Sandvik L, Bragadottir, R. Ranibizumab or Bevacizumab for Neovascular Age-Related Macular Degeneration According to the Lucentis Compared to Avastin Study Treat-and-extend protocol: Two Year Results. Ophthalmology 123(1): 51-9, 2016 Jan

The first author, dr. Karina Berg was invited to present the first-year and second-year results of the study at the American Academy of Ophthalmology Subspecialty Day in 2013 and 2014, and she was also invited to present the results at Euretina in 2014.

4. Details of the impact

This study is one of the most important contributions to the treatment of AMD. It is cited over 600 times in medical papers. Avastin is the first line of choice in the treatment of nAMD in most countries, and the Treat and Extend protocol is the preferred treatment modality worldwide. The use of Avastin has led to a very significant reduction in costs, with every injection being 40 times cheaper with Avastin than with Lucentis. The treat and extend modality also showed that treatment must be individualised. Some patients need treatment every 4 weeks, while other patients can be treated less intensively.

5. Sources to corroborate the impact

Age-related macular degeneration
P Mitchell, G Liew, B Gopinath, TY Wong - The Lancet, 2018

Anti-vascular endothelial growth factor for neovascular age-related macular degeneration
SD Solomon, K Lindsley, SS Vedula… - Cochrane Database …, 2014 - cochranelibrary.com

Age-related macular degeneration preferred practice pattern®
CJ Flaxel, RA Adelman, ST Bailey, A Fawzi, JI Lim… - …, 2020 - aaojournal.org

Optimizing anti-VEGF treatment outcomes for patients with neovascular age-related macular degeneration
CC Wykoff, WL Clark, JS Nielsen, JV Brill… - Journal of managed …, 2018 - jmcp.org

Anti-vascular endothelial growth factor treatment for retinal conditions: a systematic review and meta-analysis
SM Thomas, E Lillie, T Lee, J Hamid, T Richter… - BMJ open, 2019 - bmjopen.bmj.com

Managing neovascular age-related macular degeneration in clinical practice: systematic review, meta-analysis, and meta-regression
D Veritti, V Sarao, V Soppelsa, C Danese… - Journal of Clinical …, 2022 - mdpi.com

Off-label use of bevacizumab for wet age-related macular degeneration in Europe
T Bro, M Derebecka, ØK Jørstad… - Graefe's Archive for Clinical …, 2020

Real-world outcomes of anti–vascular endothelial growth factor therapy in neovascular age-related macular degeneration in the United States
TA Ciulla, F Huang, K Westby, DF Williams, S Zaveri… - Ophthalmology …, 2018

Intravitreal bevacizumab versus ranibizumab for treatment of neovascular age-related macular degeneration: findings from a cochrane systematic review
SD Solomon, KB Lindsley, MG Krzystolik, SS Vedula… - Ophthalmology, 2016

Treat & extend in neovascular age-related macular degeneration: how we got here and where do we go next?
V Chaudhary - Eye, 2023 - nature.com

Department of Ophthalmology, Oslo University Hospital [Impact case 1]

Institution: Department of Ophthalmology, Division for Head, neck and reconstructive surgery
Administrative unit: Oslo University hospital/ University of Oslo
Title of case study: Pharmaceutical compounding of prefilled syringes for intravitreal injection
Period when the underpinning research was undertaken: 2018 – present
Period when staff involved in the underpinning research were employed by the submitting institution: 2018 – present
Period when the impact occurred: 2018 – present

Summary of the impact

Intravitreal injection of biologics is a key treatment approach in ophthalmology. It involves withdrawing drug from a vial into a syringe, a task preferably entrusted to a compounding pharmacy to optimize hygiene standards, save clinician time, and allow for secure splitting of vials into multiple syringes. Biologics are delicate proteins, and pharmaceutical compounding and storage of prefilled syringes must take place without impairing drug properties. We have developed and validated a compounding procedure that has become national gold standard and has been implemented internationally in several different departments.

Underpinning research

The underpinning research has focused on three topics:

A. Does pharmaceutical compounding and storage of prefilled syringes impair drug properties? In this regard, our research has shown that our compounding procedure does not affect structural integrity, stability, or VEGF- and Fc-binding properties of the drugs. Several biologics for intravitreal injection have been introduced since 2018, and accordingly, our research has been gradually extended to include all available drugs, most lately faricimab and its new therapeutic target angiopoietin-2. The research is still ongoing, and we are now planning studies on additional drugs.

B. Does pharmaceutical compounding and storage of prefilled syringes alter the risk of post-injection endophthalmitis, the most feared complication of Intravitreal injection? In this regard, our research has shown that our compounding procedure is not associated with an increased risk of post-injection endophthalmitis and that splitting of vials can be carried out safely. This research was carried out in our department from 2019 to 2022, and the key researchers were Ph.D. student Kathrine Blom and Professor Ragnheidur Bragadottir, in addition to Øystein K. Jørstad.

C. What is the optimal design of a syringe for intravitreal injection? In this regard, we have established an Inven2-based collaboration with the Dutch company SJJ Solutions to develop a line of products for pharmaceutical compounding of prefilled syringes for intravitreal injection, Zero Residual, which includes two different syringes: the Zero Residual 0.3-mL low-silicone-oil syringe and the Zero Residual 0.2-mL silicone-oil-free syringe. Our research has shown that pharmaceutical compounding and storage of biologics in these syringes does not affect structural integrity, stability, or VEGF- and Fc-binding properties. Our research has also shown that these syringes are highly accurate and precise in the pertinent setting of small-volume injections. The Inven2-based industry development agreement was signed in 2020, and the collaboration is still ongoing. The key researchers in this project are Øystein K. Jørstad, Magne S. Sivertsen, Morten C. Moe, and Jan Terje Andersen.

Main responsible persons:

To carry out our research, we have established a strong multidisciplinary team with specialist from many departments:

- Department of Ophthalmology, Oslo University Hospital/University of Oslo
- Department of Pharmacology, University of Oslo

- Department of Immunology, Oslo University Hospital
- Precision Immunotherapy Alliance (PRIMA), University of Oslo
- The Hospital Pharmacy Oslo

Key researchers from our department are Øystein K. Jørstad, Head of R&D Section, Magne S. Sivertsen, Consultant ophthalmologist and Morten C. Moe, Professor and Head of the Department of Ophthalmology. Key researchers from other departments are Professor Jan Terje Andersen, who is affiliated with the Department of Pharmacology, Department of Immunology, and PRIMA, as well as The Hospital Pharmacy Oslo, Ullevål. All key researchers have been involved since the project began in 2018 and are still team members.

References to the research:

Topic-A key references:

Sivertsen MS, Jørstad ØK, Grevys A, Foss S, Moe MC, Andersen JT. Pharmaceutical compounding of aflibercept in prefilled syringes does not affect structural integrity, stability or VEGF and Fc binding properties. Sci Rep. 2018 Feb 1;8(1):2101*. doi: 10.1038/s41598-018-20525-8. PMID: 29391560; PMCID: PMC5794981. * This paper received prize for outstanding original article published in the first half of 2018 at Oslo University Hospital.

Lode HE, Gjølberg TT, Foss S, Sivertsen MS, Brustugun J, Andersson Y, Jørstad ØK, Moe MC, Andersen JT. A new method for pharmaceutical compounding and storage of anti-VEGF biologics for intravitreal use in silicone oil-free prefilled plastic syringes. Sci Rep. 2019 Dec 2;9(1):18021. doi: 10.1038/s41598-019-54226-7. PMID: 31792234; PMCID: PMC6888834.

Jørstad ØK, Foss S, Gjølberg TT, Mester S, Nyquist-Andersen M, Sivertsen MS, Fossum D, Gleditsch E, Moe MC, Andersen JT. Pharmaceutical compounding and storage of faricimab in a syringe for intravitreal injection do not impair stability and bi-specific binding properties. Int J Retina Vitreous. 2023 Nov 7;9(1):65. doi: 10.1186/s40942-023-00507-3. PMID: 37936232; PMCID: PMC10631190.

Topic-B key reference:

Blom K, Bragadóttir R, Sivertsen MS, Moe MC, Jørstad ØK. Does Pharmaceutical Compounding of Vascular Endothelial Growth Factor Inhibitors for Intravitreal Use Alter the Risk of Post-injection Endophthalmitis? Ocul Immunol Inflamm. 2022 Apr 3;30(3):713-716. doi: 10.1080/09273948.2020.1820530. Epub 2020 Oct 7. PMID: 33026900.

Topic-C key references:

Gjølberg TT, Lode HE, Melo GB, Mester S, Probst C, Sivertsen MS, Jørstad ØK, Andersen JT and Moe MC (2022) A Silicone Oil-free Syringe Tailored for Intravitreal Injection of Biologics. Front. Ophthalmol.2:882013. doi: 10.3389/fopht.2022.882013

Agra LLM, Sverstad A, Chagas TA, Araújo RH, Oliveira LG, Kristianslund O, Petrovski G, Maia M, Moe MC, Jørstad ØK, Melo GB. Accuracy, Precision, and Residual Volume of Commonly Used Syringes for Intravitreal Injections and the Impact on Intraocular Pressure. Ophthalmol Retina. 2023 Oct;7(10):892-900. doi: 10.1016/j.oret.2023.06.003. Epub 2023 Jun 9. PMID: 37302655.

4. Details of the impact

Intravitreal injection of biologics is a defining element in contemporary ophthalmology. From 2011 to 2021, Norway experienced a three-fold increase in the number of unique patients and a four-fold increase in the number of injection episodes, and in 2021 alone, at least 125 000 injections were administrated nationally. Accordingly, improvements of the quality and cost-effectiveness of the intravitreal injection procure have the potential for large impact.

Each public eye department in Norway has strong autonomy over organizing its intravitreal injection service, and the Norwegian healthcare system rarely exercises formal governance of the service or establishes national guidelines. Still, the Norwegian Board of Health Supervision recommends splitting anti-VEGF vials only in compounding pharmacy facilities, in direct effect of our research and occasional clusters of post-injection endophthalmitis in some departments before the establishment of pharmaceutical compounding.

Our procedure for pharmaceutical compounding and storage of prefilled syringes has gradually become national gold standard, and almost all Norwegian ophthalmology departments have now implemented identical practices. Similar procedures have also been implemented in other European countries, such as Sweden and Finland. Consequently, hundreds of thousands of prefilled syringes have been administrated in accordance with our procedure, for the benefit of both patients, who receive safe and effective treatment, and society, which saves millions in drug costs because vials can be split.
At our department alone, we save about 65 mNOK per year by this compounding procedure. Furthermore, the Zero Residual syringes we have helped develop are about to be introduced in several Norwegian ophthalmology departments, hopefully further improving the quality and cost-effectiveness of intravitreal injection in the coming years.

5. Sources to corroborate the impact

Husum YS, Bråten RH, Saether EM, Moe MC, Kristiansen IS, Jørstad ØK. Intravitreal anti-vascular endothelial growth factor therapy for retinal diseases in Norway from 2011 to 2021: A combined registry and survey study. Acta Ophthalmol. 2023 Dec 9. doi: 10.1111/aos.16598. Epub ahead of print. PMID: 38071435.

Pekko Hujanen, Anja Tuulonen, Hannele Uusitalo-Järvinen. Real-world efficacy and safety of dividing aflibercept into three syringes in the treatment of wet age-related macular degeneration. Acta Ophthalmol . 2019 Aug;97(5):e812-e813.

Department of Ophthalmology, Oslo University Hospital [Impact case 3]

Institution: Oslo University Hospital
Administrative unit: Department of Ophthalmology
Title of case study: Randomized clinical trials on intraocular lens (IOL) dislocation surgery – improving outcome for a common eye condition in society
Period when the underpinning research was undertaken: 2013 to present
Period when staff involved in the underpinning research were employed by the submitting institution: 2013 to present
Period when the impact occurred: 2016 to present

1. Summary of the impact

In this impact case, we describe the results of the world´s two first randomized clinical trials of the eye condition late in-the-bag intraocular lens (IOL) dislocation and its surgical treatment. Two different operation methods were compared and several clinical parameters were measured with a follow-up of two years in both trials. The results have had a significant impact on how this condition is being understood, treated and communicated to the patients, both nationally and internationally. The studies have also increased the focus and attention towards this condition both in the scientific community and in society.

2. Underpinning research

Late in-the-bag intraocular lens (IOL) dislocation is an eye condition with loosening of the artificial lens, usually many years after uneventful cataract surgery. Cataract surgery is the most common operation in humans, and in Norway, more than 50 000 operations are performed each year in the public health care system. Hence a large proportion of the elderly population has an IOL in their eyes. In some cases, this IOL loosens after some time. Late in-the-bag IOL dislocation has increased in frequency, possibly affecting around 1 % of all eyes with an IOL. However, there has previously been no clear consensus among eye surgeons regarding treatment strategy. The research question whether IOL repositioning or IOL exchange is the superior treatment option formed the basis for this research project and led to the initiation of the world´s first randomized clinical trial on such surgery in 2013. In the following years, 104 patients were enrolled in the study and randomized to either IOL repositioning by suturing of the dislocated lens to the eye wall or IOL exchange with removal of the dislocated lens and placement of a new lens clipsed to the iris (iris-claw IOL). Patients were comprehensively examined before surgery by PhD candidates and optometrists, operated by one experienced surgeon, and followed in our department for two years as part of the study. This included measurement of several clinical parameters such as surgical complications, vision, refraction (need for glasses), eye pressure and loss of cells in the cornea (transparent front part of the eye). The results for visual acuity were good and almost similar for the two groups, indicating that both operation methods are good choices in these patients. However, the trial led to new questions, in particular whether the inflammatory reaction inside the eye is different after the two types of surgery, which could possibly affect the retina in the posterior part of the eye. To answer these questions, we initiated a second randomized clinical trial – LION – in 2017. In the following years, 100 patients were enrolled by new PhD candidates, and operated by the same surgeon as the previous trial, and the study patients were followed for two years. The focus was intraocular inflammation measured with a laser flare instrument. Results so far have shown equal inflammation in the two operation groups after surgery. Surprisingly, we showed increased flare in eyes with eye dislocation before surgery, indication that inflammation may be a part of the disease entity of this condition. At least 15 publications in international

journals have been published from this project so far. More results from the LION trial are planned in the years to come.

The project with the two clinical studies was conducted in the Department of Ophthalmology, Oslo University Hospital. The project is affiliated to the Research group for anterior eye segment.

Key researchers involved

Olav Kristianslund, MD MPh PhD. Head of section, Professor, Research group leader. PhD candidate in start of the project, later supervisor and project coordinator.
Liv Drolsum, MD PhD. Professor emeritus, project leader for both clinical trials, supervisor.
Marius Dalby, MD PhD. Previous PhD candidate in the project
Helle Medin, MD, PhD candidate in the project
Ingeborg Slørdal Hjort Kure, PhD candidate in the project
In addition, research optomestrists, -nurse and -secretary were involved.

3. References to the research

1. Kristianslund O, Råen M, Østern AE, Drolsum L. Late In-the-Bag Intraocular Lens Dislocation: A Randomized Clinical Trial Comparing Lens Repositioning and Lens Exchange. **Ophthalmology 2017** Feb;124(2):151-159.
2. Kristianslund O, Råen M, Østern AE, Drolsum L. Glaucoma and Intraocular Pressure in Patients Operated for Late In-the-bag Intraocular Lens Dislocation: A Randomized Clinical Trial. **Am J Ophthalmol 2017**;176:219-27.
3. Kristianslund O, Dalby M, Moe MC, Drolsum L. Cost-effectiveness analysis in a randomized trial of late in-the-bag intraocular lens dislocation: repositioning versus exchange. **Acta Ophthalmol 2019** Dec;97(8):771-777.
4. Dalby M, Kristianslund O**,** Drolsum L. Long-Term Outcomes after Surgery for Late In-The-Bag Intraocular Lens Dislocation: A Randomized Clinical Trial. **Am J Ophthalmol 2019** Nov;207:184-194.
5. Medin HI, Dalby M, Kure ISH, Drolsum L, Kristianslund O. Intraocular Inflammation in Eyes Operated for Late In-the-bag intraOcular lens dislocatioN (LION): A Randomized Clinical Trial. **Am J Ophthalmol** 2022 Jan 5;238:66-74
6. Kristianslund O**,** Dalby M, Drolsum L. Late in-the-bag intraocular lens dislocation. (Major review) **J Cataract Refract Surg** 2021 Jul 1;47(7):942-954

4. Details of the impact

The number of patients with late in-the-bag IOL dislocation referred for surgery has increased, and in parallel, there has been more attention towards recommended treatment strategies. This has become a focus on national and international congresses in ophthalmology. In the present project, we have conducted two randomized clinical trials and compared important clinical parameters between the two main treatment strategies – IOL repositioning versus IOL exchange. Randomized clinical trials has been scarce in eye surgery, and in particular for this condition. Hence, the present project has provided necessary scientific and clinical knowledge. Study findings have been presented at several international and national congresses over the last 7 years and have gained much attention. Furthermore, the project has resulted in at least 15 scientific publications, and several texts and presentations for patients and society. So far, two PhDs has been completed and two more PhDs are ongoing related to this project. With the rapidly growing international interest in intraocular lens (IOL) dislocation, our research group has a unique opportunity to contribute, having already acquired comprehensive clinical and scientific expertise for this condition.

The results from the two trials have led to important clinical implications both in our clinic and in other centers, and has also been commented in several ophthalmological magazines. The first article from the project has been cited 76 times so far. The project has shown with comprehensive data and across several clinical parameters that both main operation methods for

this condition are good treatment options. The patients´ vision (visual acuity) is good both in the short and the long-term perspective after surgery in both groups, supporting the view that these patients should be offered surgery, and that both operation methods can be used. This is promising for the patients, as well as society, since many of these patients are elderly and dependent upon good sight to be able to manage daily life activities and live in their own homes for as long as possible. Further, our studies have shown that a large proportion of the patient have increased eye pressure and glaucoma. This information is important to consider in the management of this patient group, as the pressure should be treated in parallel. Further, we have performed a cost analysis especially relevant in countries with less access to surgical instruments and/or special IOLs. The second randomized trial – LION – focused on inflammation in the eye. Again, similar results have been shown after surgery in the two operation groups. However, the inflammation associated with late in-the-bag IOL dislocation should be studied in more depth, as results indicate that more intensive anti-inflammatory treatment may be considered. The conclusion of similarity between the two methods has made a great impact since not all surgeons manage both methods, and this seems to be adequate.

Since these were clinical studies that involved ordinary patients referred to a hospital department, the results have a direct impact on the corresponding patient population, and implementation of new knowledge in clinical practice is manageable. The two trials were conducted in the largest ophthalmology department in Norway, which aim to share knowledge with other ophthalmology departments. Hence, implementation of the results nationally should be feasible, making patients throughout the country benefit from the study. The studied operation methods are widely recognized and much used even internationally, and through previous and future publications and presentations we strive to ensure that even patients worldwide benefit from our research.

This project has affected treatment strategies for the studied patient group, and as such, it has had made an impact for ophthalmologists, these patients and the health care system.

5. Sources to corroborate the impact

1. EyeWorld. Review of “Repositioning surgery of different intraocular lens designs in eyes with late in-the-bag intraocular lens dislocation.” ASCRS/EyeWorld Journal Club, 2021. https://www.eyeworld.org/2021/intraocular-lens/
2. EyeNetMagazine. Late In-the-Bag IOL Dislocation: Lens Repositioning vs. Lens Exchange. AAO EyeNetMagazine, 2017. https://www.aao.org/eyenet/article/late-in-bag-iol-dislocation-lens-repositioning-vs
3. OcularSurgeryNews. Two surgical methods effective for late in-the-bag IOL dislocation. Healio OcularSurgeryNews, 2017.https://www.healio.com/ophthalmology/cataract-surgery/news/print/ocular-surgery-news/%7B545b46ca-9963-4572-a950-9e8ed92052a6%7D/two-surgical-methods-effective-for-late-in-the-bag-iol-dislocation
4. Oetting TA. Late in-the-bag intraocular lens dislocation - a randomized clinical trial comparing lens repositioning and lens exchange. Ann Eye Science 2017;2(23).
5. EyeWorld. Managing late in-the-bag IOL dislocation. ASCRS EyeWorld, 2018. https://www.eyeworld.org/managing-late-bag-iol-dislocation (no longer available)
6. Kristianslund O, Dalby M, Drolsum L. Hva hvis linsen løsner etter operasjon for grå stær? Ekspertsykehuset, Feb 12, 2018. https://ekspertsykehusetblog.wordpress.com/2018/02/12/hva-hvis-linsen-losner-etter-operasjon-av-gra-staer/
7. Kristianslund O, Drolsum L. Blir du blind hvis linsen i øyet løsner? Forskningssykehuset, Jun 16, 2017. https://blogg.forskning.no/forskningssykehuset-oye-og-syn/blir-du-blind-hvis-linsen-i-oyet-losner/1096576
8. Kristianslund O, Dalby M, Drolsum L. Dislokasjon av kunstig linse. Tidsskr Nor Legeforen 2020. https://tidsskriftet.no/2020/05/kort-kasuistikk/dislokasjon-av-kunstig-linse

9. Oftalmolog Dec 2019, comment PhD Kristianslund, Kongens gullmedalje. https://oftalmolog.com/wp-content/uploads/2021/04/Kongens-gullmedalje_2019_Dec.pdf
10. EyeWiki. AAO.org. Dislocated Intraocular Lens. (the present project cited) https://eyewiki.aao.org/Dislocated_Intraocular_Lens

Impact case guidelines

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Timeframes

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If relevant, describe any reason to keep this case confidential:

Please write the text here

Oslo university hospital, HHA, ØNH

[Name of the institution and name of the administrative unit] [case number]

Institution: Oslo university hospital / University of Oslo
Administrative unit: HHA, ØNH
Title of case study: The impact of ethnicity on cochlear implantation in Norwegian Children
Period when the underpinning research was undertaken: 2015-2017 (study data from 2004-2010)
Period when staff involved in the underpinning research were employed by the submitting institution:
Period when the impact occurred: 2017 -

1. Summary of the impact (indicative maximum 100 words)

This section should briefly state what specific impact is being described in the case study.

The main finding was that congenitally deaf children with non-Nordic parents are at risk of receiving cochlear implants (CI) later than Nordic children. Thus, there might be an age-at-surgery-delay for children with non-Nordic parents. The study has an impact on the follow-up of hearing-impaired children in how the families are informed and followed to make sure that the parents know that early implantation is important. More specifically, the clinicians are aware of the findings and will change their clinical practice to reduce the risk of an ethnicity effect. However, more could have been done in the follow-up outside the hospital to prevent a possible effect of ethnicity on cochlear implantation and hearing rehabilitation.

2. Underpinning research (indicative maximum 500 words)

This section should outline the key research insights or findings that underpinned the impact, and provide details of what research was undertaken, when, and by whom. This research may be a body of work produced over a number of years or may be the output(s) of a particular project. References to specific research outputs that embody the research described in this section, and evidence of its quality, should be provided in the next section. Details of the following should be provided in this section:

- The nature of the research insights or findings which relate to the impact claimed in the case study.
- An outline of what the underpinning research produced by the submitted unit was (this may relate to one or more research outputs, projects or programmes).
- Dates of when it was carried out.

Study data were data from our internal register for cochlear implant (CI) patients at Oslo University Hospital (OUH). Missing data were collected and registered, and the completed data set was exported from the register and analyzed in conjunction with a medical doctor's “Master thesis”, and subsequently published in Int J Pediatr Otorhinolaryngol. The title of the paper was ‘The impact of ethnicity on cochlear implantation in Norwegian’.

As described in the paper, the objective of the study was to explore the impact of parental ethnicity on cochlear implantation in children in Norway concerning incidence rates of cochlear implants (CIs), comorbidities, age at onset of profound deafness, age at first implantation, uni- or bilateral CI, and speech recognition. This retrospective cohort study included all children (N = 278) aged <18 years in Norway who received their first CI during the years 2004-2010. 86 children

(30.9%) in our study sample had parents of non-Nordic ethnicity, of whom 46 were born in Nordic countries with two non-Nordic parents.

The study concluded that the incidence of CI was significantly higher in children with a non-Nordic vs. a Nordic ethnicity, reflecting a higher incidence of profound deafness. Children born in Norway have equal access to CIs regardless of their ethnicity, but despite being born and receiving care in Norway, prelingually deaf children with non-Nordic parents are at risk of receiving CI later than Nordic children. Moreover, prelingually deaf children who arrive in Norway at an older age may be at risk for a worse prognosis after receiving a CI due to lack of auditory stimulation in early childhood, which is critical for language development and late implantation; this is a serious issue concerning deafness among refugees.

- Names of the key researchers and what positions they held at the administrative unit at the time of the research (where researchers joined or left the administrative unit during this time, these dates must also be stated).
- Any relevant key contextual information about this area of research.

The study was initiated by Marie Bunne, full-time senior ear surgeon (MD/PhD) at the ENT department, supervising a medical student, Viktoria Vedeler Amundsen, at the Institute of Clinical Medicine, Faculty of Medicine, University of Oslo. Key researchers were also Ona Bø Wie holding a full-time position at the Department of Special Needs Education, Faculty of Education, the University of Oslo, and Marte Myhrum, employed as a Senior engineer at the Institute of Clinical Medicine, Faculty of Medicine, University of Oslo. None of the authors had researcher positions.

This study is typical for the research and quality studies done at our unit (Øreseksjonen, ØNH, OUH) and the research group. Most of the research or quality studies are carried out by full-time clinicians. In addition, the CI industry has in recent years sponsored a half-time position for an audio physicist (MSc/PhD) to investigate CI electrode array insertions to preserve residual hearing and to make objective measurements during CI surgery, performing these surgeries at the Intervention center with excellent imaging facilities. The PhD students who have occasionally been connected to the group have also done valuable research in the field of the research group's focus area.

The research group is a multidisciplinary team mostly consisting of clinicians: medical doctors/ear surgeons (MD or MD/PhD), audio physicists (MSc/PhD), audio pedagogues (MEd), and audiologists (BSc). This opens up for research within different disciplines and across disciplines. In the last 12-13 years clinicians have been registering data (systematic journal data) in internal registers so valuable study data are available. The CI register contains data on all children who have received a CI in Norway. Thus the data is unique since it includes one country's whole paediatric CI population. However, we lack time, research positions, and resources, to concentrate on data extraction, data analysis, and writing/publication of retrospective studies.

The main aim of our research group is to conduct research related to ear and hearing and to investigate how patients benefit from intervention, treatment, and rehabilitation of ear surgery, including cochlear implantation (CI). Research on the diagnosis and treatment of superior semicircular canal dehiscence disorder has also become another main research aim of the group.

3. References to the research (indicative maximum of six references)
This section should provide references to key outputs from the research described in the previous section, and evidence about the quality of the research. All forms of output cited as underpinning

research will be considered equitably, with no distinction being made between the types of output referenced. Include the following details for each cited output:
- Author(s)
- Title
- Year of publication
- Type of output and other relevant details required to identify the output (for example, DOI, journal title and issue)
- Details to enable the panel to gain access to the output, if required (for example, a DOI or URL).

All outputs cited in this section must be capable of being made available to panels. If they are not available in the public domain, the administrative unit must be able to provide them if requested by RCN or the evaluation secretariate.

Amundsen VV, Wie OB, Myhrum M, Bunne M: The impact of ethnicity on cochlear implantation in Norwegian children. Int J Pediatr Otorhinolaryngol 2017;93:30-36.

4. Details of the impact (indicative maximum 750 words)

This section should provide a narrative, with supporting evidence, to explain:
- How the research underpinned (made a distinct and material contribution to) the impact;
- The nature and extent of the impact.

The following should be provided:
- A clear explanation of the process or means through which the research led to, underpinned or made a contribution to the impact (for example, how it was disseminated, how it came to influence users or beneficiaries, or how it came to be exploited, taken up or applied).
- Where the submitted administrative unit's research was part of a wider body of research that contributed to the impact (for example, where there has been research collaboration with other institutions), the case study should specify the particular contribution of the submitted administrative unit's research and acknowledge other key research contributions.
- Details of the beneficiaries – who or what community, constituency or organisation has benefitted, been affected or impacted on.
- Details of the nature of the impact – how they have benefitted, been affected or impacted on.
- Evidence or indicators of the extent of the impact described, as appropriate to the case being made.
- Dates of when these impacts occurred.

The paper is valuable in that it indicates that parents' ethnicity was affected when the children were receiving a cochlear implant (CI) during the years 2004 - 2010. When born deaf or hard of hearing, implantation at a young age is important to gain the best benefit of the CI. At OUH the recommended surgery age is 8 months when all other factors for surgery is OK. A replicate of the study should be done for the same data in the recent period, 2010-2022.

The paper also documents characteristics of the pediatric CI group; additional abilities, non-use of CI, etc, which are important data.

5. Sources to corroborate the impact (indicative maximum of ten references)

The paper was used as a reference in an important government investigation/report, NOU 2023:20, "Tegnspråk for livet". Ref: Høring - NOU 2023:20 Tegnspråk for livet. Forslag til en helhetlig politikk for norsk tegnspråk (https://www.regjeringen.no/no/dokumenter/nou-2023-20/id2984187/).

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If relevant, describe any reason to keep this case confidential:

Not relevant

[Department of Cardiology (KAD), Division of Cardiovascular and Pulmonary Diseases (HLK)] [3]

Institution: Oslo University Hospital
Administrative unit: Department of Cardiology (KAD), Division of Cardiovascular and Pulmonary Diseases (HLK)
Title of case study: Invasive strategy in patients aged 80 years or older with non-ST elevation myocardial infarct or unstable angina pectoris
Period when the underpinning research was undertaken: 2010-19
Period when staff involved in the underpinning research were employed by the submitting institution: 2010-19
Period when the impact occurred: 2020

1. Summary of the impact (indicative maximum 100 words)
This section should briefly state what specific impact is being described in the case study.

This large randomised controlled study of patients aged 80 years or more with non-ST elevation acute coronary syndrome (NSTE-ACS) demonstrated that an invasive strategy was superior to a conservative strategy in the reduction of composite events. The results have had a major impact on how we treat very old patients with NSTE-ACS , i.e. non-ST elevation myocardial infarction (NSTEMI) and unstable angina pectoris (UAP).

2. Underpinning research (indicative maximum 500 words)

Guidelines recommend medical optimization followed by an invasive strategy including coronary angiography and subsequent revascularization, with percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) for eligible patients with non-ST elevation acute coronary syndrome (NSTE-ACS), i.e. unstable angina pectoris and non-ST elevation myocardial infarction. However, these recommendations are not age-specific, and the lack of evidence of what is the optimal choice of treatment in the different subsets of a heterogeneous very old population may be an explanation why older patients are less likely to receive an invasive strategy compared with a more conservative medical strategy.
Thus, the invasive part of our group has focused on how to treat older patients with acute coronary syndromes, particularly those with NSTEMI and UAP. In this open-label randomized controlled multicenter trial, patients aged 80 years or older with NSTEMI or UAP were randomly assigned to an invasive or conservative strategy. The primary outcome was a composite of myocardial infarction, need for urgent revascularization, stroke, and death. The study was performed in 16 hospitals in the South-East Health Region of Norway.
The study demonstrated that an invasive strategy is superior to a conservative strategy in reducing composite events, and no differences in complication rates were seen between the two strategies An intention-to-treat analysis was used. This study is registered with ClinicalTrials.gov, number NCT01255540

- Names of the key researchers and what positions they held at the administrative unit at the time of the research (where researchers joined or left the administrative unit during this time, these dates must also be stated).

- Any relevant key contextual information about this area of research.

Bjørn Bendz, consultant cardiologist 2010- 14, assoc professor 2014-19
Nicolai Tegn, PhD student 2010-2016, fellow in cardiology 2016-19
Lars Aaberge, Head of department 2010 – 13, section head 2014-19

3. References to the research (indicative maximum of six references)

Tegn N, Abdelnoor M, Aaberge L, Endresen K, Smith P, Aakhus S, Gjertsen E, Dahl-Hofseth O, Ranhoff AH, Gullestad L, Bendz B; After Eighty study investigators. Invasive versus conservative strategy in patients aged 80 years or older with non-ST-elevation myocardial infarction or unstable angina pectoris (After Eighty study): an open-label randomised controlled trial. Lancet. 2016 Mar 12;387(10023):1057-1065. doi: 10.1016/S0140-6736(15)01166-6.

Tegn N, Abdelnoor M, Aaberge L, Hylen Ranhoff A, Endresen K, Gjertsen E, Skårdal R, Gullestad L, Bendz B; After Eighty study investigators. Health-related quality of life in older patients with acute coronary syndrome randomised to an invasive or conservative strategy. The After Eighty randomised controlled trial.
Age Ageing. 2018 Jan 1;47(1):42-47. doi: 10.1093/ageing/afx121

4. Details of the impact (indicative maximum 750 words)

The After Eighty study significantly impacted the treatment strategy for elderly patients with acute coronary syndromes globally. The research findings were disseminated through publications, conferences, and collaborations with international cardiology societies. The invasive strategy recommended by the study has been incorporated into clinical guidelines in many developed countries since 2020.

The results from the After Eighty study has been recommended in both Asian, American and European guidelines. The impact of the research on the treatment approach is evident in the change of practice in various healthcare settings. Cardiologists and healthcare providers have adopted the invasive strategy for older patients with NSTEMI or UAP, resulting in a reduction of composite events, including myocardial infarction, the need for urgent revascularization, stroke, and death.

The After Eighty study made a distinct and material contribution to this impact by providing robust evidence through a randomized controlled trial. The dissemination of the study results, collaboration with international researchers, and incorporation into clinical guidelines demonstrate the far-reaching nature of the impact beyond academia. The beneficiaries include elderly patients aged 80 years or more with NSTEMI or UAP, who now receive a more effective and evidence-based treatment strategy.

The impact is characterized by improved patient outcomes, reduced healthcare costs associated with complications, and a shift towards evidence-based practice in the management of acute coronary syndromes in the elderly.

The impact has been substantial, with the After Eighty study contributing to changes in clinical practice and guidelines globally. The evidence from the study continues to influence decisions made by healthcare professionals regarding the treatment of older patients with acute coronary syndromes.

The impact of the After Eighty study began to manifest in 2019, increased after the implementation in of the results in the European and American guidelines in 2020, and continues to influence clinical practice.

5. Sources to corroborate the impact (indicative maximum of ten references)

Kimura K, Kimura T, Ishihara M, Nakagawa Y, Nakao K, Miyauchi K, Sakamoto T, Tsujita K, Hagiwara N, Miyazaki S, Ako J, Arai H, Ishii H, Origuchi H, Shimizu W, Takemura H, Tahara Y, Morino Y, Iino K, Itoh T, Iwanaga Y, Uchida K, Endo H, Kongoji K, Sakamoto K, Shiomi H, Shimohama T, Suzuki A, Takahashi J, Takeuchi I, Tanaka A, Tamura T, Nakashima T, Noguchi T, Fukamachi D, Mizuno T, Yamaguchi J, Yodogawa K, Kosuge M, Kohsaka S, Yoshino H, Yasuda S, Shimokawa H, Hirayama A, Akasaka T, Haze K, Ogawa H, Tsutsui H, Yamazaki T; Japanese Circulation Society Joint Working Group. JCS 2018 Guideline on Diagnosis and Treatment of Acute Coronary Syndrome. Circ J. 2019 Apr 25;83(5):1085-1196. doi: 10.1253/circj.CJ-19-0133 Published April 25th 2019

Collet JP, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, Dendale P, Dorobantu M, Edvardsen T, Folliguet T, Gale CP, Gilard M, Jobs A, Jüni P, Lambrinou E, Lewis BS, Mehilli J, Meliga E, Merkely B, Mueller C, Roffi M, Rutten FH, Sibbing D, Siontis GCM; ESC Scientific Document Group. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J. 2021 Apr 7;42(14):1289-1367. https://doi.org/10.1093/eurheartj/ehaa575 Published April 7th 2021

Abdulla A Damluji, Daniel E Forman, Tracy Y Wang, Joanna Chikwe, Vijay Kunadian, Michael W Rich, Bessie A Young, Robert L Page 2nd, Holli A DeVon, Karen P Alexander; American Heart Association Cardiovascular Disease in Older Populations Committee of the Council on Clinical Cardiology and Council on Cardiovascular and Stroke Nursing; Council on Cardiovascular Radiology and Intervention; and Council on Lifestyle and Cardiometabolic Health. Management of Acute Coronary Syndrome in the Older Adult Population: A Scientific Statement From the American Heart Association. Circulation 2023 Jan 17;147(3):e32-e62. doi: 10.1161/CIR.0000000000001112. Published Dec 15 2022

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If relevant, describe any reason to keep this case confidential:

Please write the text here

[Oslo University Hospital – Division of Cardiovascular and Pulmonary Diseases] [case number #]

Institution: Oslo University Hospital
Administrative unit: Division of Cardiovascular and Pulmonary Diseases
Title of case study: CCN proteins as preproproteins that requires bioactivation by endopeptidase cleavage following secretion can be exploited to develop novel biologic therapeutics
Period when the underpinning research was undertaken: 2016 - 2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2016-2022
Period when the impact occurred: 2019-2022

1. Summary of the impact (indicative maximum 100 words)

Several members of the CCN protein family are established targets of the disease mechanisms of progressive fibrosis. The novel finding disclosed in this study was that CCN proteins are secreted preproproteins that must undergo endopeptidase cleavage in order to release the bioactive signalling entity. The finding also applied to a divergent member of the CCN family, CCN5, or Wnt-inducible signalling pathway protein-2, which antagonises pro-fibrotic members of the CCN family. This discovery led to the generation of a biologic therapeutic based on the bioactive entity of CCN5 fused to a half-life extending biologic molecule as a novel pharmacologic principle to target fibrotic diseases. Together with key investors Novo Nordic and HealthCap, the start-up company Tribune Therapeutics was established to commercialize and develop the potential product towards clinical testing in man.

2. Underpinning research (indicative maximum 500 words)

Purification of recombinant human CCN2 – connective tissue growth factor – from mammalian expression systems showed that specific activity decreased with increasing purity. Ultimately, highly purified CCN2 was virtually inactive. In parallel we observed that a carboxyl-terminal fragment of CCN2 comprising domains III and IV was bioactive and even existed in a homo-dimeric form that was 20-fold more potent than the monomeric fragment. We subsequently showed that highly purified full-length CCN2 could be activated by endopeptidase cleavage releasing the carboxyl-terminal fragment (domains III and IV). We concluded that CCN2 is secreted as a preproprotein that is constrained in inactive conformation by the N-terminal part of the protein. These findings led to further investigation of other members of the CCN family in order to provide evidence that these proteins are all secreted as preproproteins. Although we were not able to conclude that endopeptidase cleavage is an absolutely necessary step for all family members, we found that the carboxyl-terminal fragment broadly confers the bioactivities previously reported for the full-length proteins.

This discovery led to the idea that the bioactive entity of a CCN protein might be exploited therapeutically. This concept would be particularly relevant for CCN5/WISP2 which is a CCN family member with antagonistic functions relative to the other members. For example, CCN5 inhibits the profibrotic functions of several members of the CCN family (CCN1, CCN2, and CCN4). The bioactive entity of CCN5 is quite small (approx. 6 kDa) and would need to be fused with a larger half-life extending protein in order to be used therapeutically. The idea was submitted as a DOFI to the TTO of Oslo University Hospital, and the therapeutic principle was developed further with support from commercialisation programs of the Research Council of Norway. In late 2020, the intellectual property rights were licenced by Tribune Therapeutics, a biotech company founded by the inventors together with two major investors, Novo Nordic and the Swedish venture capital company HealthCap AB. Tribune Therapeutics (www.tribunetx.com), based in the Oslo Science Park, currently employing 5-6 people, is now

working to develop the therapeutic product towards clinical testing in man as a novel pharmacologic principle to curb progressive fibrosis in diseases in which fibrosis is leading to organ failure.

- Names of the key researchers and what positions they held at the administrative unit at the time of the research (where researchers joined or left the administrative unit during this time, these dates must also be stated):

  Håvard Attramadal, MD, PhD, professor/group leader/head of Institute
  Ole Kaasbøll, MD, PhD, postdoc
  Sima Zolfaghari, PhD student
  Vivi T. Monsen, PhD, Senior Engineer
  Else Marie Hagelin, MSc, dept. engineer

3. References to the research

Kaasbøll OJ, Gadicherla AK, Wang JH, **Monsen VT, Hagelin EMV**, Dong MQ, **Attramadal H.** Connective tissue growth factor (CCN2) is a matricellular preproprotein controlled by proteolytic activation. **J Biol Chem. 293(46):17953-17970, 2018.** doi: 10.1074/jbc.RA118.004559. PMID: 30262666
https://www.sciencedirect.com/science/article/pii/S0021925820312497?via%3Dihub

Zolfaghari S, Kaasbøll OJ, Monsen VT, Sredic B, Hagelin EMV, Attramadal H. The carboxyl-terminal TSP1-homology domain is the biologically active effector peptide of matricellular protein CCN5 that counteracts profibrotic CCN2. **J Biol Chem. 2023 Jan;299(1):102803. doi: 10.1016/j.jbc.2022.102803.** PMID: 36529291

https://www.sciencedirect.com/science/article/pii/S0021925822012467?via%3Dihub

5. Sources to corroborate the impact (indicative maximum of ten references)

www.tribunetx.com

Storinvestorer inn i norsk biotekforskning – E24

Tribune Therapeutics har inngått utviklings- og produksjonsavtale med Bayer — MedWatch

Impact case guidelines

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In this evaluation, impact is defined as an effect on, change or benefit to the economy, society, culture, public policy or services, health, the environment or quality of life, beyond academia.

Timeframes

- The impact must have occurred between 2012 and 2022
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- The administrative units are encouraged to prioritise recent cases

Page limit

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Please use the standardised short name for the administrative unit, and the case number for the unit (1,2,3, etc) in the headline of the case. Each case should be stored as a separate PDF-document with the file name: [Name of the institution and name of the administrative unit] [case number]

Publication of cases

RCN plans to publish all impact cases in a separate evaluation report. By submitting the case the head of the administrative units consents to the publication of the case. Please indicate below if a case may not be made public for reasons of confidentiality.

If relevant, describe any reason to keep this case confidential:

Please write the text here

[Cardiogenetics and sudden cardiac death] [2]

Institution: Oslo University Hospital
Administrative unit: Department of Cardiology (KAD), Division of Cardiovascular and Pulmonary Diseases (HLK)
Title of case study: Cardiogenetics and sudden cardiac death
Period when the underpinning research was undertaken: 2012-ongoing
Period when staff involved in the underpinning research were employed by the submitting institution: 2012
Period when the impact occurred: 2022

1. Summary of the impact (indicative maximum 100 words)

This section should briefly state what specific impact is being described in the case study.

The group's research significantly influenced risk stratification in cardiogenetic diseases, contributing to the 2022 ESC guidelines for sudden cardiac death and the 2023 ESC guidelines for cardiomyopathies. Their findings on exercise restrictions based on genotypes were instrumental in guiding clinical advice. In specific cardiomyopathies, the group's work informed the guidelines on pregnancy recommendations. Additionally, their pioneering research on mitral valve prolapse, identifying the risk factor "mitral annulus disjunction," initiated international efforts for risk stratification, diagnosis, and ongoing clinical trials.

2. Underpinning research (indicative maximum 500 words)

This part of the research group is lead by prof Kristina Haugaa who is a renown scientist internationally, and more than 30 PhD candidates, PostDocs, nurses, scientific programmers have focus on cardiomyopathies and imaging as well as electrical disease and ventricular arrhythmias. This had resulted in a production of 182 papers in peer reviewed journals during the last 5 years and with numerous presentations at international conferences on these topics.

The group has made substantial contributions to understanding risk factors and stratification in cardiogenetic diseases, with publications. The impact on exercise recommendations for specific genotypes is reflected in the 2022 ESC guidelines for sudden cardiac death and the 2023 ESC guidelines for cardiomyopathies. The nuanced advice on exercise, differentiating between high and low intensity, reflects the group's careful balance between risk and benefits.

In the realm of pregnancy and cardiomyopathies, their research challenged exclusionary practices and demonstrated that pregnancy is generally well-tolerated in women with specific genotypes like ARVC or LMNA, a perspective embedded in the 2022 ESC guidelines for sudden cardiac death and the 2023 ESC guidelines for cardiomyopathies.

The group's groundbreaking work on mitral valve prolapse (MVP) identified "mitral annulus disjunction" through cardiac magnetic resonance mapping, a significant risk factor. This discovery led to international collaborative efforts, including the EHRA consensus document, which Prof. Haugaa led [16-18]. Further research by the Oslo group revealed the incidence of MVP in connective tissue disease patients and advanced risk stratification. Insights from this research informed an ongoing randomized controlled trial (RCT) (NCT05631730), on novel treatments for this patient group.

Kristina Haugaa, consultant 2011, associated professor 2014-21, professor 2022-
Mette Estensen, consultant 2011 -
Thor Edvardsen, professor 2013-

Nina Hasselberg, PhD student 2013 – 2016. Consultant and postdoc 2019-
Ida Skrinde Leren, PhD student 2013 – 2016, fellow in Cardiology 2020-
Jørg Saberniak, PhD student 2013 – 2017
Øyvind H Lie, PhD student 2015 – 2018, fellow in Cardiology 2018-22
Lars Dejgaard, PhD student 2015 – 2020, fellow in Cardiology 2018-22
Monica Chivulescu, PhD student 2017– 2021
Eystein Skjølsvik, PhD student 2017– 2021
Isotta Castrini, PhD student 2019-2024
Christine Rootwelt-Norberg PhD student 2019-22, Post Doc 2023

3. References to the research (indicative maximum of six references)

Saberniak, J., N.E. Hasselberg, R. Borgquist, P.G. Platonov, S.I. Sarvari, H.J. Smith, M. Ribe, A.G. Holst, T. Edvardsen, and K.H. Haugaa, *Vigorous physical activity impairs myocardial function in patients with arrhythmogenic right ventricular cardiomyopathy and in mutation positive family members.* **Eur J Heart Fail**, 2014. 16(12): p. 1337-44. doi: 10.1002/ejhf.181

Lie, O.H., L.A. Dejgaard, J. Saberniak, C. Rootwelt, M.K. Stokke, T. Edvardsen, and K.H. Haugaa, *Harmful Effects of Exercise Intensity and Exercise Duration in Patients With Arrhythmogenic Cardiomyopathy.* **JACC Clin Electrophysiol**, 2018. 4(6): p. 744-753. doi: 10.1016/j.jacep.2018.01.010

Skjolsvik, E.T., N.E. Hasselberg, L.A. Dejgaard, O.H. Lie, K. Andersen, T. Holm, T. Edvardsen, and K.H. Haugaa, *Exercise is Associated With Impaired Left Ventricular Systolic Function in Patients With Lamin A/C Genotype.* **J Am Heart Assoc**, 2020. 9(2): p. e012937. doi: 10.1161/JAHA.119.012937

Dejgaard, L.A., E.T. Skjolsvik, O.H. Lie, M. Ribe, M.K. Stokke, F. Hegbom, E.S. Scheirlynck, E. Gjertsen, K. Andresen, T.M. Helle-Valle, E. Hopp, T. Edvardsen, and K.H. Haugaa, *The Mitral Annulus Disjunction Arrhythmic Syndrome.* **J Am Coll Cardiol**, 2018. 72(14): p. 1600-1609. doi: 10.1016/j.jacc.2018.07.070

Chivulescu, M., K. Krohg-Sørensen, E. Scheirlynck, B.R. Lindberg, L.A. Dejgaard, H. Lie Ø, T. Helle-Valle, E.T. Skjølsvik, M.E. Estensen, T. Edvardsen, P.S. Lingaas, and K.H. Haugaa, *Mitral annulus disjunction is associated with adverse outcome in Marfan and Loeys-Dietz syndromes.* **Eur Heart J Cardiovasc Imaging**, 2020. doi: 10.1093/ehjci/jeaa324

Castrini, A.I., O.H. Lie, I.S. Leren, M.E. Estensen, M.K. Stokke, L.G. Klaeboe, T. Edvardsen, and K.H. Haugaa, *Number of pregnancies and subsequent phenotype in a cross-sectional cohort of women with arrhythmogenic cardiomyopathy.* **Eur Heart J Cardiovasc Imaging**, 2018. doi: 10.1093/ehjci/jey061

Castrini, A.I., E. Skjølsvik, M.E. Estensen, V.M. Almaas, H. Skulstad, E. Lyseggen, T. Edvardsen, H. Lie Ø, K.C.I. Picard, N.K. Lakdawala, and K.H. Haugaa, *Pregnancy and Progression of Cardiomyopathy in Women With LMNA Genotype-Positive.* **J Am Heart Assoc**, 2022. 11(8): p. e024960. doi: 10.1161/JAHA.121.024960

4. Details of the impact (indicative maximum 750 words)

The research group's work on risk stratification in cardiogenetic diseases had a substantial impact on clinical guidelines. The integration of their findings into the 2022 ESC guidelines for sudden

cardiac death and the 2023 ESC guidelines for cardiomyopathies demonstrates the influence of their research on shaping clinical recommendations and practices. Their contributions provide a nuanced understanding of exercise recommendations, emphasizing the differentiation between high and low-intensity exercise based on specific genotypes, thus enhancing patient care.

The research findings challenging the exclusion of pregnancy in women with ARVC or LMNA genotypes have significantly impacted clinical guidelines. The endorsement of these findings in the 2022 ESC guidelines for sudden cardiac death highlights the transformative nature of the research. This recognition has broader implications, ensuring that women with specific genotypes can make informed decisions about family planning without unnecessary restrictions.

The Oslo group's pioneering research on MVP, particularly the identification of "mitral annulus disjunction" as a risk factor, has been groundbreaking. This discovery laid the foundation for an EHRA consensus document, establishing diagnosis and risk stratification for life-threatening events in patients with MVP [16-18]. Their subsequent work on the incidence of MVP in connective tissue disease patients and further risk stratification has expanded the understanding of this condition internationally [19-21].

The impact of this research extends beyond guidelines, influencing ongoing clinical trials. Insights from their work paved the way for an RCT on novel treatments for patients with MVP (NCT05631730), showcasing the translational impact of their research on patient care.

The primary beneficiaries of this research include clinicians, cardiologists, and patients globally. The impact is evident in improved risk stratification, more informed exercise recommendations, and inclusive family planning for women with cardiogenetic diseases. The Oslo group's work has contributed to safer and more personalized clinical practices, ensuring that patients receive tailored care based on the nuances of their genotypes and conditions.

The integration of research findings into ESC guidelines, including specific mentions in the 2022 ESC guidelines for sudden cardiac death, serves as tangible evidence of the extent of impact. The ongoing RCT on novel treatments for MVP further attests to the enduring influence of the research on clinical practices and advancements in patient care.

5. Sources to corroborate the impact (indicative maximum of ten references)

Sabbag, A., B. Essayagh, J.D.R. Barrera, C. Basso, A. Berni, B. Cosyns, J.C. Deharo, T. Deneke, L. Di Biase, M. Enriquez-Sarano, E. Donal, K. Imai, H.S. Lim, N.A. Marsan, M.K. Turagam, P. Peichl, S.S. Po, K.H. Haugaa et al, *EHRA expert consensus statement on arrhythmic mitral valve prolapse and mitral annular disjunction complex in collaboration with the ESC Council on valvular heart disease and the European Association of Cardiovascular Imaging endorsed cby the Heart Rhythm Society, by the Asia Pacific Heart Rhythm Society, and by the Latin American Heart Rhythm Society.* **Europace**, 2022. 24(12): p. 1981-2003. doi: 10.1093/europace/euac125

Zeppenfeld, K., J. Tfelt-Hansen, M. de Riva, B.G. Winkel, E.R. Behr, N.A. Blom, P. Charron, D. Corrado, N. Dagres, C. de Chillou, L. Eckardt, T. Friede, K.H. Haugaa, M. Hocini, P.D. Lambiase, E. Marijon, J.L. Merino, P. Peichl, S.G. Priori, T. Reichlin, J. Schulz-Menger, C. Sticherling, S. Tzeis, A. Verstrael, and M. Volterrani, *2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death.* **Eur Heart J**, 2022. 43(40): p. 3997-4126. doi: 10.1093/eurheartj/ehac262

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Publication of cases

RCN plans to publish all impact cases in a separate evaluation report. By submitting the case the head of the administrative units consents to the publication of the case. Please indicate below if a case may not be made public for reasons of confidentiality.

If relevant, describe any reason to keep this case confidential:

Please write the text here

[Department of Cardiology (KAD), Division of Cardiovascular and Pulmonary Diseases (HLK)] [1]

Institution: Oslo University Hospital
Administrative unit: Department of Cardiology (KAD), Division of Cardiovascular and Pulmonary Diseases (HLK)
Title of case study: The use of myocardial strain in myocardial diseases
Period when the underpinning research was undertaken: 2007-ongoing
Period when staff involved in the underpinning research were employed by the submitting institution: 2005-
Period when the impact occurred: 2019-

1. Summary of the impact (indicative maximum 100 words)

Our research on myocardial strain and global longitudinal strain (GLS) has had a transformative impact on clinical cardiology, influencing European and American guidelines, clinical practices, and healthcare reimbursement policies. The implications of our work extend beyond academia, bringing substantial benefits to patient care, healthcare systems, and the broader society.

2. Underpinning research (indicative maximum 500 words)

Our research group has been at the forefront of investigating the application of myocardial strain and global longitudinal strain (GLS) across a spectrum of myocardial diseases. Pioneering experimental studies, we were the first to validate the first strain technique based on Doppler signals, meticulously comparing it to myocardial function assessed by cardiac magnetic resonance imaging (CMR).

The research group was also the first to validate speckle tracking strain as a superior measure of LV function. Experimental studies conducted in their lab, complemented by validations using CMR techniques at Johns Hopkins Hospital, established speckle tracking strain as an innovative and effective approach. This advancement marked a significant step forward in assessing LV function with improved accuracy.

Our group led important studies demonstrating the superiority of GLS in both chronic and acute coronary syndromes. This research provided critical insights into the diagnostic power of GLS in the context of coronary diseases, and also how GLS could add to the early diagnosis of acute coronary syndromes, and risk prediction after acute coronary syndromes.

In the domain of cardio-oncology, the research group demonstrated the superior efficacy of GLS over traditional ejection fraction measurements. This finding is particularly relevant in assessing LV function in long-term survivors after cancer treatment. The application of GLS in this context provides more accurate insights into cardiac health, influencing treatment strategies and long-term care for cancer survivors.

Collaborations with renowned institutions such as Johns Hopkins Hospital in the USA and UZ Leuven in Belgium underscore the international significance of the research. These collaborations facilitated the validation of methodologies, ensuring the robustness and applicability of the findings across diverse clinical settings.

The cumulative impact of this research is reflected in the recognition of myocardial strain and GLS as a recommended parameter in European and American cardiology guidelines. Additionally, the groundbreaking work played a pivotal role in myocardial strain becoming the first echocardiographic technology to secure Medicare reimbursement in the USA, signifying its clinical and economic significance.

The underpinning research, marked by innovation and influential collaborations, has elevated myocardial strain GLS to its current status as a recommended and reimbursed parameter, significantly shaping global clinical practices.

- Thor Edvardsen, professor, Department of Cardiology 2007-
- Otto A Smiseth, professor, 2007-2019
- Kristina Haugaa, PhD student – 2010 and assoc prof, 2014-2022
- Ola Gjesdal, PhD student -2009
- Christian Eek, PhD student -2011
- Trond Vartdal, PhD student -2012
- Thomas Helle-Valle, PhD student -2013

The research conducted by the team on the application of myocardial strain and global longitudinal strain (GLS) in myocardial diseases has been an integral part of the research group. The collaboration with prominent international institutions has enriched the research context, fostering a global perspective and ensuring the relevance and impact of the findings in diverse clinical settings. The impressive output of around 150 scientific papers on myocardial strain underscores the group's commitment to advancing knowledge and disseminating findings to the scientific community. Furthermore, the group's innovative contributions have resulted in the patenting of two methods, which have been implemented in high-end echocardiographic machines. This achievement highlights the translational impact of the research, with the developed methods finding practical applications in clinical settings.

3. References to the research (indicative maximum of six references)

1) Amundsen BH, **Helle-Valle T, Edvardsen T**, Torp H, Crosby J, **Lyseggen E**, Støylen A, **Ihlen H,** Lima JA, **Smiseth OA**, Slørdahl SA: Non-invasive myocardial strain measurement by speckle tracking echocardiography - validation against sonomicrometry and tagged magnetic resonance imaging J Am Coll Cardiol 2006;47:789-93 doi: 10.1016/j.jacc.2005.10.040 Cited: 1145 times (Jan 2024)
2) **Helle-Valle T**, **Crosby J, Edvardsen T, Lyseggen E, Amundsen BH**, Smith H-J, Rosen BD, Lima JA, Torp H, **Ihlen H, Smiseth OA**: New Non-Invasive Method for Assessment of LV Torsion - Speckle Tracking Echocardiography Circulation 2005;112:3149-3156 doi: 10.1161/CIRCULATIONAHA.104.531558 Cited: 617 times (Jan 2024)
3) **Gjesdal O, Hopp E, Vartdal T, Lunde K, Helle-Valle T, Aakhus S,** Smith H-J, **Ihlen H, Edvardsen T**: Longitudinal Strain by Two-Dimensional Speckle Tracking Echocardiography Correlates to Myocardial Infarct Size by MRI in Chronic Ischemic Heart Disease, Clin Science 2007;113:287-296 doi: 10.1042/CS20070066 Cited: 180 times (Jan 2024)
4) **Vartdal T,** Brunvand H, **Pettersen E,** Smith H-J, **Lyseggen E, Helle-Valle T, Skulstad H, Ihlen H, Edvardsen T**: Early Prediction of Infarct Size by Strain Doppler Echocardiography after Coronary Reperfusion. J Am Coll Cardiol 2007;49:1715-21 doi: 10.1016/j.jacc.2006.12.047 Cited: 128 times (Jan 2024)
5) **Eek C**, Grenne B, Brunvand H, **Aakhus S, Endresen K**, Hol PK, Smith HJ, **Smiseth OA, Edvardsen T, Skulstad H**: Strain echocardiography and wall motion score index predicts final infarct size in patients with non ST segment elevation myocardial infarction. **Circulation:**

Cardiovasc Imaging 2010;3:187-94. doi: 10.1161/CIRCIMAGING.109.910521 Cited: 88 times (Jan 2024)

6) **Haugaa KH,** Grenne B, **Eek CH,** Ersbøll MK, Svendsen JH, Florian A, Sjølie B, Brunvand H, Køber L, Voigt JU, Desmet W, **Smiseth OA, Edvardsen T**: Strain echocardiography improves risk prediction of ventricular arrhythmias in patients after myocardial infarction. JACC Cardiovasc Imaging 2013 Aug;6(8):841-50 doi: 10.1016/j.jcmg.2013.03.005 Cited: 212 times (Jan 2024)

3. Details of the impact (indicative maximum 750 words)

Our research on myocardial strain and global longitudinal strain (GLS) has made a distinct and material contribution to clinical practice and guidelines, particularly in the domains of coronary syndromes and heart failure.
The dissemination of our research findings occurred through prominent scientific publications, notably in high-impact journals such as the Journal of the American College of Cardiology and Circulation. Another important contribution came from our active participation in the standardization committee of the EACVI/ASE/Industry Task Force. This collaborative effort played an important role in ensuring consistency and comparability of strain measurements across major echocardiographic vendors. This collaborative effort addressed the need for standardization in deformation imaging, contributing to the widespread adoption of GLS as a standardized measure of LV function.

While acknowledging that our research was part of a broader body of knowledge, collaborations with renowned international institutions, such as Johns Hopkins Hospital, USA, and UZ Leuven, Belgium, have been important. These collaborations enriched the research context, ensuring a global perspective and enhancing the credibility and applicability of our findings.

The primary beneficiaries of our research are clinicians, cardiologists, and patients worldwide. The incorporation of myocardial strain and GLS into guidelines has fundamentally changed the way LV function is assessed in clinical settings. Clinicians benefit from a more accurate and sensitive tool for diagnosing and managing myocardial diseases, leading to improved patient outcomes.

The impact is substantial, evident in the adoption of myocardial strain and GLS as recommended measures of LV function in European and American guidelines. Noteworthy is the recognition of myocardial as a reimbursable parameter by Medicare in the USA, highlighting its acceptance and impact in health policies. Our publications, with significant citations, indicate the research's continuous influence on subsequent studies and clinical applications.

2019 ESC guidelines on chronic coronary syndromes (31. Aug 2019). Cites three of our articles as evidence for recommendations on strain imaging techniques in patients with clinical suspicion of chronic coronary syndromes (CCS) and provides recommendations on risk assessment using GLS. “Recommendations on risk assessment: Echocardiographic assessment of GLS provides incremental information to LVEF and may be considered when LVEF>35%. Class IIb Level B”. (Citing one of our articles for this recommendation.)

2020 ESC guidelines on acute coronary syndromes (29. Aug 2020). Cite two of our studies for recommendations on the diagnostic and prognostic value of myocardial perfusion and reduced regional function using strain and strain rate imaging.

Joint European and American expert consensus document on Non-invasive Imaging in Coronary Syndromes (Apr 2022). Recommends myocardial strain and GLS in the diagnostics, monitoring and risk prediction in patients with coronary syndromes.

2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death recommends GLS and myocardial strain. (26 August 2022) Recommends GLS and myocardial strain for assessing LV function, detecting subtle changes, and assessing mechanical dispersion associated with an increased risk of ventricular arrhythmias, when citing 3 of our studies.

5. Sources to corroborate the impact (indicative maximum of ten references)

2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, Prescott E, Storey RF, Deaton C, Cuisset T, Agewall S, Dickstein K, Edvardsen T, Escaned J, Gersh BJ, Svitil P, Gilard M, Hasdai D, Hatala R, Mahfoud F, Masip J, Muneretto C, Valgimigli M, Achenbach S, Bax JJ; ESC Scientific Document Group. **Eur Heart J.** 2020 Jan 14;41(3):407-477 doi: 10.1093/eurheartj/ehz425 **Cited 4 works from our group and further 3 expert consensus documents where we have participated.**

2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Collet JP, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, Dendale P, Dorobantu M, Edvardsen T, Folliguet T, Gale CP, Gilard M, Jobs A, Jüni P, Lambrinou E, Lewis BS, Mehilli J, Meliga E, Merkely B, Mueller C, Roffi M, Rutten FH, Sibbing D, Siontis GCM; ESC Scientific Document Group. **Eur Heart J.** 2021 Apr 7;42(14):1289-1367. https://doi.org/10.1093/eurheartj/ehaa575 **Cited 3 works from our group and further 3 expert consensus documents/guidelines where we have participated.**

Non-invasive Imaging in Coronary Syndromes - Recommendations of the European Association of Cardiovascular Imaging and the American Society of Echocardiography, in Collaboration with the American Society of Nuclear Cardiology, Society of Cardiovascular Computed Tomography and Society for Cardiovascular Magnetic Resonance. Edvardsen T, Asch FM, Davidson B, Delgado V, DeMaria A, Dilsizian V, Gaemperli O, Garcia MJ, Kamp O, Lee DC, Neglia D, Neskovic AN, Pellikka PA, Plein S, Sechtem U, Shea E, Sicari R, Villines TC, Lindner JR, Popescu BA. **J Am Soc Echocardiogr**. 2022 Apr;35(4):329-354 doi: 10.1016/j.echo.2021.12.012 **Cited 3 works from our group and further 4 expert consensus documents/guidelines where we have participated.**

2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. Zeppenfeld K, Tfelt-Hansen J, de Riva M, Winkel BG, Behr ER, Blom NA, Charron P, Corrado D, Dagres N, de Chillou C, Eckardt L, Friede T, Haugaa KH, Hocini M, Lambiase PD, Marijon E, Merino JL, Peichl P, Priori SG, Reichlin T, Schulz-Menger J, Sticherling C, Tzeis S, Verstrael A, Volterrani M; ESC Scientific Document Group. Eur Heart J. 2022 Oct 21;43(40):3997-4126. doi: 10.1093/eurheartj/ehac262. **Cited 4 works from our group and further 3 expert consensus documents where we have participated.**

OUS, HLK Case 5

Institution: Oslo University Hospital
Administrative unit: HLK
Title of case study: Diastolic myocardial function and dysfunction
Period when the underpinning research was undertaken: 2017-2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2017 -
Period when the impact occurred: 2018-

1. Summary of the impact

Researchers in HLK have studied heart failure for decades. With increasing awareness about the fact that more than half of all new cases of heart failure have preserved ejection fraction (HFPEF), significant parts of the unit`s research has shifted towards this condition. In this research, understanding diastolic function and dysfunction is key. The establishment of the KG Jebsen Center for Cardiac Research in 2017 has resulted in a number of high impact publications, increased collaborations between basic and clinical researchers, and lead to insights that have been brought towards clinical use.

2. Underpinning research

Studies of diastolic function and dysfunction in different patient groups, as well as a large body of basic research by HLK researchers laid the foundation for the establishment of the KG Jebsen Center for Cardiac Research (KGJCCR) in 2017. The primary objective was to better understand the mechanisms of heart failure. Specifically, the involved partners wanted to identify mechanisms regulating myocardial stiffness, and new therapeutic targets for diastolic dysfunction. The Center is hosted by the Institute for Experimental Medical Research (IEMR), and comprises six partners from two different administrative units in OUS (HLK and KRE). The partners represent basic, translational and clinical research with complementary expertise. The work in the Center has been focused on two main aspects of diastolic function: Active relaxation and passive stiffness.

Active relaxation is one of the key components in diastolic function of the heart. It is controlled by ion channels and pumps, and tightly coupled with contraction. Researchers in the KGJCCR researchers have contributed to this field by detailed studies of the regulation of the sarco-endoplasmic reticulum Ca2+ ATPase (Serca 2) and the sodium-potassium ATPase (NKA). Such proteins are positioned in cardiac muscle cells by the cellular ultrastructure, of which t-tubules are important. KGJCCR researchers have provided original insights in the regulation of these structure in heart failure of different etiologies, and how such pathological remodelling of the cellular ulstrastructure relates to regional diastolic dysfunction, a new concept in this field.

Passive stiffness is the other key component in diastolic function. Resarchers in KGJCCR have provided novel insights in how proteoglycans, a large group of molecules in the extracellular matrix, contribute to stiffness, and is altered in disease. Other molecules that have been studied in detailed are integrins and Syndecan 4, which are important for the hypertrophic response.

To bring these fundamental biological insights towards clinical use, KGJCCR have identified new potentially therapeutic molecules, established the mechanisms for emerging treatment strategies, studied myocardial function in patients with aortic stenosis, and explored new treatment options for patients with hypertrophic cardiomyopathy.

3. References to the research (indicative maximum of six references)

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Thienpont B, Aronsen JM, Robinson EL, Okkenhaug H, Loche E, Ferrini A, Brien P, Alkass K, Tomasso A, Agrawal A, Bergmann O, Sjaastad I, Reik W, Roderick HL. The H3K9 dimethyltransferases EHMT1/2 protect against pathological cardiac hypertrophy. J Clin Invest. 2017 Jan 3;127(1):335-348. doi: 10.1172/JCI88353. Epub 2016 Nov 28. PMID: 27893464; PMCID: PMC5199699.

Frisk M, Le C, Shen X, Røe ÅT, Hou Y, Manfra O, Silva GJJ, van Hout I, Norden ES, Aronsen JM, Laasmaa M, Espe EKS, Zouein FA, Lambert RR, Dahl CP, Sjaastad I, Lunde IG, Coffey S, Cataliotti A, Gullestad L, Tønnessen T, Jones PP, Altara R, Louch WE. Etiology-Dependent Impairment of Diastolic Cardiomyocyte Calcium Homeostasis in Heart Failure With Preserved Ejection Fraction. J Am Coll Cardiol. 2021 Feb 2;77(4):405-419. doi: 10.1016/j.jacc.2020.11.044. PMID: 33509397; PMCID: PMC7840890.

Skogestad J, Albert I, Hougen K, Lothe GB, Lunde M, Eken OS, Veras I, Huynh NTT, Børstad M, Marshall S, Shen X, Louch WE, Robinson EL, Cleveland JC Jr, Ambardekar AV, Schwisow JA, Jonas E, Calejo AI, Morth JP, Taskén K, Melleby AO, Lunde PK, Sjaastad I, Carlson CR, Aronsen JM. Disruption of Phosphodiesterase 3A Binding to SERCA2 Increases SERCA2 Activity and Reduces Mortality in Mice With Chronic Heart Failure. Circulation. 2023 Apr 18;147(16):1221-1236. doi: 10.1161/CIRCULATIONAHA.121.054168. Epub 2023 Mar 6. PMID: 36876489.

Vistnes M, Erusappan PM, Sasi A, Nordén ES, Bergo KK, Romaine A, Lunde IG, Zhang L, Olsen MB, Øgaard J, Carlson CR, Wang CH, Riise J, Dahl CP, Fiane AE, Hauge-Iversen IM, Espe E, Melleby AO, Tønnessen T, Aronsen JM, Sjaastad I, Christensen G. Inhibition of the extracellular enzyme A disintegrin and metalloprotease with thrombospondin motif 4 prevents cardiac fibrosis and dysfunction. Cardiovasc Res. 2023 Aug 19;119(10):1915-1927. doi: 10.1093/cvr/cvad078. PMID: 37216909; PMCID: PMC10439713.

Nordén ES, Bendiksen BA, Andresen H, Bergo KK, Espe EK, Hasic A, Hauge-Iversen IM, Veras I, Hussain RI, Sjaastad I, Christensen G, Cataliotti A. Sacubitril/valsartan ameliorates cardiac hypertrophy and preserves diastolic function in cardiac pressure overload. ESC Heart Fail. 2021 Apr;8(2):918-927. doi: 10.1002/ehf2.13177. Epub 2021 Jan 26. PMID: 33497525; PMCID: PMC8006657.

4. Details of the impact (indicative maximum 750 words)

The translational studies from the KGJCCR has been brought towards practical impact for diagnostics and treatment strategies for patients with heart disease, as well as increased inter- and transdisciplinary collaborations.

With regard to diagnostics, studies from KGJCCR researchers has led to increased awareness about diastolic dysfunction in new patient groups, such as patients with rheumatic diseases. This has been included in clinical guidelines, and ongoing research has expanded the research to kidney donors. Other projects have resulted in new methods for parameterisation of diastolic dysfunction in animal models by echocardiography and cardiac MRI, as well as the emerging technique MR elastography. These results are now in the pipeline for clinical use, with possible prediction of reverse remodelling response and effect on diastolic dysfunction after TAVI.

With regard to treatment, translational studies from KGJCCR have underpinned testing of existing therapies for patients with HFPEF, and identified new potential therapeutic molecules. Some work has also proved emerging therapies as futile in randomized clinical studies, while others are currently underpinning device-based treatment of select patient groups.

Collaborations and resulting research in the KGJCCR have also resulted in new initiatives, including the Convergence environment at UiO on fibrosing diseases (FibroPET).

In sum, the research on HFPEF, diastolic function and dysfunction in HLK, culminating in the highly prestigious KGJCCR, has resulted in publications with high academic impact, as well as immediate, intermediate and long-term benefit for patients, new collaborations, and improved opportunities for basic, translational and academic researchers in HLK and beyond.

5. Sources to corroborate the impact (indicative maximum of ten references)

Oldroyd AGS, Lilleker JB, Amin T, Aragon O, Bechman K, Cuthbert V, Galloway J, Gordon P, Gregory WJ, Gunawardena H, Hanna MG, Isenberg D, Jackman J, Kiely PDW, Livermore P, Machado PM, Maillard S, McHugh N, Murphy R, Pilkington C, Prabu A, Rushe P, Spinty S, Swan J, Tahir H, Tansley SL, Truepenny P, Truepenny Y, Warrier K, Yates M, Papadopoulou C, Martin N, McCann L, Chinoy H; British Society for Rheumatology Standards, Audit and Guidelines Working Group. British Society for Rheumatology guideline on management of paediatric, adolescent and adult patients with idiopathic inflammatory myopathy. Rheumatology (Oxford). 2022 May 5;61(5):1760-1768. doi: 10.1093/rheumatology/keac115. PMID: 35355064; PMCID: PMC9398208.

Kobayashi I, Akioka S, Kobayashi N, Iwata N, Takezaki S, Nakaseko H, Sato S, Nishida Y, Nozawa T, Yamasaki Y, Yamazaki K, Arai S, Nishino I, Mori M. Clinical practice guidance for juvenile dermatomyositis (JDM) 2018-Update. Mod Rheumatol. 2020 May;30(3):411-423. doi: 10.1080/14397595.2020.1718866. Epub 2020 Feb 3. Erratum in: Mod Rheumatol. 2020 May;30(3):607. PMID: 31955618.

[Oslo University Hospital, Division of Laboratory Medicine; 1]

Institution: Oslo University Hospital
Administrative unit: Division of Laboratory Medicine
Title of case study: Alcohol, drugs and health
Period when the underpinning research was undertaken: 2011-2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2011-2022
Period when the impact occurred: 2018 - ongoing

1. Summary of the impact

Overall aim of this impact case is to ensure better treatment, reduce complications during hospital stays, and minimize ongoing use and further damage to health by identification of harmful use of alcohol and psychoactive drugs. The result of this impact case is that emergency patients admitted to Oslo University Hospital (OUH) will be asked a standard set of questions about alcohol consumption and for patients taking at least one drug, and where use may be related to the patient's reason for admission, a serum analysis will be carried out. The aim is to implement similar guidelines at Lovisenberg Diaconal Hospital (Lovisenberg) and St Olavs Hospital (SOH). The impact has contributed to the National alcohol strategy.

2. Underpinning research

The aim of our research has been to improve current knowledge on prevalence and health consequences of alcohol and psychoactive medicinal drug use by developing laboratory methods for assessment of drugs and biomarkers for alcohol in blood and studying associations between alcohol and drug use and various sociodemographic and clinical variables using questionnaires, patient records and national registers. It started with a study of alcohol and substances of abuse among patients in an emergency department in Oslo (2011), where the results indicated a higher prevalence than anticipated. 38% of the women and 48% of the men had a positive blood sample for psychoactive substances upon admission, and the most prevalent psychoactive substance was alcohol. In an emergency department, use of psychoactive substance is somewhat expected due to higher risk of trauma occurring when being under the influence. This was also shown for a rural arctic emergency department (2016), where a significant proportion (36%) of injured patients had used psychoactive substances prior to admission. Use was associated with violence, falls, at-risk alcohol consumption, decreased level of consciousness on admittance and head injury. To study whether the high prevalence also applied to somatic patients, a large study was performed in the general medicinal wards at Lovisenberg (2017). The results indicated that 21% were harmful alcohol users, measured by AUDIT-4, while the prevalence of the alcohol biomarker PEth-positive patients was lower (11%), and a total of 32% were positive for one or more psychoactive medicinal drugs (benzodiazepines, z-hypnotics, opioids or barbiturates). Excessive use of medicinal drug was also seen in the increase of overdose deaths where potentially prescribed medications were detected (2019a). These deaths, where no illicit drug was detected at autopsy, were more common among women and among individuals with higher age. In more generalized populations, where we also contribute with research, psychoactive substance use was found in 4,9% of drivers in normal traffic, 4% of workers and 94% attendees at music festivals, while 63% of a group of participants in a nightlife study had detectable concentrations of illegal substances. This emphasizes that substances, and alcohol in particular, are widely used in everyday settings in Norway. In addition to validated questionnaires and registry data, our work is based on analytical laboratory research that contributes to our scientific progress, productivity and high-quality research (2019b). It should be

specially noted that the prevalence of drug use in general patients on admission to hospitals was sparsely assessed earlier and the problem little known to the Norwegian society before the results from this impact case. These results were crucial for developing the new hospital procedures and an important contribution to the National alcohol strategy.

Key contributors to the impact case according to the references above:

2011

Per Trygve Normann - Head of Department/ Head of research (1999-2015), Stig Tore Bogstrand- PhD-student (2007-), Jørg Mørland - Head of Division (1980-2017).

2016

Thomas Wilson – PhD-student (2015-), Per Trygve Normann - Head of Department/ Head of research (1999-2015), Vigdis Vindenes – Head of Department (2012-2022), Ragnhild Jamt – Project worker (2014-), Håvard Furuhaugen – Senior Engineer (2014-2022), Stig Tore Bogstrand - Head of Research (2007-)

2017

Saranda Kabashi – PhD-student/project coordinator (2014-), Vigdis Vindenes – Head of Department (2012-2022), Danil Gamboa – PhD-student (2019-), Benedicte Jørgenrud - Project coordinator (2017-), Anna Armika T Nyman - Researcher/Project worker (2018-), Stig Tore Bogstrand - Head of Research (2007-)

2019a

Hilde M Erøy Edvardsen – Senior Researcher (2010-)

2019b

Benedicte Jørgenrud - Project coordinator (2017-), Håvard Furuhaugen – Senior Engineer (2014-2022), Thomas Berg – Senior Researcher (2015-)

3. References to the research

- Edvardsen HME, Clausen T (2022)
  Opioid related deaths in Norway in 2000-2019
  Drug Alcohol Depend, 232, 109281
  doi: 10.1016/j.drugalcdep.2022.109281. PMID: 35042099 (11 citations)

- **Jørgenrud B**, Skadberg E, de Carvalho Ponce J, Furuhaugen H, Berg T (2021)
  Determination of the alcohol biomarker phosphatidylethanol 16:0/18:1 and 33 compounds from eight different drug classes in whole blood by LC-MS/MS.
  J Pharmacol Toxicol Methods. Jan-Feb;107:106939.
  doi: 10.1016/j.vascn.2020.106939. PMID: 33257303 (9 citations)

- **Wilson T**, Wisborg T, **Vindenes V, Jamt RG, Furuhaugen H, Bogstrand ST** (2021)
  Psychoactive substances have major impact on injuries in rural arctic Norway - A prospective observational study
  Acta Anaesthesiol Scand. Jul;65(6):824-833.
  doi: 10.1111/aas.13807. PMID: 33638866 (3 citations)

- **Gamboa D, Jørgenrud B**, Bryun EA, **Vindenes V**, Koshkina EA, Nadezhdin AV, **Kabashi S**, Tetenova EJ, **Berg T, Nyman AAT,** Kolgashkin AJ, Petukhov AE, Perekhodov SN, Davydova EN, Lerdal A, Nordby G, **Bogstrand ST** (2020)

Prevalence of psychoactive substance use among acutely hospitalised patients in Oslo and Moscow: a cross-sectional, observational study
BMJ Open. Sep 17;10(9):e032572.
doi: 10.1136/bmjopen-2019-032572. PMID: 32948540 (5 citations)

- **Kabashi S, Vindenes** V, Bryun EA, Koshkina EA, Nadezhdin AV, Tetenova EJ, Kolgashkin AJ, Petukhov AE, Perekhodov SN, Davydova EN, **Gamboa D,** Hilberg T, Lerdal A, Nordby G, Zhang C, **Bogstrand ST** (2019)
  Harmful alcohol use among acutely ill hospitalized medical patients in Oslo and Moscow: A cross-sectional study
  Drug Alcohol Depend. Nov 1;204:107588.
  doi: 10.1016/j.drugalcdep.2019.107588. PMID: 31590131 (30 citations)

- **Bogstrand ST**, Normann PT, Rossow I, Larsen M, Mørland J, Ekeberg Ø (2011)
  Prevalence of alcohol and other substances of abuse among injured patients in a Norwegian emergency department
  Drug Alcohol Depend, 117 (2-3), 132-8
  doi: 10.1016/j.drugalcdep.2011.01.007. PMID: 21316163 (108 citations)

4. Details of the impact

Traditionally, the research in the department of Forensic Medicine, Clinic of laboratory Medicine, focused on development of laboratory methods for drug detection, supporting routine functions. The bulk of any clinical studies examining alcohol and psychoactive substance use have been based on self-reported consumption, utilizing questionnaire, or determined via clinical assessments. Correspondingly, assessment of use of alcohol or psychoactive substances at the hospital is often done by clinical assessment, and the availability of relevant laboratory analysis has been very limited.

Based on the results of our studies and emerging evidence from other studies of the health effects of alcohol and psychoactive drug use, our aim has been to expand the methodology for better identification of patients with problematic use of alcohol and psychoactive drugs.

In 2014, two members of the research group participated as national experts in the EU Joint Action on Reducing Alcohol Related Harm, where different approaches and guidelines for low-risk consumption of alcohol were developed. Based on our extensive work in the field of substance use and health outcomes, we have had several international projects which have had local impact. In Malawi, alcohol-related traffic injuries were assessed through a World Bank financed competence sharing project. We have had similar collaborative projects with the University of Sao Paulo in Brazil, funded by national Brazilian sources. A collaboration with Moscow Research and Practical Centre on Addiction on alcohol use among medical patients was funded by the Norwegian Ministry of Health and lasted from 2014-2021.

From 2014-15, all Norwegian Hospitals were requested to establish systems for better identification of patients with harmful use of alcohol or other psychoactive substances. When the results from the Lovisenberg study of medical patients showed that 20 % of the patients had hazardous alcohol consumption and 30 % screened positive for one or more psychoactive medicinal substances, the Minister of Health and Care services invited the project group to a meeting. In this meeting, the group was challenged on how hospitals could implement measures to give better identification and

follow up of these patients. This was also iterated in the National alcohol strategy published in 2021 with reference to some of the research group's studies presented in section 2 of this document.

A new collaborative project was initiated at the Oslo University Hospital, where there already was ongoing work on better identification and treatment of delirium tremens patients. The already existing collaboration with Lovisenberg Diaconal Hospital was developed further. Two clinical guidelines were developed at OUH and underwent a health technology assessment (in Norwegian: Mini-metodevurdering). It was then decided to be used hospital wide by the hospital leader group. This was in March 2020, and after some covid-related delay, the implementation process started.

The implementation was designed as a study which was funded by the NRC (Grant #: 319820). The Norwegian Minister of Health requested the findings from this implementation study in a meeting with the principal investigators (PIs) of this research group on 26.10.2018. A consortium consisting of participants from the OUH Department of Pharmacology, Department of Forensic Sciences at the Division of Laboratory Medicine and the Division of Mental Health and Addiction. External partners were Lovisenberg Deaconal Hospital where professor Anners Lerdal was PI for the whole project. A collaboration was also established with Oslo Municipality and The University of South-East Norway.

Through the project, baseline data was collected, and the new procedures were implemented. Information material and training sessions were held for clinical personnel. New laboratory methods were developed for the new procedures at the Department of Pharmacology. The baseline data collection started at OUS in 2021 and ended in 2022 at Lovisenberg and St Olavs Hospital with 2000 patients recruited from the medical departments. After implementation, data will be collected at all sites from 2022-2024.

The process has had extensive user involvement. Different user groups have been involved in designing the study and discussing the organizational and ethical considerations. Users, primarily those with experience related to problematic alcohol or drug use, contributed to the implementation study outline and to information brochures aimed at patients. User involvement is still ongoing with planning of seminars and interpretation and dissemination of results. User involvement in the planning phase also involved the Ministry of Health, the Health Directorate, the directors for the Oslo municipality districts, and directors of OUH and Lovisenberg Diaconal Hospital.

5. Sources to corroborate the impact

National alcohol strategy (2021–2025). A health-promoting and solidarity-based alcohol policy. Plan/strategy | Date: 11.03.2021	Nasjonal alkoholstrategi (regjeringen.no) The government continues the main lines of alcohol policy, and proposes several new measures to ensure that we reach the target of reducing harmful alcohol consumption. Three references and fact box based on our research.
Presentation in the Norwegian Medical Association Journal	Systematic screening of substance use upon hospitalisation | Tidsskrift for Den norske legeforening (tidsskriftet.no)

Description of the project at the research group web page	OUH - Alcohol and health (ous-research.no)
Alcohol use and health Information, recommendations and advice /Brochure	https://www.oslo-universitetssykehus.no/4a9eed/contentassets/7988f5c843cd42dfb8ab2d487f641a91/pasientbrosjyre-om-alkohol-leseversjon_a4_alcotail.pdf
Information about psychoactive medicinal drugs /Brochure	https://www.oslo-universitetssykehus.no/4a9f14/contentassets/7988f5c843cd42dfb8ab2d487f641a91/brosjyre-om-vanedannende-legemidler-a4-leseversjon_alcotail.pdf
AUDIT-C pocket cards for health personnel	https://www.oslo-universitetssykehus.no/4a9ef5/contentassets/7988f5c843cd42dfb8ab2d487f641a91/lommekort-om-alkohol_alcotail.pdf
Delirium tremens (alkoholdelir) – prevention and treatment/ Level 1 procedure at OUS	https://ehandboken.ous-hf.no/document/101625
Serumanalysis og psycaactive medicinal drugs / Level 1 procedure at OUS	https://ehandbok.ous-hf.no/document/140751
E-learning course for health personnel on psychoactive medicinal drugs	Kursbygger (ihelse.net)

[Oslo University Hospital and University of Oslo; Division of Laboratory Medicine; 2]

Institution: Oslo University Hospital and University of Oslo
Administrative unit: Division of Laboratory Medicine (KLM)
Title of case study: Research impacting savings in health expenditures
Period when the underpinning research was undertaken: 2013-2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2013-2022
Period when the impact occurred: 2020-2022 (and onwards)

1. Summary of the impact

There has been a steady increase in the cost of drugs in Norway, mainly driven by expensive biologics (antibodies). In Norway, the annual cost of antibodies for treating inflammatory diseases amounts to 1,5-2 billion NOK, while annual costs for antibody-based therapeutics for eye diseases amounts to >1.5-2 billion NOK only at OUS. Two innovations at KLM have enabled a significant cost-reduction for purchasing these types of drugs. The first innovation involved careful measurements of individual patient's biologic drug and anti-drug antibody levels that contributed to increased use of low-cost biosimilars. The second innovation involved the establishment and validation of a new pharmaceutical compounding procedure for antibody-based therapeutics that drastically reduced treatment-associated costs of eye diseases.

2. Underpinning research

Innovation related to biosimilars:

In-house assays for biologic drugs and anti-drug antibodies were developed and automated using existing laboratory infrastructure at the Dept of Medical Biochemistry at Oslo University Hospital from 2012. This was a collaboration between researchers at the Dept of Medical Biochemistry and leading clinicians in gastroenterology and rheumatology. These assays were rapidly integrated in clinical care in Norway, and became integral in two important cross-disciplinary research projects:

NOR-SWITCH, 2014-17 (ClinicalTrials.gov ID NCT02148640), where switching to biosimilar infliximab was shown to be non-inferior to continued treatment with originator infliximab. No differences were observed in clinical outcome, serum drug levels or anti-drug antibody levels, documenting the safety of switching. Following this study, patients could be switched to the lowest priced infliximab product, and drug companies were forced to compete for market access on pricing alone in the annual, national tender. This means that the cost of treatment (per patient) is reduced, and ultimately that more patients get access to effective treatment.

NOR-DRUM, 2017-22 (ClinicalTrials.gov ID NCT03074656) where individualised infliximab treatment based on serum drug and anti-drug antibody levels was shown to be superior to standard treatment. Individualised dosing based on serum levels of infliximab and anti-drug antibodies reduced the number of disease flares and infusion reactions, without increased drug use overall, compared with standard dosing. By individualising dosing, we can improve treatment effect and patient safety without increasing drug use and drug costs overall.

Innovation related to compounding:

The research was centred on establishing and validating a new pharmaceutical compounding procedure for antibody-based therapeutics used for treatment of eye diseases in close collaboration with the Department of Ophthalmology at OUS. The compounding procedure

improved patient safety and hospital logistics, while drastically reducing treatment-associated costs. Prior to the research, these therapeutics were administered by use of suboptimal syringes in a manner that led to significant waste of valuable therapeutics and increased risk of delivery-associated side effects for the patient. The relevant procedure is performed on >30,000 patients annually at Oslo University Hospital alone.

In-house compounding procedures of four different antibody-based therapeutics were established and tested in a variety of clinically relevant syringes. In parallel, assays for assessing the stability and reactivity of biologic drugs following the new pharmaceutical compounding procedure were established and performed to study whether compounding and storage in various syringes affected their overall functionality and stability. A total of four independent such stability studies were performed, each of which led to immediately implemented practices at Oslo University Hospital. In follow-up studies, clinical observations showed an improved safety profile of the relevant treatment in several patient groups. The performed work also triggered an industrial collaboration agreement in which a new syringe was developed to be tailored for intraocular injection.

Key researchers:
2013-2022: David J. Warren, researcher. Nils Bolstad, senior consultant
2016-2022: Rolf A. Klaasen, researcher. Johanna E. Gehin, resident/senior consultant.
2018-2022: Jan Terje Andersen, professor, FAR, OUS/UiO
2018-2022: Heidrun E. Lode, PhD student, FAR, OUS/UiO
2018-2022: Torleif T. Gjølberg, PhD student, FAR, OUS/UiO
2018-2022: Morten Carstens Moe, Professor II, Dept of ophtamology, OUS/UiO

3. References to the research

Jørgensen et al.: Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial. Lancet. 2017 Jun 10;389(10086):2304-2316.
PMID: 28502609 DOI: 10.1016/S0140-6736(17)30068-5

Syversen et al.: Effect of Therapeutic Drug Monitoring vs Standard Therapy During Maintenance Infliximab Therapy on Disease Control in Patients With Immune-Mediated Inflammatory Diseases: A Randomized Clinical Trial. JAMA. 2021 Dec 21;326(23):2375-2384.
PMID: 34932077 PMCID: PMC8693274 DOI: 10.1001/jama.2021.21316

Brun et al.: Risk factors for anti-drug antibody formation to infliximab: Secondary analyses of a randomised controlled trial. J Intern Med. 2022 Sep;292(3):477-491.
PMID: 35411981 PMCID: PMC9545769 DOI: 10.1111/joim.13495

Sand et al: Pharmaceutical compounding of aflibercept in prefilled syringes does not affect structural integrity, stability or VEGF and Fc binding properties (ref: https://www.nature.com/articles/s41598-018-20525-8)

Lode & Gjølberg et al: A new method for pharmaceutical compounding and storage of anti-VEGF biologics for intravitreal use in silicone oil-free prefilled plastic syringes (ref: https://www.nature.com/articles/s41598-019-54226-7)

Gjølberg & Lode et al: A silicone oil-free syringe tailored for intravitreal injection of biologics (ref: https://www.frontiersin.org/articles/10.3389/fopht.2022.882013/full)

4. Details of the impact

Innovation related to biosimilars:
The NOR-SWITCH trial was the first high quality, randomised controlled clinical trial to examine safety and efficacy of switching from originator to biosimilar infliximab. When the study was published in The Lancet in 2017, it was the first documentation that switching patients to biosimilar infliximab was safe. This had obvious impact on the view of biosimilars among patients, clinicians and regulatory agencies, but also on pharmacological companies developing or considering investing in biosimilars. Ultimately, it meant that costs could be reduced and more patients gain access to effective treatment. Before NOR-SWITCH, many stakeholders voiced concerns regarding immunogenicity, i.e. the likelihood the biosimilar would illicit an immune response in the patient after switching. This would result in production of anti-drug antibodies, lower drug levels, loss of effect and increased risk of adverse events. The data on drug levels and anti-drug antibodies in NOR-SWITCH showed similar pharmacokinetic and immunogenic properties, further confirming equivalence between originator and biosimilar infliximab.
Biosimilars to several biologics are currently in use in Norway, which creates a beneficial competition in the annual tenders. This is the main reason we can treat twice as many patients today compared to 2017, at the same cost. When biosimilars become available, prices tend to drop to a fraction compared to prices before biosimilars were available. Clinicians then have to switch their patients to the low-cost biosimilar. Patient samples taken before and after switching to biosimilars are often sent to our department. Documentation that drug levels are stable, and anti-drug antibodies remain undetectable, help reassure patients and clinicians that switching is safe. This contributes to loyalty to the recommendations in the tender, which again ensures continued competition in future tenders. The NOR-DRUM study was the first randomised controlled trial to show superiority of individualised therapy with infliximab based on serum drug and anti-drug antibody measurements compared to standard therapy. The study showed that individualised therapy can reduce risk of both disease flares and infusion reactions, without increasing drug use overall.

Innovation related to compounding:
Several eye diseases are driven by pathological neovascularization, and are treated by injection of antibody-based therapeutics directed against angiogenic factors directly into the eye. However, recommended injection practices are sub-optimal, and result in drug wastage and a chance of complications for the patient. Furthermore, all available therapeutics bind the same angiogenic molecule, and not all patients respond well to treatment. The established pharmaceutical compounding of the relevant therapeutics has been implemented in several hospitals, in Norway and internationally, where it increases patient safety while reducing both the time spent per patient and associated costs. For OUS, the procedure has led to an annual cost reduction of 60 million NOK. In addition, a silicon-free syringe for intra-ocular injections has been developed. This so-called Zero Residual™ Silicone Free 0.2 mL Syringe has unique features compared with other commercially available alternatives, and we have shown that it can be used for compounding and storage of anti-VEGF biologics for up to 30 days without affecting the structural integrity, binding, and transport properties of the biologics. The syringe has been developed together with the Dutch medical device company SJJ Solutions, has received CE under the new requirements of EU MDR, and is commercially available and implemented in several clinics.

5. Sources to corroborate the impact

https://blogg.forskning.no/forskningssykehuset/antistoffer-kan-redde-synet-ditt/1656419

https://pharma.dagensmedisin.no/industri-legemidler/unikt-samarbeid-om-ny-sproyte-for-oyeinjeksjoner/350248

https://www.dagensmedisin.no/forskning/ous-sparer-50-millioner-arlig-pa-billigere-oyebehandling/380604

https://pharma.dagensmedisin.no/industri-legemidler/norskutviklet-oyeinjeksjon-fikk-europeisk-ce-merking-veldig-goy/156018

https://www.inven2.com/sjj-solutions-signs-industry-development-agreement-with-inven2/?lang=en

https://sjjsolutions.com/resources/press-release-01122022-zr-sio-free-recieves-ce/

[Oslo University Hospital and University of Oslo, Division of Laboratory Medicine; 3]

Institution: Oslo University Hospital and University of Oslo
Administrative unit: Division of Laboratory Medicine (KLM)
Title of case study: Implementation of genomic medicine
Period when the underpinning research was undertaken: 2007-2023
Period when staff involved in the underpinning research were employed by the submitting institution: 2012-2023
Period when the impact occurred: 2013-2023

1. Summary of the impact

Implementation of novel genomics technologies, in particular next generation sequencing, into mainstream healthcare has improved precision diagnostics and precision medicine. KLM is a leading provider of such services nationally. Diagnostic genomic medicine is implemented for rare diseases and cancer, and has led knowledge building for genomic medicine in microbiology and pharmacology. Our offering to patients is comparable to the leading international centers. The early adoption and scaling of genomic precision diagnostics has been made possible by the national research infrastructure NorSeq at KLM surrounded by strong research environments.

2. Underpinning research

The impact of KLM on implementation of genomic medicine in Norway goes on four plans:

- Precision diagnostics of genetic disorders (AMG)

Department of Medical Genetics (AMG), KLM has been partner of the national, NFR funded, research infrastructure for DNA sequencing since its start in 2007 and has been leading the infrastructure (NorSeq) since 2015. It acquired the first Illumina (GAII) sequencer in Norway in 2008 and has since then been offering DNA sequencing to researchers in Norway and abroad, as well as conducting own research. Supported by other strong research groups in KLM focusing on genetic causes for disease, early research demonstrated clearly the potential for finding a genetic diagnosis where other diagnostic modalities failed. The listed publications illustrate that research has been essential for the impact from the start to this day. Ref 1 is an early example of the identification of the genetic cause of a rare syndrome using NGS as method. Ref 2 is one of several examples of the importance of technological research for improving diagnostics. Ref 3 is an example of ongoing research on long read sequencing and optical mapping as promising new tools for diagnostic purposes which most likely will be implemented in diagnostic routine in the foreseeable future. Increasingly, a precise genetic diagnosis leads to more precise treatment.

- Precision medicine in infectious diseases (MIK)

Traditional diagnostic methods depend on either searching for a specific microbe or a specific gene, antigen, or antibody (molecular methods and serology), or on the ability of the relevant microbe to grow ex vivo (culture). The diagnostics are good for known agents but often fall short when an infectious agent cannot be cultured, is unknown, or has changed. Metagenomic sequencing can identify and characterize "all" the microbes in a patient sample, and is expected to improve microbiological diagnostics in a number of cases where current methods fall short. The Department of Microbiology (MIK) has been leading the establishment diagnostic metagenomic medicine. Microbial whole-genome sequencing is now implemented in routine use for investigating outbreak cases, in 2022 particularly associated with national outbreaks of Pseudomonas aeruginosa and Serratia marcescens as well as local outbreaks, including with Klebsiella pneumoniae. Within virology, there are projects to use sequencing for the detection of resistance (HIV, CMV) and detection of various virus variants (SARS-CoV-2). In NorPreM (National Competence Network for

Personalized Medicine), MIK is leading the projects to develop a national database solution for sharing microbial whole-genome sequences for outbreaks involving multiple hospitals. The solution is intended to be linked to an upcoming national genome center.

- Precision diagnostics for cancer (PAT)

KLM has been responsible for building the national infrastructure for precision diagnostics (InPreD) to implement precision diagnostics for cancer patients who are candidates for experimental treatment. InPreD at OUS is coordinated by Dept. of pathology (PAT) and received strategic research funding from the South-Eastern Regional Health Authorities in 2019-2022 to implement advanced diagnostic procedures for cancer patients where experimental treatment is an option. InPreD OUS has developed and implemented a complete pipe-line for comprehensive gene panel testing (CGP, i.e. TSO500 from Illumina) including novel data analysis and clinical decision support structure. The knowledge is now transferred to InPreD nodes at four other university hospitals in Norway, with PAT at OUS responsible for standardisation and maintenance of protocols. InPreD has transdisciplinary collaborations involving clinical geneticists at AMG, research groups at Institute for Cancer Research, Sect. for experimental cancer treatment and the NorSeq Cancer node (Cancer Clinic, OUH). PAT is also responsible for the national, virtual molecular tumor board, arranged twice weekly. As of January 2024, a total 1430 cancer patients have been evaluated and 34% are referred for experimental treatment in clinical trials or compassionate us programs. Researchers in PAT have been key persons in the initiation of the largest precision medicine trial in Norway; IMPRESS-Norway (https://impress-norway.no/) with members both in the trial management group and steering group. IMPRESS-Norway, is a researcher-initiated intervention trial opened in 2021. It is coordinated by OUS, and PAT is responsible for diagnostics and biobanking as well as of several research programs (biomarker profiling, liquid biopsy and DNA methylation). The trial runs at all hospitals in Norway with cancer care units and depends on CGP analyses from InPreD. The trial has received major public funding as well as strong support from multiple pharmaceutical and diagnostic companies.

PAT researchers have performed the large retrospective testing and implementation of the multigene test Prosigna for the national clinical researcher-initiated intervention trial EMIT-EBC (2016-ongoing) and the international OPTIMA trial (2018-ongoing: https://optimabreaststudy.com/). Researchers from PAT are heavily involved in these trials (co-PI for EMIT-EBC, trial steering group and responsible for test performance, logistics and biobank (both Norway and Sweden for OPTIMA)). Based on the dedication PAT has had towards implementing next generation diagnostics through clinical trials, PAT was central in the application to the EUforHealth project PCM4EU (https://www.matrix-fkb.no/en/pcm4eu/home) which received funding in 2022 (PAT leads WP2, 2023-2024). PAT leads the national precision medicine network NorPreM built upon appointment from the Ministry of health to the regional health authorities, as well as several subprojects focusing on implementing precision diagnostics in the public health care.

- Pharmacogenomics/pharmacogenetics in genome medicine

The implementation of pharmacogenomics/pharmacogenetics pipelines in clinical applications has been carried out my AMG and Dep of Pharmacology through mechanisms for individual variability in drug response and personalized dosing in selected pharmacotherapies related to immunosuppression, chemotherapy, anti-infectives and statins.

Names of the key researchers and what positions they held at the administrative unit at the time of the research (where researchers joined or left the administrative unit during this time, these dates must also be stated). Any relevant key contextual information about this area of research.

Dag Undlien, professor, M.D., PhD. Head of AMG (2009-present) and NorSeq (2015-present)
Gregor Gilfillan, MSc, PhD, researcher and lab leader of AMG's NorSeq node (2010-present)
Eirik Frengen, MSc, PhD, professor (2007 - present) and leader of R&D section in AMG (2010-2018)
Vessela Kristensen, MSc, PhD, professor at AMG and leader of R&D section in AMG (2018 – present)
Doriana Misceo, MSc, PhD, researcher at AMG (2009 – present)
Elin Tønne, M.D., PhD, clinical geneticist at AMG (2011 – present), head of section for clinical genetics (2018-present)

Arvind Sundaram, MSc, PhD, bioinformatics researcher in NorSeq (2013-present)
Pål Marius Bjørnstad, MSc, PhD, bioinformatics researcher in NorSeq (2014-present)
Frode jansen, Frode Lars Jahnsen, professor, MD, PhD. - Avdeling for patologi
Fredrik Müller, professor, M.D., PhD. Head of MIK (2009-present)
Tone Tønjum, professor, MD, PhD. - Avdeling for mikrobiologi
Stein Bergan, group leader, Department of Pharmacology
Nils Tore Vethe, PhD, Head of section clinical pharmacology, Department of Pharmacology
Hege Russnes, professor, MD; PhD (2010), Head of Sect. for experimental pathology (2019-present), national coordinator of InPred (2019-present), head, NorPreM (2019-present).
Vigdis Nygård, PhD, molecular biologist, coordinating the molecular biologist team at InPreD (2019-present)
Tonje Lien, PhD, biostatstician, coordinating the bioinformatics and IT team at InPreD (2019-present)

3. References to the research

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2. Ribarska T, Bjørnstad PM, Sundaram AYM, Gilfillan GD. Optimization of enzymatic fragmentation is crucial to maximize genome coverage: a comparison of library preparation methods for Illumina sequencing. BMC Genomics. 2022 Feb 1;23(1):92. doi: 10.1186/s12864-022-08316-y. PMID: 35105301; PMCID: PMC8805253.

3. Bjørnstad PM, Aaløkken R, Åsheim J, Sundaram AYM, Felde CN, Østby GH, Dalland M, Sjursen W, Carrizosa C, Vigeland MD, Sorte HS, Sheng Y, Ariansen SL, Grindedal EM, Gilfillan GD. A 39 kb structural variant causing Lynch Syndrome detected by optical genome mapping and nanopore sequencing. Eur J Hum Genet. 2023 Nov 29. doi: 10.1038/s41431-023-01494-7. Epub ahead of print. PMID: 38030917.

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5. Helland Å, **Russnes HG**, et al. Improving public cancer care by implementing precision medicine in Norway: IMPRESS-Norway. J Transl Med. 2022 May 14;20(1):225. doi: 10.1186/s12967-022-03432-5. Erratum in: J Transl Med. 2022 Jul 15;20(1):317. PMID: 35568909; PMCID: PMC9107632. ***The outline of IMPRESS-Norway trial***

6. Taskén K, **Russnes HEG**, Aas E, Bjørge L, Blix ES; CONNECT Public–Private Partnership Consortium; Enerly E, Fagereng GL, Flobak Å, Gilje B, Gjertsen BT, Guren TK, Heix J, Hovig E, Hovland R; **InPreD-Norway and National Molecular Tumor Board Consortium**; **IMPRESS-Norway Consortium**; Lønning PE, Meza-Zepeda LA, Mæhle PM, Nilsen HL, Thoresen SØ, Widerberg K, Smeland S, Helland Å. A national precision cancer medicine implementation initiative for Norway. Nat Med. 2022 May;28(5):885-887. doi: 10.1038/s41591-022-01777-4. PMID: 35513529. ***Describing the Norwegian Ecosystem for Precision Medicine including InPreD and IMPRESS***

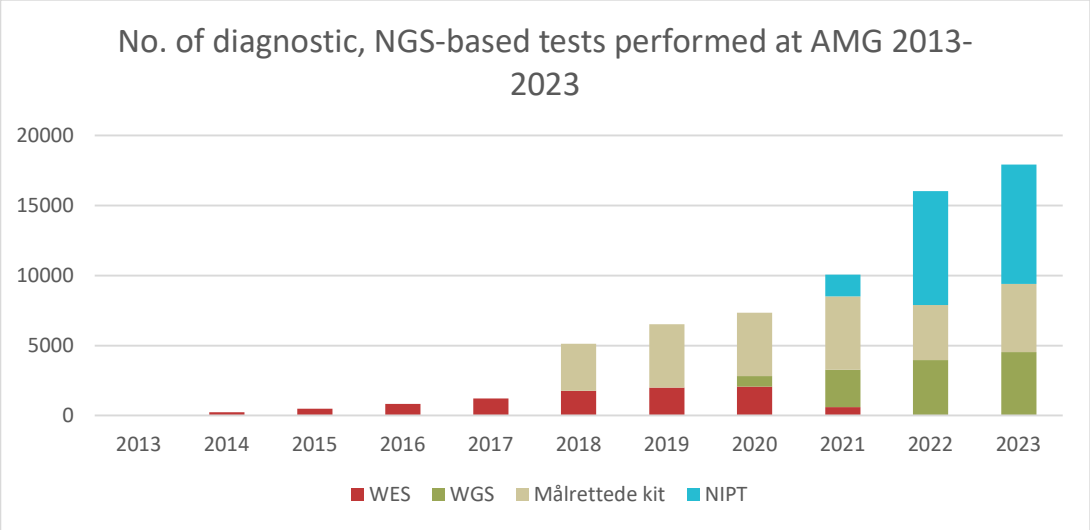
4. Details of the impact

This section should provide a narrative, with supporting evidence, to explain:

- How the research underpinned (made a distinct and material contribution to) the impact;
- The nature and extent of the impact.

Implementation of genomic diagnostics for rare genetic disorders (AMG). After an initial start of diagnostic exome sequencing in 2013, it quickly became apparent that scalability, in particular for downstream bioinformatics analysis was a big challenge. To address this, AMG started recruiting personell with bioinformatics and informatics background. These positions were initially funded by several innovation grants from Research Council Norway. Key products from these innovation grants was the automation of a variant calling pipeline and the development of an in house software for genetic variant interpretation (ELLA; https://allel.es). ELLA was put into diagnostic production in 2017 and has also been implemented at Department of Medical Genetics at St. Olav hospital in Trondheim, and is currently under evaluation for implementation in the other medical genetics departments in Norway.

Taken together the research in genomics has greatly facilitated the implementation of genomic diagnostics for rare genetic disorders. The table below shows the number of patients receiving NGS based diagnostic testing since the start in 2013:



WES=whole exome sequencing, WGS=whole genome sequencing, målrettede kit=targeted capture kits, NIPT=non-invasive prenatal testing.

The development illustrates the initial challenges with scalability which has been solved through research and innovation activities in KLM. The numbers should be viewed in the context of the population that OUS-KLM caters to. We have the responsibility for providing services to 3 million inhabitants in Norway and the fact that we now offer WGS to more than 4000 patients with rare disease/year documents that our coverage of WGS testing/capita is on par with or higher than other countries generally considered to be internationally leading, such as UK.

Precision microbiology (MIK)

MIK has been heavily involved in the development of two important software tools used in pipelines to analyse the microbiome of the human gut or other environments to determine the composition of microbial species present, primarily by amplicon sequencing (e.g. 16S rRNA). In collaboration with leading international groups, the open-source software tools Swarm and VSEARCH (4) have been developed, published, and made freely available to the world-wide metagenomics community. The software has saved time and costs, as well as improved accuracy, for numerous users, both in clinical and biological research, evident by more than 8000 citations since 2014. VSEARCH is an essential component in QIIME, one of the most widely utilized pipelines.

Precision cancer medicine (PAT)

The transcdisciplinary effort to strengthen research and implementation started in 2019 with three main goals: (1) to establish equal access to advanced molecular diagnostics, enabling stratification

for clinical trials; (2) to increase the volume of precision cancer medicine trials and initiate a large national precision cancer medicine trial; and (3) to work on mechanisms to implement precision cancer medicine within standard-of-care. The establishment and development of InPreD OUS (increased from 4 employees in 2019 to 17 in 2022) and IMPRESS-Norway have been key points towards these goals (5,6). Researchers in PAT have now gained key roles in the national research centre for clinical cancer research, MATRIX as well as in the EU4Health project PCM4EU. InPreD gets frequent research assignments such as establishing evaluating the methodology and cost/benefit for whole genome sequencing of paediatric cancer patients (2022-2025) and evaluating needs for implementing multimodal diagnostics (including drug sensitivity screening methods, 2024-2026). The InPreD work in 2019-2020 resulted in acceptance for GCP testing as part of public health care and was reimbursement from 2021. Based on parts of the EMIT-EBC study, the Prosigna test was implemented into routine diagnostics in 2019 (with reimbursement).

5. Sources to corroborate the impact

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5. https://oslocancercluster.no/tag/inpred/
6. https://www.regjeringen.no/no/dokumenter/strategi-for-persontilpasset-medisin/id2959463/?ch=8
7. https://www.kreftregisteret.no/Generelt/Nyheter/2022/internasjonal-oppmerksomhet-for-satsning-pa-presisjonsmedisin/
8. https://translational-medicine.biomedcentral.com/articles/10.1186/s12967-022-03432-5
9. https://bigmed.no/assets/bigmed_reflections-on-the_2021_v1.0.pdf
10. https://businessnorway.com/articles/norways-precision-medicine-takes-aim-at-cancer

[Oslo University Hospital and University of Oslo; Division of Laboratory Medicine; 4]

Institution: Oslo University Hospital and University of Oslo
Administrative unit: Division of Laboratory Medicine (KLM)
Title of case study: Fostering biotech excellence, a Case showcasing KLM's innovations and startups
Period when the underpinning research was undertaken: 2012-2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2000-2022
Period when the impact occurred: 2012-2022

1. Summary of the impact

This Case exemplifies innovation at KLM by presenting one chosen example (from numerous others): Innovations and three startup companies in the Biotech sector that arose from the RCN CoE Centre for Immune Regulation (CIR). The first, Vaccibody (now Nykode) was based on targeted vaccines against cancer and infectious disease, was established in 2007, currently has 200 employees, is listed on the Oslo Stock Exchange and has extensive list of trials and industrial collaborations. Nextera was based on a novel phage display technology applied in target discovery and TCR and antibody drug development in oncology and autoimmunity. Authera was based upon breakthrough understandings of complex FcRn biology and its ligands, IgG antibodeis and albumin, and collaborates with a range of global biotech and pharma companies. All three companies have expanding activities, value and impact and exemplify an emergent biotek sector in Norway.

2. Underpinning research

The following text covers academic research driven innovations that underpin the establishment of these three companies. The research driven innovations were conducted by KLM staff: Bjarne Bogen, Agnethe Fredriksen, Piere Ruffini, Inger Sandlie, Geir Åge Løseth, Jan Terje Andersen and some of their colleagues. Fredriksen and Løseth became CSOs in Vaccibody and Nextera, Bogen was head of Vaccibody's scientific panel (2007-2022). ● The driven innovation relating to Vaccibody included 10 PhDs and >50 research papers, encompassing a diverse collection of publications on vaccines for cancer and infectious disease. The technology was based upon targeted delivery of vaccine antigen for strong B (antibody) and T cell responses. The first successful experiments were done by Bogen's PhD candidate Agnete Fredriksen in 2006, Fredriksen later became CSO of Vaccibody. Vacccibody vaccines are delivered as DNA encoding proteins, thus avoiding costly and inefficient protein production (Tjelle et al., 2004; A.B. Fredriksen, Sandlie, & Bogen, 2006). Preclinical cancer work was performed for multiple myeloma (5 papers, 2006-20), influenza (8 papers, 2013-22), HIV (2014) and malaria (2021). A variety of targeting specificities and formats have been developed (focus in 9 papers) in addition to diverse antigenic cargoes (10 papers), suggesting most protein antigens can be successfully expressed after Vaccibody vaccines. Further research has demonstrated the ability to influence type of vaccine immune response such as preferential cell-killing, and anti-cancer responses, or antibody subtypes (5 papers 2013-15). Further developments of vaccine designs are ongoing resulting in high impact publications. ● The research basis of Authera derives from an in-depth molecular and cellular understanding of complex FcRn biology related to how the receptor is engaging its two ligands, albumin and IgG. FcRn is a cellular receptor that regulates the pharmacokinetics and biodistribution of its two ligands. As antibodies are the fastest growing class of therapeutics and albumin increasingly explored as a carrier of a range of modalities, FcRn biology is extremely important or consider during development of the next generation of tailored antibody- and albumin- based therapeutics. Molecular mapping of how FcRn binds its two ligands combined with development of state-of the-art in vivo mouse model systems have resulted in a unique toolbox that is attractive for the biotech sector (34 papers, 2006-2020). This included seminal discoveries of binding and transport properties of the ligands and designed versions (Andersen, J. T. et al. Nat Comm 2012, 2020), of IgG and albumin homeostasis (Journal of Controlled Release, 2015), opportunities for design of albumin-based therapeutics (2015), extending serum half-life of albumin by engineering FcRn binding (Journal of Biological Chemistry, 2014), and development of a versatile biomedical technology

platform for design of long-acting protein-based therapeutics. This included an engineered human albumin variant with enhanced half-life and ability to deliver cargo over the intestinal mucosa (Sci Transl Med. 2020).

3. References to the research

1. Ruffini, P. A. *et al.* Targeted DNA vaccines eliciting crossreactive anti-idiotypic antibody responses against human B cell malignancies in mice. *J Transl Med* **12**, 207 (2014). https://doi.org:10.1186/1479-5876-12-207
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3. Anderson, A. M., Baranowska-Hustad, M., Braathen, R., Grodeland, G. & Bogen, B. Simultaneous Targeting of Multiple Hemagglutinins to APCs for Induction of Broad Immunity against Influenza. *J Immunol* **200**, 2057-2066 (2018).https://doi.org:10.4049/jimmunol.1701088
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5. Andersen, J. T. *et al.* Structure-based mutagenesis reveals the albumin-binding site of the neonatal Fc receptor. *Nature Communications* **3**, 610 (2012). https://doi.org:10.1038/ncomms1607
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4. Details of the impact

The following provides impact of the three companies: The research enabled the Vaccibody startup, milestones in 2012-22: 30/07/2012 Vaccibody raises 875 000 € in new share issues including from The Norwegian Radium Hospital Research Foundation. 23/11/2012 Vaccibody received 2 million € grant from the Norwegian Research Council. 21/6/2013. Vaccibody raised 733.000 € from existing owners for development of VB10.16, a therapeutic vaccine against cervical cancer. 24/04/2014 The Norwegian Cancer Society invests 500 000 € in Vaccibody with a focus on developing novel cancer therapies. 23/2/2015 Vaccibody announces filing of a clinical trial application to initiate the first in man clinical study of its lead drug candidate VB10.16 in women with high grade cervical intraepithelial neoplasia (CIN 2/3) at 4 centers in Germany. 04/06/2015 Vaccibody AS announces participation in a research project on veterinary vaccines receiving NOK 78 million from the EU Horizon 2020 program. 14/9/2015 Vaccination of the first patient in its multicentre trial VB C-01 – an exploratory, open-label, multicenter phase I/IIa study VB10.16 immunotherapy for the treatment of high grade Cervical Intraepithelial Neoplasia (CIN 2/3) caused by human papillomavirus 16 (HPV 16). 25/8/2016. Vaccibody announces positive results from the phase I part of the clinical trial VB C-01 in patients with high-grade cervical dysplasia and recommendation by the cohort review committee as well as the independent data monitoring board to continue to the expansion phase (IIa). 08/1/2018 Pre-clinical data support elicitation of strong killer T cell responses (CD8+ T cells) towards cancer neoantigens. 26/09/2018 Positive results from the 6-months Interim analysis of the phase IIa clinical study in high grade cervical dysplasia provides Proof-of-Concept for Vaccibody's immunotherapy platform. 14/02/2019 Vaccibody AS – NOK 230 million (eur 23.6 million) private placement successfully placed. 26/06/2019 Vaccibody announces strong neoantigen-specific t cell responses induced in cancer patients with low mutational burden after vb10.neo vaccination 05/11/2019 Vaccibody announces initial positive clinical responses in patients with locally advanced or metastatic cancer treated with vb10.neo neoantigen cancer vaccine. 01/10/2020 Vaccibody enters into worldwide license and collaboration agreement with Genentech, a member of the Roche Group, to develop individualized neoantigen cancer vaccines. 06/11/2020 Vaccibody announces the closing of the worldwide license and collaboration agreement with Genentech. 12/07/2021. Vaccibody enters into worldwide license agreement with Adaptive Biotechnologies for clinically validated SARS-CoV-2 T cell epitopes to combine in a second-generation T cell vaccine candidate to specifically address emerging SARS-CoV-2 variants of concern. 23/11/2021 Nykode Therapeutics (formerly Vaccibody) enters into multi-target license and collaboration agreement with Regeneron. 15/12/2021 New chairman at Nykode Therapeutics as the Company enters a new stage of internationalization. 09/05/2022 Nykode Therapeutics announces positive interim results from its Phase 2 trial with VB10.16 in combination with immune checkpoint inhibitor atezolizumab in advanced cervical cancer. 26/10/2022 Nykode Therapeutics Announces Presentation of Positive Immunogenicity Results from Phase 1/2a Study of VB10.NEO, an Individualized Therapeutic Cancer Vaccine, at the Neoantigen-Based Therapies Summit. 07/11/2022 Nykode Therapeutics

presents additional efficacy analysis in Phase 2 study of VB10.16 in combination with atezolizumab in advanced cervical cancer. ● Nextera: Løset and Sandlie highlight next generation phage display by use of pVII and pIX as display scaffolds (2012) and Phage display engineered T cell receptors as tools for the study of tumor peptide-MHC Interactions (2015). Løset et al present improved Multivalent pIX phage display for improved antibody properties (2016) and use such technology to define gluten peptide MHC-expressing cells in inflamed intestinal tissues from patients with celiac disease (2019) and in immune cell collaboration (2019). 8/1/2020 The proprietary NextCore platform is protected by 8 world-wide patent families, and parts of its development have received commercialization grants through NRC and IN. Parts of the target discovery module was co-developed with Janssen Biotech Inc. (2015 – 2018: BioCentury 2015 (52/41:19). In 2022, Nextera AS entered into a strategic collaboration with Zelluna Immunotherapy AS on development of optimized TCRs for redirected cancer immunotherapy into their proprietary NK cell based platform.
● Authera is a pre-clinical-stage biotechnology company dedicated to the discovery and development of novel therapeutic biologics. The company's knowledge is based on the understanding of crucial biological processes involving FcRn combined with a high-end and sophisticated technology platform. This platform can educate and fine-tune molecular designs to secure their optimal FcRn mediated cellular transport behavior, which translates into favorable in vivo pharmacokinetic parameters in state-of-the-art mouse models. Authera is a spinout from the Laboratory of Adaptive Immunity and Homeostasis headed by Jan Terje Andersen, and the co-founders are professor emerita Inger Sandlie, and two previous PhD students from the lab; CEO Simone Mester and CSO Torleif Tollefsrud Gjølberg. Authera has initiated about 10 collaborations with international companies, and has two lead preclinical development programs, with undisclosed targets and indications. One of the programs is running in partnership with argenx - a global immunology-focused company. The company has received soft funding from the Research Council of Norway, TEKNA and Innovation Norway.

5. Sources to corroborate the impact

1. Fossum E, Grødeland G, Terhorst D, Tveita AA, Vikse E, Mjaaland S, et al. Vaccine molecules targeting Xcr1 on cross-presenting DCs induce protective CD8+ T-cell responses against influenza virus. European journal of immunology. 2015;45(2):624-35.
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5. Løset GÅ, Sandlie I. Next generation phage display by use of pVII and pIX as display scaffolds. Methods. 2012;58(1):40-6.
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8. Pyzik M, Sand KM, Hubbard JJ, Andersen JT, Sandlie I, Blumberg RS. The neonatal Fc receptor (FcRn): a misnomer? Frontiers in immunology. 2019;10:1540.
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10. Bern M, Sand KMK, Nilsen J, Sandlie I, Andersen JT. The role of albumin receptors in regulation of albumin homeostasis: Implications for drug delivery. Journal of Controlled Release. 2015;211:144-62.

[Oslo University Hospital and University of Oslo, Division of Laboratory Medicine; 5]

Institution: Oslo University Hospital and University of Oslo
Administrative unit: Division of Laboratory Medicine
Title of case study: Pandemic preparedness @KLM
Period when the underpinning research was undertaken: 2012-2019
Period when staff involved in the underpinning research were employed by the submitting institution: 2000->
Period when the impact occurred: 2020-2023

1. Summary of the impact

KLM contributed to the very successful pandemic response in Norway: KLM was the main national provider of PCR-based Covid testing and SARS-CoV-2 whole genome sequencing. Sufficient test capacity was a crucial of the pandemic management strategy (TISK strategy) and the *in-house* capacity to run up to 15.000 covid tests per day gave direct savings of 300 million NOK compared to commercial tests. The 80.000 covid genome sequences was instrumental for variant surveillance. KLM contributed to monitoring of SARS-CoV-2 vaccine efficacy and, through clinical trials, provided data that informed the national vaccination strategy, and established prospect research biobank with broad consent to facilitate research at the institutions and collaborators.

2. Underpinning research

The strategy chosen by the government to limit spread of the SARS-CoV-2 virus in the society relied on high test capacity. The rapid implementation of high throughput protocols was possible by the strong research environments in KLM researchers (with Profs. Fredrik Müller, Dag Undlien researcher Magnar Bjørås as central drivers) were actively involved in capacity building, technology implementation, and operations during the pandemic.

The Department of Microbiology (MIK) established *in-house* PCR test to detect SARS-CoV-2 in February 2020. In April 2020, MIK was asked to establish a facility for screening large numbers of samples (up to 15.000 tests/day). The production of magnetic beads and extraction reagents by The Norwegian University of Science and Technology was crucial. MIK validated PCR methods, optimized extraction with "NTNU beads" on new robots and validated variant PCR. In March and April 2020, Arne Sørås (MIK) included 150.000 participants in a prospective cohort study to obtain research data about the spread of the SARS-CoV-2 virus and the effects of the disease (www.koronastudien.no).

Department of Medical Genetics (AMG) in collaboration with The Norwegian Institute for Public Health (NIPH) and MIK carried out large-scale whole genome sequencing of SARS-CoV-2 samples for variant characterization. The investments in genomic research and technology AMG (www.norseq.org), the national research infrastructure for DNA sequencing, was essential for the establishment of a high throughput covid sequencing protocol including bioinformatics pipeline. The method was implemented in just two weeks´ time upon request from the national pandemic laboratory at NIPH which had run out of capacity. To prepare for future pandemics, KLM has established a multidisciplinary integrated environment (MIK, AMG, and Department of Pathology (PAT)) to detect and characterize microbes with pandemic potential for future outbreaks, including novel pathogens.

Researchers at the Department of Immunology (IMM) holds extensive competence on vaccine development. In the summer of 2021, IMM started a trial, the Coallision for Epigenic Preparedness

Innovations (CEPI) -trial, to monitor SARS-CoV-2 vaccine efficacy where the study design was population-based and included 6000 immunocompromised patients in addition to 10 000 controls. The trial had an observational study module of the standard vaccination program in immunocompromised patients (and controls) and an interventional study module where nonresponding immunocompromised patients were revaccinated. Initial data from the observational module and the interventional module (about 500 patients) indicated that standard vaccination was quite insufficient for this population, results were presented for the National Corona Vaccination Program, Norwegian Institute of Public Health (NIPH) 24th August 2021. Results were discussed between NIPH, the Dept of Health and the Government and resulted in a revised recommendation on the 30th August 2021 – all immunosuppressed were to receive a third dose (vaccination was implemented from 10th Sept 2021). Results presented to NIPH/Dept of Health resulted in a new revised recommendation of 4th dose for all patients in November 2021. At present there are 87 Projects and 19 multi-centre studies related to COVID-19 and SARS CoV-2 infection with the participation of Oslo University Hospital.

3. References to the research

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4. Details of the impact

At the very start of the COVID-19 pandemic, researchers at the Department of Microbiology (MIK) established their own PCR test to detect SARS-CoV-2, which was ready for use in February 2020[1].

There was limited access to reagents and plastics for extraction early on, and the Section for research at MIK was asked for suggestions for alternative protocols if other types of reagents had to be used. In April 2020, MIK was tasked to establish a facility for screening up to 15.000 samples/day. The production of magnetic beads and extraction reagents by NTNU combined with the ability to develop "in house" PCR tests was absolutely crucial for achieving this in and also saved the laboratory approx. 300 million NOK throughout the pandemic compared to a commercial high-volume SARS-CoV-2 test. MIK validated *in-house* PCR methods, optimized extraction with "NTNU beads" on new robots, and validated variant PCR[2]. Relocation of competent personnel from both the diagnostic- and research sections in MIK contributed to analyzing the large number of samples. Researchers at the Department of Immunology and Transfusion Medicine (IMM) developed a serological test with high capacity based on antigen-labelled beads and flow cytometry for use in research projects. The early project sample collections were consolidated into a prospective research biobank with broad consent: https://www.ous-research.no/covidbiobank.

NorSeq-Oslo (AMG) has the largest sequencing capacity in Norway and by serving researchers with sequencing services in more than 400 projects annually they have built up an impressive technology competence. In February 2021, NorSeq-Oslo received a request for helping National Institute of Public Health with covid sequencing as they did not have capacity to cover the increasing need for surveillance of covid evolution. NorSeq established a novel and improved high throughput sequencing protocol in two weeks´ time. In addition to increasing capacity for covid sequencing in Norway, the new protocol turned out to be important as NIPH existing protocol missed detection of the omicron variant whereas the method established at KLM detected it. The methods established at NorSeq-Oslo were quickly disseminated to the other NorSeq nodes (Bergen, Trondheim, Tromsø) thereby increasing capacity in all health regions in Norway. As illustrated by some of the listed references in point 2, information of covid evolution has been used as to establish policies for preventing covid transmission and therefore helped all in the Norwegian society by limiting risk for covid infection. NorSeq-Oslo's covid sequencing effort ended in March 2023 when the need for covid sequencing had subsided. During the covid pandemic NorSeq has helped the Norwegian Institute of Public Health (FHI) to substantially increase the capacity in Norway for whole genome sequencing of SARS-COV2 for the surveillance of virus variants. This also shows the strength of pulling together at a national scale, and it shows the implications of having strong national infrastructures supported by the Research Council of Norway.

KLM made significant contributions to knowledge about COVID-19, both in terms of understanding mechanisms of disease, treatment, and complications: The Norwegian Corona Cohort study provided the Norwegian government officials with very early high-quality data on spread of SARS-cov-2 virus, data on risk factors for severe disease and about long-covid. Study staff also participated in the WHO Delphi consensus process on long-covid and initiated a large-scale intervention study in late 2020 where 35.000 participants were randomized to vitamin D or placebo. KLM was central in The Nor-Solidarity multicentre treatment trial on the efficacy of different anti-viral drugs in SARS-COV-2 infected patients.

Results from the CEPI project continued to deliver high quality data on vaccine efficacy throughout the pandemic and beyond. In 2023, vaccination of sub-cohorts of organ transplanted patients had progressed past 7th dose. Within the startup of the CEPI project Norway discontinued vaccination with AstraZeneca vaccine due to vaccine induced SAE, VITT ChAdOx1 vaccine can result in thrombotic cascade, VITT in healthy individuals(Schultz, Sørvoll et al. 2021), this was mechanistically followed up within the CEPI trial (Holm, Kared et al. 2021). As to mRNA vaccines, we found no increased SAE rate compared to normal. No increased rate with successive vaccinations (König, Torgauten et al. 2022, Syversen, Jyssum et al. 2022, Syversen, Jyssum et al. 2022, König, Lorentzen Å et al. 2023). Venous thrombosis after mRNA vaccination is not associated with anti-PF4

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5. Sources to corroborate the impact

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1. Summary of the impact (indicative maximum 100 words)

Diagnostic radiology faces significant challenges due to a steady increase in referral rates, the volume of data generated per patient combined with a lack of radiologists, leading to long waiting lists and potentially delayed and suboptimal disease management. In response to these challenges and observing the rapid progress of AI in radiology, our division, in 2019, established a **new centre for computational radiology and artificial intelligence (CRAI)**. During the four years since its inception, CRAI has built essential IT infrastructure for AI research and initiated a range of AI-related research projects with the aim of providing AI-driven radiology support, providing in-house AI expertise and addressing new research questions by innovative use of AI in medical diagnostics.

2. Underpinning research (indicative maximum 500 words)

CRAI was established to become a division-wide research hub for AI related imaging research and to evaluated clinically approved AI solutions for radiology. CRAI is led by Prof Atle Bjørnerud and the centre is part of the department of physics and computational radiology (FBA), led by Kyrre E Emblem. Setting up CRAI, the first challenge was a lack of necessary IT infrastructure at OUS for effective AI research. We therefore had to invest significant resources into establishing the infrastructure needed for a large-scale AI lab. To this end, we have established an in-house GPU server park with necessary IT infrastructure for modern machine learning development, model training and big data management. We have developed a unique platform named NeoMedSys (neomedsys.io) which enables radiologists, clinicians and researchers' direct access to in-house developed AI models for use in research and for testing on clinical data. The platform also enables clinical researchers to train models on their own data using an automated training procedure for image segmentation. The NeoMedSys platform ensures traceability of model performance and the ability of end-user to provide feedback regarding model performance to iteratively make models better over time. The platform is integrated into the hospital infrastructure so that the users can access all functionality directly via a web interface on their own workstation. Legal and regulatory aspects of using clinical data for in-house AI model development and testing have been thoroughly addressed. We initiated an early dialog with the Directory of Health (Helsedirektoratet) and applied for exemption from confidentiality ('helseprsonelloven §29') for using clinical imaging data to train in-house machine learning models. The application was approved in 2023, allowing us to test in-house machine learning models on clinical data via the NeoMedSys platform without having to obtain informed consent from the patients. This puts us in a unique position to develop and validate state-of-the-art AI models.

In terms of AI research projects, CRAI has focused on the following areas:

1) AI based detection and characterization of brain bleeds (ICH) from CT. This research started in 2021 and is headed by senior scientist at CRAI (and Univ of Toronto), Prof. Brad MacIntosh. This is a multi-centre, multi-national initiative and the research group includes neuroscientists, software engineers, neruoradiologists, neurosurgeons and neurologists.
2) AI based detection, characterization, and progression prediction of brain tumors from MRI. This project is a continuation of our department's efforts into brain tumour research over the last 15 years. Led by head of department Kyrre E Emblem OUS) and senior scientist Elies Fuster-Garcia (OUS and Universitat Politècnica de València), we have successfully established state-of-the-art AI models, both for detection and disease progression predictions in brain tumor patients. The project makes use of the CRAI infrastructure to test the models on clinical radiological data.

3) AI based prediction of Alzheimer's disease onset and progression. In close collaboration with the LCBC group at the University of Oslo (https://www.oslobrains.no/) the project is led by Professor Anders Fjell at LCBC and Prof Atle Bjørnerud at CRAI. The project started in 2022, building on many years of Alzheimer's research by LCBC and CRAI associated researchers. The project aims at predicting early onset of Alzheimer's disease based only on MR images. By having access to very large datasets, both externally and internally for validation we have obtained very encouraging results, which will be published in 2024.

See crai.no for more information.

3. References to the research (indicative maximum of six references)

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4. Details of the impact (indicative maximum 750 words)

Here, we summarize the impact of the four major activities at CRAI: 1) development of the NeoMedSys AI production and deployment platform 2) AI methods for brain bleed detection and characterization 3) AI methods for brain tumor characterization and progression predictions and 4) AI methods for early detection of Alzheimer's disease onset and progression.

1) The NeoMedSys platform (neomedsys.io). This platform has enabled efficient production of domain expert annotations of medical image data for deep learning model training. The platform also enables easy deployment of AI models developed by in-house research projects so that they can be readily tested on clinical data from the hospital-wide medical image archive system (PACS). Currently, AI based research rarely reach clinical prospective testing

due to lack of methods to integrate the models into the clinical workflow. Having obtained approval from the Directory of Health (Helsedirektoratet, ref 23/18192-9) to train and test our AI models on clinical data through the NeoMedSys platform we are now able to bring all our AI models into prospective evaluation on clinical radiological data. The platform also enables interactive feedback from end-users regarding model performance so that the models can be made recursively better. The end impact of this activity is to provide the hospital with validated and continuously improving AI based radiology tools.

2) AI methods for cerebrovascular infarcts, bleed detection and characterization. Our research activity relating to brain infarcts focuses on using AI to determine ischemic stroke volume, predict outcome and time of stroke onset from MRI. Further, to develop models for brain bleed detection (intracerebral haemorrhage, ICH) from CT images. We aim to extract additional information about ventricular volume and midline shift to provide better predictions of patient prognosis and optimal treatment. We have developed AI models for ICH segmentation that perform on par with state-of-the-art in international competitions (MICCAI 2022). The vascular stroke project is strengthened by close collaboration with ongoing stroke projects both locally at OUS (The Oslo Acute Revascularization Stroke Study, OSCAR: ous-research.no/home/aamodt/Research+projects/22500) and nationally (Norwegian Cognitive Impairment After Stroke,Nor-COAST: ntnu.no/inb/nor-coast), securing access to high quality imaging data for model training and testing. The ICH project is a multi-centre international collaboration securing access to large, curated datasets for model development and testing. The projects are supported by grants from the South-Eastern Health Authority (HSØ Innovation grant 23/00672-13, HSØ research grant 2022054) and by Eureka Eurostar grant in collaboration with industrial partner Cerebriu (Copenhagen).
3) AI methods for brain tumour characterization and progression predictions. We have developed highly accurate methods for segmentation of brain metastases and post- operative residual tumour in glioblastoma patients. In collaboration with researchers in Valencia, Spain we have a large ongoing project with the aim of earlier detection of tumour progression and prediction of future progression using advanced AI methods. Further, we have access to one of the largest databases of glioblastoma patients in Europe (the BrainPower database), comprising longitudinal MRI data from about 1200 glioblastoma patients collected over the last 10 years. Here, we train AI models for accurate detection of postoperative residual tumour, and important predictor of outcome. AI models combining preoperative and postoperative tumour detection enables large scale investigation into tumour characteristics that better predict treatment response and outcomes. The project is supported by grants from HSØ (projects no 2021057 and 2021031) and the Research Council of Norway (NFR FRIPRO project no 325971).
4) AI methods for early detection of Alzheimer's disease (AD) onset and progression. This is a project run in close collaboration with the LCBC group at the department of psychology and University of Oslo. The aim is to develop predictive AI models for early detection and progression of based only on magnetic resonance images (MRI). We have trained models on very large open datasets (UK Biobank and ADNI) and are currently starting testing on MRI data from ongoing national dementia study (DDI prosjektbanken.forskningsradet.no/en/project/FORISS/217780). The project is supported by grant from HSØ (project no: 2021079)

5. Sources to corroborate the impact (indicative maximum of ten references)

1. Anne Hege Aamodt, MD PhD. Senior Consultant and Senior Researcher at the Department of Neurology, Oslo University Hospital, Rikshospitalet, Oslo, Chair of the Headache and Stroke Research group at Oslo University Hospital.
2. Per Selnes, MD PhD. Head, Clinical Neuroscience Group at University of Oslo, Akershus University Hospital.
3. Johan Wasselius. Interventional radiologist and associate professor at Skåne University Hospital, Lund, Sweden.
4. Akshay Pai. CTO at Cerebriu (cerebriu.com)
5. Elin Melby. Technology Strategy Manager, Inven2, Oslo, Norway
6. Prof Hege G. Russnes. Head of NorPrem Norway (norprem.no)
7. Prof Einar Vik-Mo. Dept of Neurosugery. OUS

A compilation of the 5 most important Impact Cases

Oslo University Hospital – Clinic of Medicine

Oslo University Hospital- Clinic of Medicine – Case number 1

Institution: Oslo University Hospital (OUH)
Administrative unit: Division of Medicine (MED)
Title of case study: *StressProffen* – Stress-management in Cancer
Period when the underpinning research was undertaken: 2015-2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2015-2022
Period when the impact occurred: 2019-ongoing

1. **Summary of the impact** (indicative maximum 100 words)
This section should briefly state what specific impact is being described in the case study.

The evidence-informed, user-centered digital stress-management intervention *StressProffen©™* has through a randomized controlled trial (RCT) been shown to be effective for cancer survivors in terms of reduced stress, depression, anxiety and self-regulatory fatigue, as well as improved health-related quality of life (HRQoL). Given this significant impact for cancer survivors, the *StressProffen* application (app) has been made available for individual download through the company dHealth AS, and is also offered to cancer survivors through cancer coordinators in Norwegian municipalities. *StressProffen©™* is available in Norwegian and English, and is also being offered through studies for health care providers, students and additional cancer survivors.

2. **Underpinning research** (indicative maximum 500 words)
This section should outline the key research insights or findings that underpinned the impact, and provide details of what research was undertaken, when, and by whom.

This research project aimed to design, develop, feasibility pilot and efficacy test a digital health intervention to support stress-management for cancer survivors. The project was led by Principal Investigator Lise Solberg Nes (PI) at the Department of Digital Health Research (DIG) in the Division of Medicine (MED) at Oslo University Hospital (OUH) and funded by OUH and the Norwegian Cancer Society (Project # 4602492). The design and development (2015-2016) was evidence-informed and user-centered, with significant user/stakeholder (i.e., cancer survivors and health care providers) involvement throughout. Content development was led by the PI, a clinical health psychologist having extensive international clinical experience working with stress-management for cancer survivors. The final digital intervention, an app called *StressProffen* (i.e., inspired from Stress Professor/Professional) contains 10 modules related to cognitive-behavioral based (CBT) stress-management for cancer survivors, with a combination of CBT-based psychoeducational material and related exercises (e.g., diaphragmatic breathing, progressive muscle relaxation, mindfulness, visualization).

In line with the Medical Research Council framework for complex intervention evaluation (Skivington et al., 2021), *StressProffen* was subsequently tested in a feasibility pilot (2017) to evaluate use, user friendliness, usability and preliminary efficacy prior to efficacy testing in an RCT. The *StressProffen* intervention was delivered in a simple blended care model with one in-person introduction session, the 10 app-based stress-management modules, and one follow-up phone call. Results showed *StressProffen* to be perceived as promising, providing a new, appreciated, and easily accessible stress-management tool for cancer survivors. Evaluation of use of outcome measures also indicated pre-post intervention effects with statistically significant decrease in stress, anxiety and self-regulatory fatigue, and improved health related quality of life (HRQoL) after 8-week access.

Following minor adjustments for optimization, a 12-month RCT was conducted (2017-2020). Participants (N=172) were mainly female (82%), mean age 52 (range 20-78 years), with a variety of cancer types (majority breast cancer 48%). Over the 12-month study time, the intervention group reported significantly decreased stress (i.e., primary outcome), depression, and self-regulatory fatigue, as well as improved HRQoL in comparison with controls. Even larger effects in favor of the intervention group were detected at 6 months, then also with significant reductions in symptoms of anxiety in favor of the group receiving *StressProffen*.

Study Website: https://www.digitalhealth.no/english/projects/stressproffen/stress-management-in-cancer/index.html

The *StressProffen* project has so far (end 2022) four peer-reviewed publications and three popular science publications/blogs, more than 20 national and international presentations, and one completed post-doctoral fellowship (Elin Børøsund - 2017). The project has been presented in the National Report on Research and Innovation in Norwegian Specialist Health Services 2022, the *StressProffen* app is available in Norwegian and English, has been implemented and is available for download through the company dHealth AS (app store/Google play), and there are ongoing studies with *StressProffen* for health care providers at OUH (i.e., the largest hospital in Northern Europe), a large ongoing RCT for patients with breast cancer through the Norwegian Cancer Registry in Norway, and other studies, including with students in Uganda, and preparation for testing in cancer survivors at the Mayo Clinic in Minnesota.

- Key researchers and positions held at the administrative unit at the time of the research.
- Any relevant key contextual information about this area of research

***Lise Solberg Nes**, Principal Investigator *StressProffen* and Head of Department, DIG, MED, OUH.

***Elin Børøsund**, Post-doctoral fellow *StressProffen* (2015-2017) and Senior Researcher (2017-2022), DIG, MED, OUH.

Being diagnosed with cancer and going through treatment can be associated with substantial physical and psychosocial challenges, and coping can be difficult. Decades of research has shown how cognitive behavioral cancer distress- and stress-management interventions can reduce stress, anxiety and depression, and improve quality of life. Unfortunately, such interventions are not always available due to aspects such as not being offered, geographical limitations, financial concerns, and patients not feeling well enough to travel or attend in-person sessions. Digital health solutions may have the potential to improve outreach of evidence-based interventions, but such remote options are still in their infancy, with published results from RCTs testing psychosocial digital health interventions being scarce, and findings so far mixed and inconclusive.

Scientific reviews have pointed to a need to focus on design and adjustment of evidence-based interventions, while involving patients and healthcare provider stakeholders in the development process. Attrition has also been a major challenge for digital intervention studies, pointing to a need for attention to intervention adherence at an early stage for digital interventions.

Taking these challenges to the delivery of evidence-based stress-management interventions for cancer survivors into account, this research team developed *StressProffen*™©, a digital cognitive-behavioral stress-management intervention program for cancer survivors.

3. References to the research (indicative maximum of six references)

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Børøsund, E. & **Solberg Nes, L.** (2022). StressProffen™ - Effektiv, digital stressmestring for pasienter med kreft. BestPractice Nordic. https://bpno.no/artikler/stressproffen-effektiv-digital-stressmestring-for-pasienter-med-kreft/

4. Details of the impact (indicative maximum 750 words)

This section should provide a narrative, with supporting evidence, to explain:

- *How the research underpinned (made a distinct and material contribution to) the impact;*
- *The nature and extent of the impact.*

The *StressProffen* research project sought to address current challenges with existing digital health research and interventions, including incorporating a theoretical base/evidence, involving users/stakeholders in the design and development process, seeking to create a design to motivate and encourage adherence to the intervention, as well as to test use and usability in a feasibility study before optimization and testing *StressProffen* in a 12-month RCT. Design and development, feasibility testing and efficacy testing are well documented in peer-reviewed publications (i.e., in recognized journals such as *Journal of Medical Internet Research Formative Research*, *Translational Behavioral Medicine*, *Cancer Medicine* and *Cancer*), and methods and findings have been presented in more than 20 national and international presentations, including peer reviewed publications with published abstracts. In addition, the project was chosen to represent the South-Eastern Norway Health Authorities (i.e., largest regional authorities in Norway) in the National Report on Research and Innovation in Specialist Health Care in Norway 2022 (https://www.helse-sorost.no/helsefaglig/forskning/forskning-og-innovasjon-til-pasientens-beste.

Despite extensive documentation of the positive impact of CBT-based stress-management interventions for cancer survivors in terms of particularly psychosocial benefits, evidence-based

stress-management interventions have limited outreach, with barriers such as availability only in larger cities or medical centers, costs, and patients not feeling physically or emotionally well enough to attend in person, often group, sessions. The thorough documentation on research methods and evidence of effects (i.e., reduced stress, anxiety, depression and improved self-regulatory capacity and quality of life) for cancer survivors from the *StressProffen* research project hence lead the Technology Transfer Office of the South-Eastern Norway Health Authorities, Inven2, to establish a new company, dHealth AS, to market, commercialize and make the *StressProffen* program available for individuals, companies and authorities alike (May 2020).

As of end 2022, more than 700 individuals have downloaded *StressProffen* in Norway based on own initiative. In addition, 6 municipalities in region Innlandet (i.e., mid Norway) with more than 20 000 inhabitants have implemented *StressProffen* through their cancer coordinators as a freely available support program for the municipalities' cancer survivors. Other municipalities in Norway have also benefited (e.g., Rauma Municipality) and recommends *StressProffen* as a support tool for their cancer surviving inhabitants.

To ensure continuous accordance with current digital health and medical device regulations, the *StressProffen* digital solutions has also been externally evaluated for Medical Device Regulations (MDR) and found not to be required for MDR legislation in its current form and use.

The *StressProffen* content (i.e., stress-management) is not specifically tailored to a cancer diagnosis or specific cancer treatment trajectory. Rather, the CBT-based content addresses stress-management in general (e.g., stress and stress-management, quality of life and planning ahead, thoughts, feelings and self-care, thought restructuring, coping, health behaviors and setting goals, social support, communication and assertiveness, anger management, and what to do when times are challenging). In fact, the word "cancer" is, based on user input during design and development, not even mentioned in the *StressProffen* app. This suggests that *StressProffen* could likely be of benefit to populations other than cancer survivors, and is currently being offered to health care providers at OUH (i.e., the largest hospital in Northern Europe), with feedback from registered nurses, physicians and physical therapists so far being highly positive (e.g., "I feel the app is giving me something in my day-to-day life. In situations where I find myself becoming easily stressed, especially at work, I have felt great benefit from the content of *StressProffen*"). There are also ongoing negotiations between the dHealth AS company and several commercial companies aiming to offer *StressProffen* through their human resource departments as an easy access stress-management program for employees, as well as pilot projects aiming to test *StressProffen* in companies seeking to aid people in remaining or returning to employment. In addition, the *StressProffen* program is currently offered to students in Uganda in a depression-intervention study through the University of Oslo, and versions of *StressProffen* are also being tested in a large scale RCT through the Norwegian Cancer Registry for patients with breast cancer.

StressProffen has also inspired the design and development of ZuperSmart, a digital stress-management intervention for children ages 6-12 years https://www.digitalhealth.no/english/projects/supersmart/index.html. The ZuperSmart project is led by *StressProffen* PI Lise Solberg Nes, ZuperSmart content is further developed based on *StressProffen* and tailored to children within the age group, ZuperSmart - et nytt stressmestringsverktøy for barn - Oslo universitetssykehus HF (oslo-universitetssykehus.no) and the final digital solution can now be downloaded for free www.ZuperSmart.no. ZuperSmart has so far been downloaded more than 30 000 times, is already recommended for use by multiple schools and after school resources in Norway, and English and Ukrainian versions are in progress.

5. Sources to corroborate the impact (indicative maximum of ten references)

**** StressProffen©™ - Commercialization:***

- dHealth AS – company commercializing and ensuring *StressProffen* available for download in the market (App store/Google Play). In Norwegian. https://www.dhealthapp.no

**** StressProffen©™ - Implemented for use.*** **StressProffen as implemented for cancer patients through cancer coordinators in Norwegian municipalities [Norwegian]:**

- Vestre Vestre Slidre municipality: https://www.vestre-slidre.kommune.no/nyheter/stressproffen.16949.aspx
- Sør-Aurdal municipality: https://www.sor-aurdal.kommune.no/tjenester/familie-helse-og-omsorg/helsetjenester/kreftomsorg/stressproffen/
- Nord-Aurdal municipality: https://www.nord-aurdal.kommune.no/nyheter/stressproffen-et-verktoy-til-deg-som-har-kreft-har-hatt-kreft-eller-er-parorende-til-noen-med-kreft-i-valdres.14792.aspx
- Reuma Municipality. StressProffen promoted as a resource for psychological health. (In Norwegian – listed under "Psykisk helse" (i.e., psychological health for cancer survivors) https://www.rauma.kommune.no/_f/p1/i99d85ef1-294c-4104-a5a3-75648b8b2bd0/ressursbank-rauma-digital-versjon-2023.pdf

**** StressProffen©™ Study Websites:***

- *StressProffen©™ overall study website:* https://www.digitalhealth.no/english/projects/stressproffen/index.html
- *StressProffen©™ original Randomized Controlled Cancer Trial Study Website:* https://www.digitalhealth.no/english/projects/stressproffen/stress-management-in-cancer/index.html
- *StressProffen©™ Healthcare Providers Study Website:* https://www.digitalhealth.no/english/projects/stressproffen/stressproffen-healthcare-providers/index.html
- *Stress Management after Breast Cancer Project Website:* https://www.kreftregisteret.no/en/Research/Projects/Stress-management-after-breast-cancer/
- *The NutriMind Project Website*: https://www.med.uio.no/imb/english/research/projects/nutrimind/index.html

https://www.digitalhealth.no/english/projects/stressproffen/stressproffen-nutrimind/

Oslo University Hospital- Clinic of Medicine – Case number 2

Institution: Oslo University Hospital
Administrative unit: Clinic of Medicine
Title of case study: Studies on the efficacy and safety of Non-vitamin K oral anticoagulants (NOACs) influencing the transition from warfarin to NOAC and resulting in health benefits to patients and the society
Period when the underpinning research was undertaken: 2012-2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2012-2022
Period when the impact occurred: from 2012 and ongoing

1. Summary of the impact (indicative maximum 100 words)

For more than 60 years, warfarin was the only available oral anticoagulant. Warfarin was very cumbersome to use, and a significant undertreatment was observed throughout the world.

Our studies on the efficacy and safety of non-vitamin K oral anticoagulants (NOACs) compared to warfarin have had a significant impact on the transition from warfarin to NOACs in clinical practice, both in Norway and the rest of the world.
This transition has health benefits for large patient groups (reduced risk of bleeding). Furthermore, larger patient groups can now be treated with oral anticoagulation, reducing their risk of stroke.

2. Underpinning research (indicative maximum 500 words)

Our studies have shown that the NOAC drugs are at least as effective as warfarin for stroke prevention in patients with atrial fibrillation and associated with a reduced risk of bleeding. We showed this both in randomised clinical trials (RCTs), subgroup analyses of RCTs, and in cohort studies from nationwide Scandinavian registries:

:

- **1.** *We contributed to the landmark trials studying the efficacy and safety of the NOACs compared with warfarin*:
- A. The subunit recruited patients to the international multicenter trial ARISTOTLE studying apixaban (a NOAC) compared to warfarin for stroke prevention in atrial fibrillation. One of the group members (D. Atar) was part of the Steering Committee and contributed as co-author to the main paper. The study showed that apixaban was superior to warfarin for stroke prevention and associated with a reduced risk of bleeding.
- B. The subunit also recruited patients to two other international multicenter RCTs comparing NOAC to warfarin in patients with atrial fibrillation and coronary artery disease (REDUAL-PCI 2017, AUGUSTUS study 2019). Professor Halvorsen was national co-ordinator for these studies and was involved as co-author in drafting of several papers. The studies showed that the NOACs were associated with a reduced risk of bleeding compared to warfarin, also in patients in need of additional antiplatelet treatment.

- **2.** *Members of the subunit took the lead to perform subgroup analyses of some of these landmark RCTs.* Particularly, the subgroup analysis on age from the ARISTOTLE study, performed by our subunit and published in Eur Heart J in 2014, had great impact. The subgroup analysis showed that apixaban (NOAC) was superior to warfarin for stroke prevention and associated with a lower risk of bleeding, irrespective of age.

- **3**. *Last, but not least, the subunit performed several observational studies on the effectiveness and safety of NOACs in clinical practice*. Patients included into RCTs are often younger and healthier compared to patients in daily clinical practice, and real-world evidence is therefore important before implementation of new treatment. Observational studies were performed by our subunit in the years 2017-22 on data from nationwide cohorts in three Scandinavian countries. These real-world studies showed very similar results as the landmark RCTs, and had great impact on clinical practice in Norway and the rest of the world.

- *Dates of when it was carried out*: 2012-2022

- *Names of the key researchers and what positions they held at the administrative unit at the time of the research*:
- Sigrun Halvorsen, Professor and Head of Department of Cardiology OUS Ullevål;
- Dan Atar, Professor at Clinic of Medicine, Oslo University Hospital Ullevål.

References to the research (indicative maximum of six references)
References to key outputs from the research described in the previous section, and evidence about the quality of the research.

1. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, **Atar D**, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Geraldes M, Gersh BJ, Golitsyn S, Goto S, Hermosillo AG, Hohnloser SH, Horowitz J, Mohan P, Jansky P, Lewis BS, Lopez-Sendon JL, Pais P, Parkhomenko A, Verheugt FW, Zhu J, Wallentin L; ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365:981-92. **Impact Factor (IF) 158**
https://doi.org/10.1056/NEJMoa1107039

Landmark trial on efficacy and safety of apixaban (NOAC) compared to warfarin. In 2019, the study was recognized by the New England Journal of Medicine's E*ditor-in-Chief as one of the 12 most practice-changing articles since 2000 (>10.000 citations).*

2. Windecker S, Lopes RD, Massaro T, Jones-Burton C, Granger CB, Aronson R,Heizer G, Goodman SG, Darius H, Jones WS, Aschermann M, Brieger D, Cura F, Engstrøm T, Fridrich V, **Halvorsen S**, Huber K,et al.; AUGUSTUS Investigators. Antithrombotic Therapy in Patients With Atrial Fibrillation and Acute Coronary Syndrome Treated Medically or With Percutaneous Coronary Intervention or Undergoing Elective Percutaneous Coronary Intervention: Insights From the AUGUSTUS Trial. Circulation. 2019;140:1921-1932. **IF 39.9**
https://doi.org/10.1161/CIRCULATIONAHA.119.043308

International multicenter RCT on the efficacy and safety of apixaban compared to warfarin in patients who need concomitant antiplatelet therapy.

3. **Halvorsen S**, **Atar D**, Yang H, De Caterina R, Erol C, Garcia D, Granger CB, Hanna M, Held C, Husted S, Hylek EM, Jansky P, Lopes RD, Ruzyllo W, Thomas L, Wallentin L. Efficacy and safety of apixaban compared with warfarin according to age for stroke prevention in atrial fibrillation: observations from the ARISTOTLE trial.
Eur Heart J 2014;35:1864-72. **IF 39.3** https://doi.org/10.1093/eurheartj/ehu046

Important subgroup analysis from the ARISTOTLE study, showing results in relation to age. (438 citations)

4. **Halvorsen S,** Ghanima W, Fride Tvete I, Hoxmark C, Falck P, Solli O, Jonasson C. A nationwide registry study to compare bleeding rates in patients with atrial fibrillation being prescribed oral anticoagulants. Eur Heart J Cardiovasc Pharmacother 2017;3:28-36. **IF 11.1** https://doi.org/10.1093/ehjcvp/pvw031

   Observational study on the effectiveness and safety of NOACs in clinical practice in Norway. Among the first real-world evidence that was published on this topic (142 citations).

5. **Halvorsen S**, Johnsen SP, Madsen M, Linder M, Sulo G, Ghanima W, Gislason G, Hohnloser SH, Jenkins A, Al-Khalili F, Tell GS, Ehrenstein V. Effectiveness and safety of non-vitamin K antagonist oral anticoagulants and warfarin in atrial fibrillation: a Scandinavian population-based cohort study. *Eur Heart J Qual Care Clin Outcomes* 2022;8:577-587. **IF 5.2.** https://doi.org/10.1093/ehjqcco/qcab048

   Observational study on the effectiveness and safety of NOACs in clinical practice in Scandinavia. Scandinavian registries are considered to be of very high quality, and results from these registries have a large impact worldwide.

6. Rutherford OW, Jonasson C, Ghanima W, Söderdahl F, **Halvorsen S.** Effectiveness and safety of oral anticoagulants in elderly patients with atrial fibrillation. Heart 2022; 108:345-352. **IF 5.7** https://doi.org/10.1136/heartjnl-2020-318753

   Observational study on the effectiveness and safety of NOACs in clinical practice in Norway, with focus on the elderly population which often is frail and has an increased risk of complications.

4. Details of the impact (indicative maximum 750 words)

First of all, the landmark trials on the efficacy and safety of the novel oral anticoagulants published in 2009-2011 had a great impact on the entire field of cardiology. As shown already, our subunit participated with inclusion of patients into these multicenter trials, and also as co-authors in several of them. The European Society of Cardiology (ESC) regularly publishes practice guidelines, and in 2012 and in 2016, ESC updated their guidelines on atrial fibrillation. Recommendations to prefer the use of NOACs over warfarin were included, based on the results of these trials. The ESC recommendations are endorsed by most countries in Europe and read by cardiologists all over the world. D. Atar from our subunit was a co-author on these guidelines both in 2012 and 2016, and had the opportunity to influence these guidelines which had a great impact on current cardiological therapeutic paradigms and ultimately on clinical practice (reference 5 and 6, section 5).

Patients included into RCTs are often younger and healthier compared to the patients we meet in daily clinical practice. The subgroup analysis on age of the ARISTOTLE trial, showing that the new drug was safe and effective also in the elderly patients, had an immense impact on the prescription rates of NOAC in Norway and many other countries. In addition to the publication, researchers from our subunit gave numerous of talks about these results, and on the new guidelines, all over the world.
When we also published the real-world evidence, showing very similar results as in the multicenter RCTs, doctors felt even more convinced and reassured that these new drugs should be the preferred treatment for patients with atrial fibrillation.

Of course, the studies performed by our subunit were not the only ones underpinning these new recommendations and the shift in clinical practice from warfarin to NOAC. With respect to the landmark trials on NOACs versus warfarin, we only made a small, yet significant contribution. However, our subunit had the lead on the subgroup analysis in relation to age published in Eur Heart J in 2014, which made a significant contribution to the field and thus, has been frequently cited (438 citations). Furthermore, the observational studies from clinical practice by our subunit were based on data from high-quality well-recognized Scandinavian registries, increasing their impact compared to data from e.g. health-insurance databases in the U.S.
The shift from warfarin to NOAC has been clearly documented in many publications. Below is a figure from Kjerpeseth et al from 2017 (*Eur J Clin Pharmacol 2017;* **73:**1417–1425) showing the reduction in the number of new users of warfarin and concomitant increase in the numbers of NOAC users. What is also evident, is the increase in the total number of new persons receiving oral anticoagulation. The NOACs are much easier to use than warfarin, making it possible to treat more patients, thereby reducing the previously observed undertreatment, and thus conferring increased protection against strokes in the society.

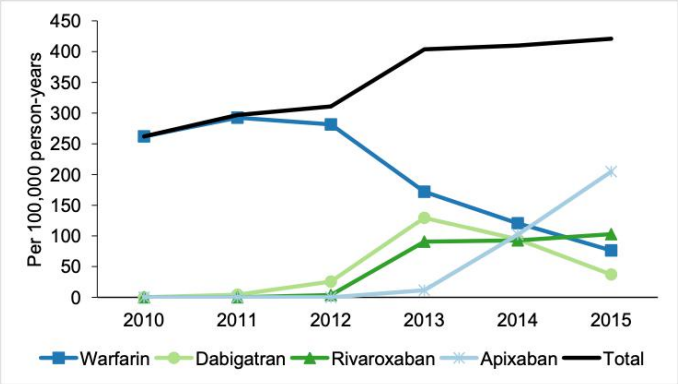

Fig. 1 Yearly number of incident users of warfarin, dabigatran, rivaroxaban and apixaban for atrial fibrillation per 100,000 person-years from January 1, 2010 to December 31, 2015 in Norway

- To sum up, our research had a large impact on the treatment transition from warfarin to NOAC throughout the world from 2014 and onward, increasing the number of patients receiving this treatment. From approx. 2014, we successfully opened a new era in the field of oral anticoagulation, with NOAC as the preferred treatment.

5. Sources to corroborate the impact (indicative maximum of ten references)

The studies 1-4 show how oral anticoagulation treatment has changed during the years 2010-2020.

1. Kjerpeseth, L.J., Ellekjær, H., Selmer, R. *et al.* Trends in use of warfarin and direct oral anticoagulants in atrial fibrillation in Norway, 2010 to 2015. *Eur J Clin Pharmacol 2017;* **73:**1417–1425. https://doi.org/10.1007/s00228-017-2296-1
2. **Halvorsen S**, Smith JA, Söderdahl F, Thuresson M, Solli O, Ulvestad M, Jonasson C. Changes in primary care management of atrial fibrillation patients following the shift from warfarin to non-vitamin K antagonist oral anticoagulants: a Norwegian population based study. BMC Prim Care 2022;23;214. https://doi.org/10.1186/s12875-022-01824-6
3. Ghanima W, Schultze A, Donaldson R, Brodin E, **Halvorsen S**, Graham S, Carroll R, Ulvestad M, Lambrelli D. Oral Anticoagulation Therapy for Venous Thromboembolism in Norway: Time Trends and Treatment Patterns. Clin Ther 2021;43:1179-1190.

https://doi.org/10.1016/j.clinthera.2021.04.017

4. Ko D, Lin KJ, Bessette LG, Lee SB, Walkey AJ, Cheng S, Kim E, Glynn RJ, Kim DH. Trends in Use of Oral Anticoagulants in Older Adults With Newly Diagnosed Atrial Fibrillation, 2010-2020. *JAMA Netw Open.* 2022;5(11):e2242964. https://doi.org/10.1001/jamanetworkopen.2022.42964

Studies 5-7 are examples of guidelines or position papers recommending the use of NOAC over warfarin, and that NOACs also can be used in elderly patients.

5. Camm AJ, Lip GY, De Caterina R, Savelieva I, **Atar D**, Hohnloser SH, Hindricks G, Kirchhof P; ESC Committee for Practice Guidelines (CPG). 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. Eur Heart J. 2012;33:2719-47. https://doi.org/10.1093/eurheartj/ehs253
6. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, **Atar D,** Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P; ESC Scientific Document Group. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J. 2016;37:2893-2962. https://doi.org/10.1093/eurheartj/ehw210
7. Andreotti F, Rocca B, Husted S, **Halvorsen S**, et al. on behalf of the ESC Thrombosis Working Group. Antithrombotic therapy in the elderly: expert position paper of the European Society of Cardiology Working Group on Thrombosis. Eur Heart J 2015; *36: 3238–3249.* https://doi.org/10.1093/eurheartj/ehv304

Studies 8-10 are further examples of publications with significant contributions from our subunit underpinning the evidence for use of NOAC over warfarin.

8. Vinereanu D, Stevens SR, Alexander JH, Al-Khatib SM, Avezum A, Bahit MC, Granger CB, Lopes RD, **Halvorsen S**, Hanna M, Husted S, Hylek EM, Mărgulescu AD, Wallentin L, **Atar D**: Clinical outcomes in patients with atrial fibrillation according to sex during anticoagulation with apixaban or warfarin: a secondary analysis of a randomized controlled trial. Eur Heart J 2015;36:3268-75.https://doi.org/10.1093/eurheartj/ehv447
9. Alexander KP, Brouwer MA, Mulder H, Vinereanu D, Lopes RD, Proietti M,Al-Khatib SM, Hijazi Z, **Halvorsen S,** Hylek EM, Verheugt FWA, Alexander JH, Wallentin L, Granger CB; ARISTOTLE Investigators. Outcomes of apixaban versus warfarin in patients with atrial fibrillation and multi-morbidity: Insights from the ARISTOTLE trial. Am Heart J 2019; 208:123-131. https://doi.org/10.1016/j.ahj.2018.09.017
10. Bahit MC, Vora AN, Li Z, Wojdyla DM, Thomas L, Goodman SG, Aronson R, Jordan JD, Kolls BJ, Dombrowski KE, Vinereanu D, **Halvorsen S**, Berwanger O, Windecker S, Mehran R, Granger CB, Alexander JH, Lopes RD. Apixaban or Warfarin and Aspirin or Placebo After Acute Coronary Syndrome or Percutaneous Coronary Intervention in Patients With Atrial Fibrillation and Prior Stroke: A Post Hoc Analysis From the AUGUSTUS Trial. JAMA Cardiol 2022;7:682-689. https://doi.org/10.1001/jamacardio.2022.1166

Name of the institution and name of the administrative unit:

Oslo University Hospital - Medical Clinic – case nr. 3

Institution: Dep. of Infectious Diseases, Oslo University Hospital (OUH)
Administrative unit: Clinic of Medicine
Title of case study: COVID-19 Research
Period when the underpinning research was undertaken: 2004-2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2010-2022 (varies for individual persons, Dyrhol-Riise employed at OUH in 2010)
Period when the impact occurred: 2020-23

1. Summary of the impact

The Covid-19 research performed by our research group at the Department of Infectious Diseases, Oslo University Hospital (OUH/UiO) exploring the immune pathogenesis of SARS CoV2 infection and testing therapeutic candidates for severe Covid-19 has contributed to guidelines and policy making both locally and globally (WHO, ISARIC Clinical Characterization Group /WHO Solidarity Trial). Our research have impact on both individual patients, society and health care services with respect to optimal treatment, better quality of life and good utilization of resources and has prepared platforms for future pandemic research and clinical management in hospitals.

2. Underpinning research

Chronic Infections Research Group (CIRG), funded by professor Dag Kvale in 2002 and since 2013 headed by professor Anne Ma Dyrhol-Riise, head of R&D at Department of Infectious Diseases, OUH, Ullevål has for 20 years focused on translational research in the topics of inflammation, immune mechanisms, diagnostics and host-directed-therapy with relevance for personalized medicine in chronic infections such as HIV and Tuberculosis. In the period 2012-2022 we have contributed to education and supervised 12 completed PhD fellows and several medical students.

The Dep. has been sponsor for several phase I/II randomized clinical trials (RCT), collected prospective ongoing biobank of patient samples from various patient cohorts with corresponding collection of clinical data in quality registers for use in translational research. CIRG holds a state-of-the-art well-equipped immunological laboratory strategically integrated within the clinical ward. The group also has access to institutional core facility infrastructure (flow cytometry, sequencing, proteomics). Thus, we have facilities and resources to perform clinical trials with equipped study rooms, blood sampling and GCP certified study nurses and technicians.

Researchers at the Dep. (professors, postdocs and PhD fellows) mostly have combined clinical positions at OUH and UiO (Institute of Clinical Medicine). CIRG collaborates interdisciplinary through a translational approach with other research groups at OUH/UiO with complimentary competence and expertise as well as with industry and non-academic stakeholders as patient organisations. We work in collaboration with national and international research networks both in Europe and in Low- and Middle-Income countries. We have aimed to secure networking to build research platforms. We believe that only through this strategy we can answer research questions, build competence, and prepare for pandemic research.

In HIV, there has been collaborations between the research group, UiO (Prof. Kjetil Tasken) and industry in vaccine and intervention research with several RCT, publications and PhD degrees.

Recently we have collaborated with Aarhus University though the HIV Cure Research network participation in the TITAN RCT (ClinicalTrials.gov identifier: NCT03837756) published in Nature Medicine (2023). https://www.nature.com/articles/s41591-023-02547-6). We have also initiated the Oslo HIV Research Network.

In Tuberculosis, we have fruitful collaborations with University of Stellenbosch, South-Africa, a leading research group in TB diagnostics sharing clinical data and biobanks since 2016. This has given several joint publications and a joint PhD fellow defending her thesis at UiO in 2022. The RCN (GlobVac) funded TBCOX2 RCT (2015-2019) http://clinicaltrials.gov/show/NCT02503839 at OUH in collaboration with Statens Serum institute in Denmark a leading institution in TB vaccine research gave eight publications, including high-ranking scientific journals and two PhD degrees. The project paved the ground for the invitation to join in the EU Horizon 2020 funded SMA-TB consortium involving institutions in seven countries (www.smatb.eu). Both projects aim to provide better and more precise and affordable therapy and thus improving TB patient's Health Quality of Life with importance for the global epidemic of TB. We have in HIV, TB and Influenza been partner in two K.G. Jebsen Centre for Medical Research; The K.G Jebsen Centre for inflammation Research and the K.G. Jebsen Centre for Influenza Vaccine.

With this research strategy and organisation we were together with our national and international collaborators on short notice able to perform high-quality research and several RTCs on therapeutic interventions when the SARS CoV2 pandemic came in March 2020 resulting in very many fast-track publications.

CIRG webpage: https://www.med.uio.no/klinmed/english/research/groups/chronic-infectious-diseases/index.html
GIRG publications: https://www.ous-research.no/home/did/Publications/10393

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3. References to the research

Andreas Lind, Kristin Brekke, Maja Sommerfelt, Jens O Holmberg, Hans Christian D Aass, Ingebjørg Baksaas, Birger Sørensen, Anne Ma Dyrhol-Riise, Dag Kvale. **Boosters of a therapeutic HIV-1 vaccine induce divergent T cell responses related to regulatory mechanisms.** Vaccine. **2013** Sep 23;31(41):4611-8. PMID: 23906886 DOI: 10.1016/j.vaccine.2013.07.037

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Malin Holm Meyer-Myklestad, Asle Wilhelm Medhus, Kristina Berg Lorvik, Ingebjørg Seljeflot, Simen Hyll Hansen, Kristian Holm, Birgitte Stiksrud, Marius Trøseid, Johannes Roksund Hov, Dag Kvale, Anne Margarita Dyrhol-Riise, Martin Kummen, Dag Henrik Reikvam. **Human Immunodeficiency Virus–Infected Immunological Nonresponders Have Colon-Restricted Gut Mucosal Immune Dysfunction**. J Infect Dis. **2022**. doi: 10.1093/infdis/jiaa714.

Synne Jenum, Kristian Tonby, Corina S. Rueegg, Morten Rühwald, Max P. Kristiansen, Peter Bang, Inge Christoffer Olsen, Kjersti Sellæg, Kjerstin Røstad, Tehmina Mustafa, Kjetil Taskén, Dag Kvale, Rasmus Mortensen & Anne Ma Dyrhol-Riise. **A Phase I/II randomized trial of H56:IC31 vaccination and adjunctive cyclooxygenase-2-inhibitor treatment in tuberculosis patients**. Nature Communications volume 12, Article number: 6774 (**2021**). https://doi.org/10.1038/s41467-021-27029-6

Chendi BH, Snyders CI, Tonby K, Jenum S, Kidd M, Walzl G, Chegou NN, Dyrhol-Riise AM. **A Plasma 5-Marker Host Biosignature Identifies Tuberculosis in High and Low Endemic Countries**. Front Immunol. **2021** Feb 24;12:608846. doi: 10.3389/fimmu.2021.608846. eCollection 2021.

4. Details of the impact

The Dep. and CIRG has during 2020-22, been responsible for and recruited patients to four international multicentre RCT of hospitalized severe Covid-19 (WHO-Solidarity, DisCoVeRy, Bari-SolidAct and AXL-SolidAct) and one international cohort study (WHO/ISARIC Covid-19) https://isaric.org/. NOR-Solidarity, an add-on trial to the WHO-Solidarity included 26 Norwegian Hospitals and was set up during some few weeks in the start of the pandemic March 2020 through intensive collaborative work by the steering committee and networks at OUH/UiO (headed by professor Pål Aukrust, PI at Ullevål professor Anne Ma Dyrhol-Riise). We have later contributed to develop EU-Response, an European study platform sponsored by Oslo University Hospital (headed by professor Marius Trøseid) for the rapid initiation of clinical studies in future pandemics (https://eu-response.eu). Principal investigators at OUH (Dep. of Infectious Diseases, Ullevål): Kristian Tonby, Aleksander Holten). The research group also established a local quality registry for patients hospitalized for Covid-19.

In collaboration with pre-existing and new networks at OUH, UiO (Institute of Clinical Medicine), nationally and internationally this joint research has so far resulted in over 50 publications in peer-reviewed journals, some fast-track publications in early 2020 including high-ranked journals as PNAS, J. Internal Medicine etc.

In 2021-22 on behalf of the Norwegian company Nykode Therapeutics we performed a phase 1/2, dose-escalating clinical multicentre study of two SARS-CoV-2 DNA plasmid vaccine candidates, (ClinicalTrials.gov, NCT05069623) testing safety and immunogenicity in healthy study participants (https://nykode.com/covid-vaccine-trial/). PI: Anne Ma Dyrhol-Riise. The VB10.2210 vaccine demonstrated safety and immunogenicity and data were presented at the international Immunology conference in Cape Town, Nov. 2023 (https://iuis.org/).

Our translational research, located at OUH/UiO (CIRG) has been established by long-term strategic work, active external fund raising, and planning through many years of securing integration and research infrastructure located close to the clinical wards. Close collaboration with institution's core facility has enabled us to develop out competence in translational immunological studies on infectious diseases. This organization of the research has also facilitated clinical studies with the mobilization of clinical doctors and research personnel on short notice, as required in pandemic research. Our research group therefore has opportunities to become a significant partner in future global as well as pandemic research. Studies of preventive vaccines as well as preparation of research platforms for future pandemics would have great impact on limiting the burden of disease with importance for the country's as well as global economy.

Our research on Covid-19 has contributed to increased knowledge about clinical management and immune mechanisms of the disease. The Covid-19 research testing therapeutic candidates for

Covid-19 has contributed to guidelines and policy making both locally and globally (WHO, ISARIC Clinical Characterization Group /WHO Solidarity Trial) with impact on both individual patients, society and health care services with respect to optimal treatment, better quality of life and good utilization of resources.

https://doi.org/10.1001/jamanetworkopen.2023.46502

https://doi.org/10.1016/s1473-3099(21)00565-x

https://doi.org/10.1056/nejmoa2023184

5. Sources to corroborate the impact

1. Trøseid M et al, SolidAct study group. **Efficacy and safety of baricitinib in hospitalized adults with severe or critical COVID-19 (Bari-SolidAct): a randomised, double-blind, placebo-controlled phase 3 trial**. Crit Care. **2023** Jan 10;27(1):9. doi: 10.1186/s13054-022-04205-8.
2. Murphy SL, Halvorsen B, Barratt-Due A, Dyrhol-Riise AM, Aukrust P, Trøseid M, Dahl TB. **Remdesivir modifies interferon response in hospitalized COVID-19 patients**. J Infect. **2022** Nov;85(5):573-607. doi: 10.1016/j.jinf.2022.07.021.
3. Lekva T, Ueland T, Halvorsen B, Murphy SL, Dyrhol-Riise AM, Tveita A, Finbråten AK, Mathiessen A, Müller KE, Aaløkken TM, Skjønsberg OH, Lerum TV, Aukrust P, Dahl TB **Markers of cellular senescence is associated with persistent pulmonary pathology after COVID-19 infection**. Infect Dis (Lond). **2022** Dec;54(12):918-923. doi: 10.1080/23744235.2022.2113135.
4. Tveita A et al, NOR-Solidarity study group and the Norwegian SARS-CoV-2 Study Group Investigators. **High Circulating Levels of the Homeostatic Chemokines CCL19 and CCL21 Predict Mortality and Disease Severity in COVID-19**. J Infect Dis. **2022** Dec 13;226(12):2150-2160. doi: 10.1093/infdis/jiac313.
5. Vestad B et al. NOR-Solidarity study group. **Respiratory dysfunction three months after severe COVID-19 is associated with gut microbiota alterations**. J Intern Med. **2022** Jun;291(6):801-812. doi: 10.1111/joim.13458.
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8. Christensen EE, Jørgensen MJ, Nore KG, Dahl TB, Yang K, Ranheim T, Huse C, Lind A, Nur S, Stiksrud B, Jenum S, Tonby K, Holter JC, Holten AR, Halvorsen B, Dyrhol-Riise AM. Norwegian SARS-CoV-2 Study Group. **Critical COVID-19 is associated with distinct leukocyte phenotypes and transcriptome patterns**. J Intern Med (**2021**); 290 (3), 677-692. DOI 10.1111/joim.13310.
9. Jøntvedt Jørgensen M, Holter JC, Christensen EE, Schjalm C, Tonby K, Pischke SE, Jenum S, Skeie LG, Nur S, Lind A, Opsand H, Enersen TB, Grøndahl R, Hermann A, Dudman S, Muller F, Ueland T, Mollnes TE, Aukrust P, Heggelund L, Holten AR, Dyrhol-Riise AM. Norwegian SARS-CoV-2 Study Group. **Increased interleukin-6 and macrophage chemoattractant protein-1 are associated with respiratory failure in COVID-19**. Sci Rep. (**2021**), 10 (1), 21697. DOI 10.1038/s41598-020-78710-7.
10. Holter JC, Pischke SE, de Boer E, Lind A, Jenum S, Holten AR, Tonby K, Barratt-Due A, Sokolova M, Schjalm C, Chaban V, Kolderup A, Tran T, Tollefsrud Gjølberg T, Skeie LG,

Hesstvedt L, Ormåsen V, Fevang B, Austad C, Müller KE, Fladeby C, Holberg-Petersen M, Halvorsen B, Müller F, Aukrust P, Dudman S, Ueland T, Andersen JT, Lund-Johansen F, Heggelund L, Dyrhol-Riise AM, Mollnes TE. **Systemic complement activation is associated with respiratory failure in COVID-19 hospitalized patients**. Proc Natl Acad Sci U S A. **2020** Oct 6;117(40):25018-25025. doi: 10.1073/pnas.2010540117.

Oslo University Hospital, Division of Medicine [case number 4]

Institution: Oslo University Hospital
Administrative unit: Division of Medicine
Title of case study: Inflammatory Bowel Disease in Southeastern Norway (IBSEN) I and III
Period when the underpinning research was undertaken: 1990 - ongoing
Period when staff involved in the underpinning research were employed by the submitting institution: 2007 - ongoing
Period when the impact occurred: 1993 - ongoing

1. Summary of the impact

Inflammatory bowel disease in South Eastern Norway –the IBSEN studies
IBSEN stands as a pivotal population-based prospective cohort study on inflammatory bowel disease (IBD). Patients were included in 1990-1994 and have been followed for three decades. The study has had profound impact on our knowledge of IBD including epidemiology, the natural disease course, risk factors for severe disease, long-term effects on mortality, cancer risk, disability, and health-related quality of life (HRQoL). As such, the IBSEN study has underpinned our modern understanding of IBD and has had important impact on IBD treatment and research worldwide.

Building upon this legacy, the sequel IBSEN III included a new cohort in 2017-2019 and is presently in the final phase of completing the five-year follow-up. Comparison of the two studies will give important knowledge on the development and real-world impact of current treatment regimes.

2. Underpinning research

2.1 The nature of the research insights or findings which relate to the impact claimed in the case study

As the first true population-based inception cohort study on IBD world-wide, the IBSEN study underpinned our current understanding of the natural course of these chronic, disabling inflammatory, e.g.:

- the high and increasing incidence of IBD in Norway
- the immense heterogeneity of IBD across various phenotypes, levels of severity, and disease course
- the importance of early mucosal healing to reduce long term complications
- the identification of prognostic clinical factors for severe disease outcome
- the occurrence and impact of extra intestinal manifestations in IBD
- the long-term impact on mortality and cancer
- the recognition of how IBD impacts on health-related quality of life and work disability
- the identification of blood-based and fecal biomarkers for predicting disease activity disease complications

The results have especially had impact on IBD guidelines where treatment strategies have evolved immensely. Notably, the concept of mucosal healing has emerged as a cornerstone and is now widely acknowledged as the most important treatment goal while normalization of health-related quality of life and avoidance of disability is currently being discussed as the most important long-term treatment.

2.2 An outline of the underpinning research produced by the submitted unit

The research produced by the unit during the years 2012 to 2022 includes completing the study 20-year clinical follow-up, developing and organising research based on biomaterials collected at the 10- and 20-years follow-ups and linking the cohort to NPR, the cancer registry and the cause of death registry after 20- and 30-years follow-up.

The output is evident in the publication of over 100 papers (approx. 40 between 2012 and 2022), spanning diverse topics. These include in-depth analyses of long-term data, exploration of clinical outcomes, investigations into health-related quality of life (HRQoL), assessments of work disability, evaluations cancer of mortality risk, and examinations of blood-based and fecal biomarkers.

2.3. Dates of when the underpinning research was carried out

This research has been ongoing continuously since the initiation of the study in 1990, until the last for PhD student defended his thesis on 30-year cancer risk and mortality of IBD, on January 18th, 2024. Still, data and materials from the IBSEN study are being used in several ongoing projects including studies on long term effects on work disability and socioeconomic impacts of IBD, and changes in familiar risk of IBD. Furthermore, the data from the IBSEN study will serve as a historical benchmark for comparisons in studies featuring the contemporary counterpart—the sequel IBSEN III.

2.4. Names of the key researchers and what positions they held at the time of the research

Professor Bjørn Moum (Department of Gastroenterology OUH/UiO, emeritus since 2022) initiated the study in collaboration with his supervisor professor Morten Vatn (emeritus since xxx) in 1989 and has been PI of the study for these over 30 years. In 2023 the PI responsibility was handed over to professor Marte Lie Høivik. In addition to professor Moum, professor Marte Lie Høivik, MD, PhD Inger Camilla Solberg, MD PhD Alvilde Ossum, MScient PhD fellow Benoit Follin-Arbelet and MD PhD fellow Iril Monstad, MD PhD Vendel Kristensen have been key researchers at OUH.

Importantly, as the study covers 15 hospitals in four (former) counties in the South Eastern Health region, several researchers at other HSØ-hospitals (including Ahus, Lovisenberg Hospital Telemark hospital, Østfold Hospital and Innlandet Hospital) have used IBSEN in research. In total eight PhD-students (Marte Lie Høivik (OUH), Øistein Hovde (Innlandet Hospital), Gert Huppertz-Hauss (Telemark Hospital), Alvilde Ossum (OUH), Iril Monstad (OUH, Lovisenberg, Ahus), Pascal Klepp (Lovisenberg) Aida Kapic Lunder (Ahus), worked on IBSEN data during these years, of whom seven have completed their PhDs and one is ongoing.

2.5. Any relevant key contextual information about this area of research.

Prior to the initiation of the IBSEN study, research on IBD relied predominantly on hospital cohorts, hampered by outdated diagnostic tools, vague disease definitions, and a lack of well-defined classification systems. The landscape changed with the advent of IBSEN, which was launched shortly after the introduction of the first diagnostic criteria for IBD (the Lennard Jones Criteria). At that time, IBSEN was as both the largest globally conducted, population-based inception study and the first to systematically employ precisely defined diagnostic criteria.

This approach, coupled with a well-functioning public health care system, facilitated the inclusion and meticulous follow-up of an exceptionally well-characterized cohort encompassing the entire spectrum of IBD patients. Even today, IBSEN remains revered as the gold standard for population-based cohort studies in IBD, with references to IBSEN studies prominently featured in every IBD conference.

Patients with suspected IBD at all 15 hospitals in the former counties of Oslo, Østfold, Vestfold and Aust-Agder were invited, and 843 patients were included and prospectively followed. The study could only be performed due to the engagement and efforts from the large majority of gastroenterologist and gastroenterology nurses in these hospitals over many years. Beyond its direct scientific contributions, this collective engagement in IBSEN has impacted Norwegian IBD care, shaping practices for decades.

3. References to the research

Høivik ML, Moum B, Solberg IC, Henriksen M, Cvancarova M, Bernklev T; IBSEN Group.
Work disability in inflammatory bowel disease patients 10 years after disease onset: results from the IBSEN Study.
Gut. 2013 Mar;62(3):368-75.
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Solberg IC, Cvancarova M, Vatn MH, Moum B; IBSEN Study Group
Risk matrix for prediction of advanced disease in a population-based study of patients with Crohn's Disease (the IBSEN Study).
Inflamm Bowel Dis. 2014 Jan;20(1):60-8.
doi: 10.1097/01.MIB.0000436956.78220.67.

Lunder AK, Hov JR, Borthne A, Gleditsch J, Johannesen G, Tveit K, Viktil E, Henriksen M, Hovde Ø, Huppertz-Hauss G, Høie O, Høivik ML, Monstad I, Solberg IC, Jahnsen J, Karlsen TH, Moum B, Vatn M, Negård A.
Prevalence of Sclerosing Cholangitis Detected by Magnetic Resonance Cholangiography in Patients With Long-term Inflammatory Bowel Disease.
Gastroenterology. 2016 Oct;151(4):660-669.e4.
doi: 10.1053/j.gastro.2016.06.021.

Huppertz-Hauss G, Lie Høivik M, Jelsness-Jørgensen LP, Henriksen M, Høie O, Jahnsen J, Hoff G, Moum B, Bernklev T
Health-related Quality of Life in Patients with Inflammatory Bowel Disease 20 Years After Diagnosis: Results from the IBSEN Study.
Inflamm Bowel Dis. 2016 Jul;22(7):1679-87.
doi: 10.1097/MIB.0000000000000806

Hovde Ø, Høivik ML, Henriksen M, Solberg IC, Småstuen MC, Moum BA.
Malignancies in Patients with Inflammatory Bowel Disease: Results from 20 Years of Follow-up in the IBSEN Study.
J Crohns Colitis. 2017 May 1;11(5):571-577.
doi: 10.1093/ecco-jcc/jjw193.

Monstad IL, Solberg IC, Cvancarova M, Hovde O, Henriksen M, Huppertz-Hauss G, Gunther E, Moum BA, Stray N, Vatn M, Hoie O, Jahnsen J.
Outcome of Ulcerative Colitis 20 Years after Diagnosis in a Prospective Population-based Inception Cohort from South-Eastern Norway, the IBSEN Study.
J Crohns Colitis. 2021 Jun 22;15(6):969-979.
doi: 10.1093/ecco-jcc/jjaa232.

4. Details of the impact

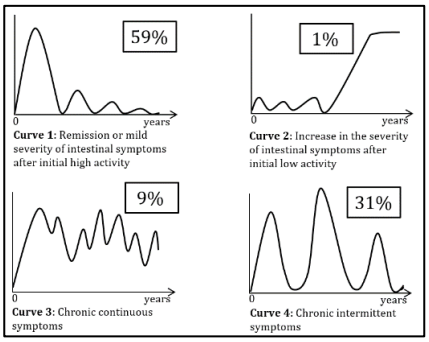
4.1. Impact of epidemiological insights

The IBSEN study has profoundly altered the epidemiological landscape by providing robust and reliable data, in contrast to earlier hospital-based populations using poor definitions of IBD diagnosis. The epidemiological findings stemming from IBSEN, up until the year 2021, stand as the most current and comprehensive incidence data on IBD in Norway.

The epidemiological data from IBSEN are still used as background for all estimations for needs in IBD care and treatment, planning of health care resources and new IBD research projects.

4.2. Impact of knowledge on the natural disease course of IBD

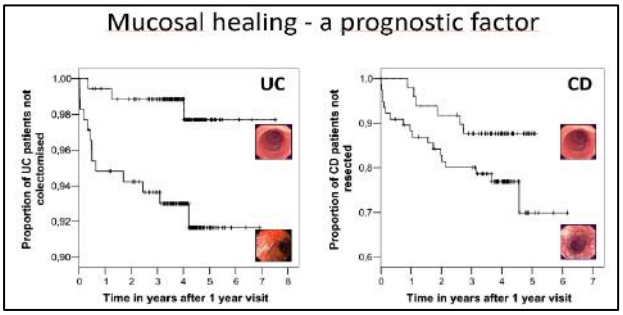
More than 20 papers describing different aspects of the clinical disease course in IBD have been published from the IBSEN study. However, it is indisputable that the IBSEN disease course curves, first published in relation to the five-year follow-up in 2006, and then repeated at the 10- and 20-year follow-ups, have had the most profound impact.
These curves describe and quantify different disease courses in IBD and thus illustrates the heterogeneity of the diseases.



These figures (here shown for UC 5 years disease course) are still today shown at every IBD conference and forms the basis of ongoing discussions on treatment strategies in IBD, e.g., is “top-down” therapy (i.e., starting with biologics in early disease course for all IBD patients) a sound strategy.

4.3. Impact of findings on mucosal healing

Historically, the treatment goal for IBD has predominantly centered around alleviating clinical symptoms. However, a paradigm shift occurred with the seminal IBSEN paper titled "Mucosal Healing in Inflammatory Bowel Disease: Results from a Norwegian Population-Based Cohort," published in Gastroenterology in 2007 (cited 1303 times). This groundbreaking study was the first to demonstrate that attaining mucosal healing, characterized by the normalization of the gut mucosa, serves as a significant prognostic factor for the risk of surgery in both ulcerative colitis and Crohn’s disease.



Over the years, the importance of mucosal healing has been validated in subsequent studies and eventually accepted and included in the current treatment goals in IBD as stated in the STRIDE (Selecting treatment targets in IBD) publications and European treatment guidelines. This knowledge has significantly influenced the clinical approach to treating IBD patients.
This impact is particularly evident in the shift towards a more proactive and early integration of biological treatments. Furthermore, there is now a heightened emphasis on a systematic approach to standardized endoscopic follow-ups, aimed at meticulously assessing the attainment of treatment goals. Preliminary results from the sequel IBSEN III study (published as abstracts) indicate a notable decline in surgery rates for both ulcerative colitis and Crohn's disease. This encouraging trend underscores the real-world implications of incorporating advanced treatment strategies, and the positive impact of a treatment strategy that prioritizes early intervention and focuses on monitoring treatment efficacy through standardized endoscopic assessments.

4.4. Impact of prognostic factors

Still today, no validated prognostic biomarkers are available for clinical use in IBD.
Risk factors for severe disease course as first shown in the IBSEN studies are therefor currently used daily aiding doctors in assessing future risks and determining the appropriateness of initiating biological therapies or opting for early surgery. As stated in section 4.3, data from IBSENE III (which reflects current IBD care in Norway) show reduced surgery rates as an example of impact from the use of data-driven risk assessments.

4.5. Impact of long-term data on cancer, mortality risk and extraintestinal manifestations
Many previous studies have indicated a significant increase in cancer risk, particularly colorectal cancer in IBD patients. However, the IBSEN data has challenged this narrative, revealing that the actual risk is relatively modest. Importantly, this heightened risk primarily pertains to specific groups, such as males with extensive colitis and those concurrently experiencing primary sclerosing cholangitis (PSC). Cancer risk data impacts guidelines for cancer surveillance – which for IBD are based on very limited evidence.
Furthermore, mortality risk is not increased. This knowledge has important implications for both patients and health care personnel influencing informed decision-making and providing crucial information for individuals seeking fair health insurance coverage.
Regarding extraintestinal manifestations, the IBSEN study described, for the first time a significant occurrence of subclinical PSC in IBD patients with 10 years IBD disease. This finding triggered ongoing discussions regarding the potential necessity for surveillance for PSC in IBD patients. The ongoing IBSEN III study promises study these aspects further to refine and update our understanding of cancer, mortality risks, and extraintestinal manifestations within modern IBD care.

4.6. Impact of patient reported data (HRQoL, fatigue) and work disability
IBSEN was the first population-based cohort study to include patient-reported data. HRQoL and work disability data was first included at the 5-year follow-up while fatigue was added at the 10- and 20-year follow-ups. These data are highly cited and providing important background information and portraying the comprehensive impact of the disease on the patient's life.

4.7. Impact via a wider body of research – research collaborations
The IBSEN study group has engaged in extensive national and international collaboration, particularly in projects using biological material in translational research. The focal point of these collaborations has been the exploration of biomarkers. This includes early work on NOD2, ANCA and ASCA as diagnostic biomarkers, serologic biomarkers for surgery risk in IBD, microbial biomarkers (microbes and microbial metabolites) in PSC and fecal biomarkers for CRC risk. This work is continued in IBSEN III - a cohort developed especially for diagnostic and prognostic biomarker research.

5. Sources to corroborate the impact

Mucosal healing in inflammatory bowel diseases: a systematic review
Neurath MF, Travis SPL
Gut 2012;61:1619-1635.
DOI: 10.1136/gutjnl-2012-302830

Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE): Determining Therapeutic Goals for Treat-to-Target
Peyrin-Biroulet, L Sandborn, W Sands, B E Reinisch W, Bemelman, et al International Organization for the Study of IBD
American Journal of Gastroenterology 110(9):p 1324-1338,
September2015. | DOI: 10.1038/ajg.2015.233

ECCO-ESGAR Guideline for Diagnostic Assessment in IBD Part 1: Initial diagnosis, monitoring of known IBD, detection of complications
Maaser C, Sturm A, Vavricka SR, Kucharzik T, Fiorino G et al ,
Journal of Crohn's and Colitis, Volume 13, Issue 2, February 2019, Pages 144–164K,
https://doi.org/10.1093/ecco-jcc/jjy113

[Oslo University Hospital – Clinic of Medicine [case number 5]

Institution: OUS
Administrative unit: Clinic of Medicine
Title of case study: The effect of a pre- and postoperative orthogeriatric service on cognitive function in patients with hip fracture: randomized controlled trial (Oslo Orthogeriatric Trial)
Period when the underpinning research was undertaken: 2009 - 2012
Period when staff involved in the underpinning research were employed by the submitting institution: 2009 - 2014
Period when the impact occurred: from 2009 and ongoing

1. Summary of the impact (indicative maximum 100 words)

This section should briefly state what specific impact is being described in the case study.

Oslo Orthogeriatric Trial (OOT) was a randomised controlled trial evaluating the effect of orthogeriatric care for patients acutely admitted for surgical repair of a hip fracture (https://pubmed.ncbi.nlm.nih.gov/24735588/). The study was planned in concert with the Trondheim Hip Fracture Trial (https://pubmed.ncbi.nlm.nih.gov/25662415/). Taken together, the studies showed clear benefits for patients that were offered orthogeriatric service (https://pubmed.ncbi.nlm.nih.gov/33765935/). Orthogeriatric care is now considered "gold standard" in treatment for such patients, and has been implemented at several hospitals internationally and in Norway.

2. Underpinning research (indicative maximum 500 words)

This section should outline the key research insights or findings that underpinned the impact, and provide details of what research was undertaken, when, and by whom. This research may be a body of work produced over a number of years or may be the output(s) of a particular project. References to specific research outputs that embody the research described in this section, and evidence of its quality, should be provided in the next section. Details of the following should be provided in this section:

- The nature of the research insights or findings which relate to the impact claimed in the case study.

The primary outcome for this study was cognitive function four months after surgery, and secondary outcomes included delirium, delirium severity, length of stay, mortality, mobility, place of residence, instrumental (iADL) and basic (bADL) function, and weight changes. We found no impact on the primary outcome, but better mobility (measured by the Short Physical Performance Battery (SPPB)) was found in patients not admitted from nursing homes.

As the study was planned in concert with the Trondheim Fracture Trial, merged data of two randomized controlled trials showed that admitting hip fracture patients to an orthogeriatric care unit directly from the emergency department had a positive effect on mobility up to twelve months after surgery. Patients had better mobility and performed in general better on activities of daily living (https://pubmed.ncbi.nlm.nih.gov/33765935/).

- An outline of what the underpinning research produced by the submitted unit was (this may relate to one or more research outputs, projects or programmes).

An important secondary outcome of OOT was to gain insights in the pathophysiology of delirium and to study the links between delirium and dementia. Samples of blood and cerebrospinalfluid were collected during the hospital stay and at the follow up controls (only blood samples). This biobank has proven to be very valuable and is the foundation for many national and international research collaboration and has resulted in more than 30 PubMed indexed publications.

- Dates of when it was carried out.

After a pilot period from June 2008 to September 2009, recruitment i the study lasted from September 2009 to January 2012.

- Names of the key researchers and what positions they held at the administrative unit at the time of the research (where researchers joined or left the administrative unit during this time, these dates must also be stated).

Professor Torgeir Bruun Wyller: PI. Planned the study. Main supervisor
Leiv Otto Watne (at the time PhD student, now Professor in geriatrics at Ahus): daily responsibility for the study.

- Any relevant key contextual information about this area of research.

Orthogeriatric care is now considered "gold standard" in treatment for such patients, and has been implemented at several hospitals internationally and in Norway.

3. References to the research (indicative maximum of six references)
This section should provide references to key outputs from the research described in the previous section, and evidence about the quality of the research. All forms of output cited as underpinning research will be considered equitably, with no distinction being made between the types of output referenced. Include the following details for each cited output:

1. Watne LO, Torbergsen AC, Conroy S, Engedal K, Frihagen F, Hjorthaug GA, Juliebo V, Raeder J, Saltvedt I, Skovlund E, Wyller TB. The effect of a pre- and postoperative orthogeriatric service on cognitive function in patients with hip fracture: randomized controlled trial (Oslo Orthogeriatric Trial). BMC Med. 2014 Apr 15; 12 (1): 63.
DOI: 10.1186/1741-7015-12-63

Imporant because: main publication of OOT. Shows positive effect on mobility in hip fracture patients not admitted from nursing homes.

2. Dakhil S, Thingstad P, Frihagen F, Johnsen LG, Lydersen S, Skovlund E, Wyller TB, Sletvold O, Saltvedt I, Watne LO. Orthogeriatrics prevents functional decline in hip

fracture patients: report from two randomized controlled trials. BMC Geriatr. 2021 Mar 25; 21(1): 208. DOI: 10.1186/s12877-021-02152-7

Imporant because: Merged data from OOT and the Trondheim Hip Fracture trial shows improved ADL in patients offered orthogeriatric care.

3. Watne LO, Pollmann CT, Neerland BE, Quist-Paulsen E, Halaas NB, Idland AV, Hassel B, Henjum K, Knapskog AB, Frihagen F, Raeder J, Godø A, Ueland PM, McCann A, Figved W, Selbæk G, Zetterberg H, Fang EF, Myrstad M, Giil LM. Cerebrospinal fluid quinolinic acid is strongly associated with delirium and mortality in hip fracture patients. J Clin Invest. 2022 Nov 2. doi: 10.1172/JCI163472.

Important because: Biomarker data from blood and CSF samples, identified how systemic inflammation, neurotoxicity, and delirium are strongly linked via the kynurenine pathway (KP) and should inform future delirium prevention and treatment clinical trials that target enzymes of the KP.

4. Details of the impact (indicative maximum 750 words)

This section should provide a narrative, with supporting evidence, to explain:

- How the research underpinned (made a distinct and material contribution to) the impact;
- The nature and extent of the impact.

The following should be provided:

- A clear explanation of the process or means through which the research led to, underpinned or made a contribution to the impact (for example, how it was disseminated, how it came to influence users or beneficiaries, or how it came to be exploited, taken up or applied).

- Where the submitted administrative unit's research was part of a wider body of research that contributed to the impact (for example, where there has been research collaboration with other institutions), the case study should specify the particular contribution of the submitted administrative unit's research and acknowledge other key research contributions.

- Details of the beneficiaries – who or what community, constituency or organisation has benefitted, been affected or impacted on.

Hip fracture patients benefit of the implementation of orthogeriatric care. A better understanding of the pathophysiology of delirium will potentially benefit also other patients population. Delirium is a very common complication to acute illness and occurs in 20-30 % of all hospitalized patients (and aprox 50 % of hip fracture patients).

- Details of the nature of the impact – how they have benefitted, been affected or impacted on.

Orthogeriatric care is now considered gold standard. It has been implemented at several hospitals in Norway and internationally .

- Evidence or indicators of the extent of the impact described, as appropriate to the case being made.

Handoll HH, Cameron ID, Mak JC, Panagoda CE, Finnegan TP. Multidisciplinary rehabilitation for older people with hip fractures. Cochrane Database Syst Rev 2021: CD007125. DOI: 10.1002/14651858.CD007125.pub3.

- Dates of when these impacts occurred.

2009 and ongoing

5. Sources to corroborate the impact (indicative maximum of ten references)

1. The effect of a pre- and postoperative orthogeriatric service on cognitive function in patients with hip fracture: randomized controlled trial (Oslo Orthogeriatric Trial). **Watne LO**, Torbergsen AC, Conroy S, Engedal K, Frihagen F, Hjorthaug GA, Juliebo V, Raeder J, Saltvedt I, Skovlund E, Wyller TB. BMC Med. 2014 Apr 15;12(1):63.
2. The effect of a pre- and post-operative orthogeriatric service on cognitive function in patients with hip fracture. The protocol of the Oslo Orthogeriatrics Trial. Wyller TB, **Watne LO**, Torbergsen A, Engedal K, Frihagen F, Juliebø V, Saltvedt I, Skovlund E, Ræder J, Conroy S.BMC Geriatr. 2012 Jul 20;12(1):36.
3. Orthogeriatrics prevents functional decline in hip fracture patients: report from two randomized controlled trials.Dakhil S, Thingstad P, Frihagen F, Johnsen LG, Lydersen S, Skovlund E, Wyller TB, Sletvold O, Saltvedt I, **Watne LO**. BMC Geriatr. 2021 Mar 25;21(1):208. doi: 10.1186/s12877-021-02152-7.
4. Cerebrospinal fluid quinolinic acid is strongly associated with delirium and mortality in hip fracture patients. **Watne LO,** Pollmann CT, Neerland BE, Quist-Paulsen E, Halaas NB, Idland AV, Hassel B, Henjum K, Knapskog AB, Frihagen F, Raeder J, Godø A, Ueland PM, McCann A, Figved W, Selbæk G, Zetterberg H, Fang EF, Myrstad M, Giil LM. J Clin Invest. 2022 Nov 21:e163472. doi: 10.1172/JCI163472.

Oslo University Hospital and University of Oslo, Division of Prehospital Services, Impact Case #1

Institution: Oslo University Hospital and University of Oslo
Administrative unit: Division of Prehospital Services (OUS-PRE)
Title of case study: Development and testing of a naloxone nasal spray for opioid overdose
Period when the underpinning research was undertaken: 2013-2022
Period when staff involved in the underpinning research were employed by the submitting institution: Arne Kristian Skulberg MD, Consultant anaesthetist OUS and research fellow/ post-doc, NTNU Anne Cathrine Braarud MD, PhD, Consultant anaesthetist OUS-PRE Fridtjof Heyerdahl MD, PhD, Consultant anaesthetist OUS-PRE Tore Skålhegg, paramedic, Study assistant OUS-PRE Tomas Drægni, Study nurse OUS-PRE
Period when the impact occurred: 2013-ongoing

1. Summary of the impact

A nasal spray of naloxone to treat overdose from heroin and other opioids has been developed in close collaboration between the Norwegian University of Science and Technology (NTNU) and Oslo University Hospital Division of Prehospital Services (OUS-PRE). The spray is now commercially available in Norway and 12 European countries.
OUS-PRE crucially contributed to this research and development program by providing real-world data. Since opioid overdoses in Norway are clustered in central Oslo, OUS-PRE's ambulance service conducted epidemiological studies and tested the spray in a phase-III trial. Beyond its economic output, the program has influenced public policy, strengthened society's response to overdose, and improved essential healthcare for people who use drugs.

2. Underpinning research

Over the course of the past decade, the rise in opioid overdose deaths has led to a global shift in public policy and search for new treatment strategies. The World Health Organisation advised in 2014 that lay people "likely to witness an opioid overdose should have access to naloxone and be instructed in its administration". This is called Take-Home Naloxone (THN) and analogous to adrenaline (EpiPen) access for people with severe allergies.

No approved naloxone product existed in 2012 that lent itself to administration by non-professionals. A nasal spray with a small volume of fluid and a high concentration of naloxone to ensure rapid effect in an emergency was needed.

People at risk of opioid overdose are often socially marginalised and overlooked by the scientific and medical establishment. The development and testing of the naloxone nasal spray has sought to

rectify this by bringing evidence-based medicine, through observational studies, randomised trials, and development of care pathways to this group of patients.

The close cooperation between NTNU and OUS-PRE involved the employment of Arne Kristian Skulberg. He was part-employed as a research fellow at NTNU (50%) and as consultant anesthetist at OUS-PRE (50%) from 2013-20. His Ph.D. supervisors were Ola Dale (NTNU) and Anne Cathrine Braarud and Fridtjof Heyerdahl at OUS-PRE.

Research led to approval, production and sale of a naloxone nasal spray

The nasal naloxone spray formulation was developed between 2012- and approved in 2018. It is marketed as Ventizolve®, Respinal® or Naloxone 1.26 mg dose.

In parallel with the pharmacological development at NTNU, OUS-PRE conducted a prospective observational study of all ambulance callouts for opioid overdoses in Oslo city centre from 2014-18. This involved collecting data on actual naloxone dosing by ambulance staff in the field to establish a safe benchmark dose against which the novel antidote formulation should be tested. (Refs 1, 2)

For the new nasal naloxone spray, cross-over trials in heathy volunteers established the maximum concentration, time to maximum concentration, and bioavailability as well as comparative pharmacodynamics by comparing the spray to intravenous and intramuscular administration. (Ref 3,4,5).

To establish the efficacy and safety of the nasal spray, a randomised, double-blinded double-dummy trial was performed in 2018- 2020. Oslo University Hospital as the main recruiting centre with Skulberg as Principal Investigator. The trial is not only unique in its blinded design and consent procedure allowing clinical drugs trial on patients in emergency medicine (ref 4), but it is the first to characterize the clinical performance of an approved spray.

OUS research and work with direct impact on public policy

The work at OUS has directly informed public policy. In the Norwegian national overdose strategy for 2014 the NTNU spray was mentioned. Findings from our research identified gaps in the care of opioid overdose survivors. Arne Skulberg led the taskforce in the Norwegian Directorate of Health that developed a national standard for care pathway from overdoses (2020).

The observational study also included a long-term link to the National Cause of Death Registry, and the cohort from this study will be followed until 2032. The results of this research will likely continue to impact public policies in the coming decades.

Focus on user-participation, empowerment and quality of life

People who use drugs, and representatives from user and family organisations have been at the core of this project, notably in designing the procedure for informed consent deployed in the randomised trial (ref 6). By conducting high-quality pharmacological and clinical research we have in a substantial and quantifiable way directly contributed to empowering people who use drugs by giving them access to a lifesaving drug and improving unmet health care needs.

3. References to the research (max 6)

Employees of OUS-PRE in bold

1. Madah-Amiri D, **Skulberg AK, Braarud AC,** Dale O, **Heyerdahl F**, Lobmaier P, et al. Ambulance-attended opioid overdoses: An examination into overdose locations and the role of a safe injection facility. Subst Abus. 2019;40(3):383-8.

2. Tylleskar I, Gjersing L, Bjornsen LP, **Braarud AC, Heyerdahl F,** Dale O, **Skulberg, AK.** Prehospital naloxone administration - what influences choice of dose and route of administration? BMC Emerg Med. 2020;20(1):71

3. Tylleskar I, **Skulberg AK,** Nilsen T, Skarra S, Jansook P, Dale O. Pharmacokinetics of a new, nasal formulation of naloxone. Eur J Clin Pharmacol. 2017 May;73(5):555-562. doi: 10.1007/s00228-016-2191-1. Epub 2017 Jan 31.

4. **Skulberg AK,** Tylleskar I, Nilsen T, Skarra S, Salvesen Ø, Sand T, Loftsson T, Dale O. Pharmacokinetics and -dynamics of intramuscular and intranasal naloxone: an explorative study in healthy volunteers. Eur J Clin Pharmacol. 2018 Jul;74(7):873-883. doi: 10.1007/s00228-018-2443-3. Epub 2018 Mar 22.

5. **Skulberg AK,** Åsberg A, Khiabani HZ, Røstad H, Tylleskar I, Dale O. Pharmacokinetics of a novel, approved, 1.4-mg intranasal naloxone formulation for reversal of opioid overdose-a randomized controlled trial. Addiction. 2019 May;114(5):859-867. doi: 10.1111/add.14552. Epub 2019 Feb 15.

6. **Skulberg AK,** Tylleskär I, Valberg M, **Braarud AC,** Dale J, **Heyerdahl F, Skålhegg T,** Barstein J, Mellesmo S, Dale O. Comparison of intranasal and intramuscular naloxone in opioid overdoses managed by ambulance staff: a double-dummy, randomised, controlled trial. Addiction. 2022 Jun;117(6):1658-1667. doi: 10.1111/add.15806. Epub 2022 Feb 8.

4. Details of the impact

OUS-PRE has been the base from with the work at NTNU could meet clinical trials, both observational and interventional. OUS-PRE has many years of experience with clinical trials in prehospital medicine in the field of cardiac arrest. This clinical experience and research infrastructure has in this project been expanded to research on opioid overdoses and clinical drugs trials. All studies conformed to Good Clinical Practice standards for the design, conduct, monitoring, analysis and reporting of clinical trials and have been published in peer-reviewed journals, with the study material shared in an open repository. OUS-PRE has provided unique evidence-based knowledge to a vulnerable patient group, knowledge that has informed both commercial development as well as public debate and policy. The project has also resulted in collaborations with internationally leading scientists in the field.

A: Research and development of a nasal naloxone spray from idea to commercial product

The NTNU/ OUS-PRE research team recognised already in 2010 that early Take-Home Naloxone programs did not have an approved and appropriate naloxone formulation that could be distributed. This knowledge gap was also recognised by the World Health Organisation, and others **(A1).**

The nasal spray Ventizolve® 1.4 mg naloxone hydrochloride/ dose (marketed as Respinal® in Sweden and Naloxone 1.26 mg/ dose in the UK) is today produced by and exported by Dne Pharma AS their factory in Oslo. It has marketing approval in 12 European countries and is now on the market in half of these. It is now the leading spray used in the Norwegian take-home naloxone program, surpassing the other product available in the market. **(A2, A3, A4)**.

Ventizolve is unique in that it is delivered in a specially designed plastic casing to facilitate THN carriage, not being stored in a medicine cabinet. This is known as "the pebble" in English and is a result of the overriding focus of this research and development program: creating a medicine that is safe and effective and can be used by lay people in an emergency setting. Dne Pharma AS, with designers at Nonspace®, Bergen took the consequence of this and worked beyond the traditional medical packaging with blister- packs or other cumbersome designs. The pebble has been internationally recognised as both a design object **(A4, A5)** and as an advantage for the implementation of take-home naloxone programs **(A1)**

B: OUS-PRE research has contributed to national public health policies

The scientific evidence provided by OUS through its studies, and by the active participation of researchers in both the public debate and as members of policy boards the naloxone program has had direct effect on national policies in Norway. The NTNU spray is specifically mentioned in the national opioid overdose strategy from the government in 2014 **(B1).** Arne Kristian Skulberg, NTNU, was from 2019-21 the chairperson of a taskforce at the Directorate of Health that developed a national standard and care pathway for patients treated for overdose in Norway. **(B2)**

C: OUS-PRE impact on society, quality of life and empowerment

Deaths from opioid overdose are preventable, and victims on average 41 years old in Europe. Reducing such deaths have taken priority in many countries, and the development of drugs to be implemented through THN programs have been at the core of this. The NTNU spray contributed to this in a significant way. The groups of patients experiencing opioid overdose have traditionally been at the fringes of society. In many ways they have been denied well researched and novel treatment options for their condition. The development of Ventizolve and studies in the ambulance services has sought to rectify this. People who use drugs have been part of the study group since the design of the phase III trial, and we have actively cooperated on many levels and platforms. Importantly, research ethical obstacles that has hindered such research were overcome with the support of people who use drugs. This paves the way for future similar studies that may resolve present knowledge gaps **(C1, C2).**

Contrary to a decade a go, people who are at risk of opioid overdose and their friends and families now have access to a safe, effective, and specially designed antidote formulation that enables them to save lives. There is no doubt that this is an empowerment of a patient group that is among our most marginalized citizens.

D: Innovation and collaboration

In this project an idea has moved all the way from academia to the international pharmaceutical market. It is an innovation that was only successful due to the close cooperation between academia represented by NTNU and its international network necessary for developing a formulation, industry represented by Dne Pharma AS and Nonspace® design and Oslo University Hospital and St. Olav's University Hospital, Trondheim. (**D1)**

5. Sources to corroborate the impact (max 10)

A1: Testimony Professor Sir John Strang; King´s College, London, UK

A2: Summary of Product Characteristics Ventizolve®/ 1.26 mg naloxone
https://www.hpra.ie/img/uploaded/swedocuments/f360ab8d-28c4-4b7f-bd8d-a0c6c2aefc99.pdf

A3: Testimony Dne Pharma AS

A4: Patient Information Leaflet, naloxone 1.26 mg/dose UK https://naloxone.uk/wp-content/uploads/sites/7/2023/03/UK-04810_Patient_How_To_Use_LP_RGB_Singles.pdf

A5: (https://www.nonspace.no/en/case/ventizolve).

B1: National Overdose strategy 2014–2017 «Ja visst kan du bli rusfri…»
https://www.regjeringen.no/contentassets/43121155483947d79316af20c68e6d7d/overdosestrategi_230414.pdf

B2: Pakkeforløp etter overdose. https://www.helsedirektoratet.no/nasjonale-forlop/rusbehandling-tsb/akuttbehandling-og-oppfolging-etter-rusmiddeloverdose

C1: User participant statement to Regional committees for medical and health research ethics (REK) 2016

C2: =Oslo, January 2020 interviews Skulberg about the clinical trial of nasal naloxone. =Oslo is Norway's first street magazine. The magazine is published monthly and is a mouthpiece for the socially marginalized, people with substance use and others

D1: Rector at NTNU, Anne Borg, Video on Facebook, October 2020
https://www.facebook.com/RektorNTNU/videos/851579882317214?locale=az_AZ

Institute of Psychiatry

at The Maudsley

National Addiction Centre
Addiction Sciences Building
4 Windsor Walk,
London SE5 8AF
UK

Tel: 020 7848 0438
Email: john.strang@kcl.ac.uk

Director & Head of Department
Professor Sir John Strang

KING'S College LONDON
Founded 1829

University of London

14th January 2024

To Whom It May Concern - Letter of Confirmation for impact case:

"Take home naloxone: Bringing evidence-based therapy and innovative design to the streets".

I am Professor Sir John Strang and I am Director of the National Addiction Centre (King's College London), the leading UK and most productive European Addictions research group. I am a medically qualified doctor with 40 years' experience in diverse areas of the Addictions Treatment field, including leadership of innovative responses. I have had major involvement with UK and international policy and practice (e.g. UN; WHO) over several decades and have published more than 600 addictions publications including extensive original research. I have a particular expertise and interest in treatment of opioid use disorders and, in particular, new options to reduce deaths from opioid overdose.

I have had the pleasure since 2015 to closely follow the research of Professor Dale, his co-workers Arne Skulberg MD, PhD, and Ida Tylleskar, MD PhD at NTNU: Norwegian University of Science and Technology:

Overall, it was striking that the group were very early to recognise the need to develop a nasal naloxone spray for take-home naloxone, and commendably set out to build their case on scientific evidence. The first aim was to lay the ground for marketing approval for a proposed new concentrated naloxone nasal spray, with the ultimate goal of demonstrating its efficacy by a controlled study in opioid overdoses in the streets.

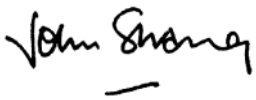
They started from the bottom by having a special formulation developed by academic pharmacists in their international scientific network. They then conducted a series of not only pharmacokinetic studies in healthy volunteers, but they also developed an elegant model to study its pharmacodynamics in these volunteers. This was a bridge between healthy volunteers and PWUOS´s (people who uses opioids). They were the first to publish the absolute bioavailability of a concentrated nasal naloxone spray.

The next step in the chain of evidence was to determine the intramuscular dose that works in the real world of drug use in the community or in 'street use'. Four years of prospectively recording clinical practice in the Oslo ambulance service showed that 0.8 mg intramuscular naloxone was highly effective. This dose was then used as reference in their pharmacokinetic study aimed at marketing approval and the upcoming randomized controlled trial. Their partner, the pharmaceutical company dne pharma in Oslo, was responsible for the marketing application, leading to the development of the commercial product 'Ventizolve' which is now extensively used to take-home naloxone schemes not only across Norway and wider Scandinavia but also in other European countries. The naloxone dose chosen for their nasal sprayer was 1.4 mg naloxone-HCL, based on the scientific studies by Professor Dale and his colleagues from their previous studies in healthy volunteers.

Finally, they compared these two administration forms in an impressive randomized controlled trial in the streets of Oslo and Trondheim not only showing the therapeutic characteristics of the administrations. This study was remarkable not only for the results which it generated but also for the demonstration that, with the right scientific creativity and sensitivity alongside Professor Dale's commitment and determination, it was possible to address ethical challenges which other groups had assumed could not be overcome.

One further observation warrants special note. It is now increasingly recognised that carriage rate of all forms of naloxone among PWUO´s may be low, thereby greatly reducing the extent to which this approach can prevent overdose deaths. This awareness alongside knowledge of the product and the need for greater portability resulted in the ‘Pebble’, a very original and user-friendly packaging of the new ‘Ventizolve’ nasal sprays.

The Pebble is on the market in several European countries. There is no doubt that the research by Professor Dale and his co-workers has added greatly to the extent to which the lifesaving benefit from take-home naloxone concept can be translated into lives truly saved.



Professor Sir John Strang. January 2024

dne pharma

Oslo 24.01.2024

To Whom It May Concern

Letter of Confirmation/support for impact case:

"Take home naloxone: Bringing evidence-based therapy and innovative design to the streets».

dne pharma is a small pharmaceutical company in Oslo focusing on both life-saving treatment and medication for opioid addiction. Through their daughter company Pharma Production AS, they perform development services as well as commercial manufacturing (CDMO/CMO) of all dne pharma pharmaceutical products.

dne pharma first met Professor Dale late 2013. dne pharma became aware of his project through their engagement in delivering "improvised" naloxone sprayers to a Norwegian Take-home naloxone program initiated by the Norwegian Government. In January 2014 dne pharma invited Professor Dale and his associate Arne Skulberg, MD, to inform dne pharma about the status of their ongoing work. dne pharma were immediately fascinated by their commitment for bringing evidence based nasal naloxone spray to the Take-Home naloxone field, and their apparent scientific capacity for implementing the research required for this. During the next 12 months a case was prepared for the dne pharma Board. The chairman of the Board the experienced academic and industrial pharmacist Martin Nicklasson, was impressed by the project and soon after this inspected the researchers' facilities and activities at NTNU. The result was that dne pharma decided to initiate the process for submitting a dossier to the Norwegian Medicines Authority with the objective of receiving marketing license I for NTNU´s nasal naloxone spray. The significance of the input of the NTNU Team, Professor Dale and his Ph.D students Arne Skulberg, MD, and Ida Tylleskär (medical student), not least for the pivotal pharmacokinetic study underpinning the marketing application, was crucial to dne pharmas final submission that ended up with approved marketing licenses I in 12 European countries in 2018.

dne pharma as
Karihaugveien 22
1086 Oslo – Norway

+47 21 60 87 00
post@dnepharma.com
dnepharma.com

Business registry/
Foretaksregisteret:
NO 991 741 208 MVA

In the initial phase we discussed a lot of how to ensure that the persons at risk always carried naloxone with them, and it became clear that we needed to work on finding a suitable packaging.

The packaging needed to be solid and able to protect the device when carried in a bag, purse or pocket. dne pharma therefore commissioned the design company ANTI in Bergen, Norway to design a groundbreaking outer packaging, the Pebble.

Secondly, the NTNU researchers did not consider comparisons of plasma concentrations of naloxone sufficient therapeutic evidence for the spray. dne pharma therefore delivered study kits for the randomized clinical study for free with no strings attached. dne pharma was pleased that the NTNU group were able to conduct this challenging study in real opioid overdoses, thus providing solid evidence for the efficacy of the spray.

Since 2018, the naloxone spray, under the trademark Ventizolve® is marketed in all Nordic countries, and last year also launched in major markets as UK and France. Through the last developments of overdose deaths in Europe we see a political trend of making the naloxone spray more available in the society. A development towards making the nasal spray to an over the counter (OTC) product in the near future, is not unrealistic, as we already happened in France. Sweden is most probably the next country to bring forward naloxone nasal spray as an OTC product. A request from the Swedish Minister of Social Affairs, encouraged dne pharma to submit an application for OTC status end of last year (2023).

In general, the cooperation with the NTNU team and dne pharma has been excellent. A unique experience and competence have been developed during these years and dne pharma /Pharma Production is now a well-established CMO/CDMO with knowledge both in manufacturing, development, and regulatory affairs. In terms of availability, we experience that the majority of naloxone nasal sprays supplied in Norway is covered by Ventizolve®, and increasing market shares are experienced in all markets where Ventizolve® is launched. Thus, we have extended our business platform.

Bibbi Paust
Head of Quality Assurance/Reg. Affairs
dne pharma as

Geir Ove Engeset
CEO
dne pharma as

Til: Regional Etisk Komite

Fra: Brukerrådet til NTNU sin studie om intranasal nalokson

Oslo 21.10.16

Vedlegg til REK søknad

Gruppas råd:
1: Den informasjonen som deles ut må være svært enkel, vedlagte A5 ark på to sider er nok. Det bør gis et visittkort med nummer og adresse som back up. I tillegg må det dannes Facebook gruppe i tillegg til websiden

2: Det bør være aktiv avmelding, ikke aktiv påmelding etter inklusjon i studien.

Begrunnelse:
1: Inforark:
Først er vi veldig spente på denne studien, og glade for at det gjøres en ordentlig studie på rusbrukere. Vi ønsker at medisinen som tilbys oss skal være så trygg og bra som mulig.

Etter en overdose vil deltagerne være sårbare og lette å forvirre. De har i det øyeblikket lite ressurser til å ta inn informasjon. Noen må videre på legevakt/ sykehus og andre vil bare bort fra situasjonen. A5 infoarket slik det legges ved denne protokollen er nok til å fortelle det aller viktigste- at de har blitt inkludert i forskning og at personopplysningen er begrenset til studieteamet, samt hvordan de kan få mer informasjon og trekke seg.

At de får et visittkort i tillegg gjør det mindre sannsynlig at de mister det ene arket som kan veilede de videre til informasjon og å trekke seg.

Når det gjelder prosedyre for å trekke seg mener vi at kombinasjonen internett og telefon er grei, men anbefaler at det opprettes en facebook gruppe også som kan være en portal til www.nalokson.no.

2: Avmelding:
Vi har gått igjennom alternativer for innmelding, avmelding etc slik det er beskrevet i protokollen punkt 16.3.5.

Etter både diskusjonene i gruppa og tilbakemeldinger fra rusbrukere vi har snakket med på byen er rådet vårt at en aktiv avmelding er det beste alternativet. Folk i aktiv rus lever ganske travle og til tider kaotiske liv, og prioriterer hard mellom hva de skal bruke energien på. De som ikke har lyst til å være med videre vil da prioritere avmeldingen. Etter vår mening er metoden tilgjengelig og enkel. De fleste har god internett tilgang- enten på telefon, hjemme eller værested og alle kan ringe nummeret som er oppgitt. For de som ønsker å fortsette, eller syns det er greit og være inkludert vil derimot en aktiv påmelding lett kunne bli nedprioritert.

Brukerne skifter ofte telefoner- de selges og kjøpes ganske fritt i miljøet, og det er få som har stabile telefonnummer. Mange lever også uten fast adresse, eller uten fast bopel. Dette gjør det umulig for studieteamet å skulle få tak i brukere etter at de har blitt inkludert.

Vi ønsker ikke at studieteamet skal ta kontakt med pårørende til de som har hatt overdose å fortelle dette for å søke samtykke.

Vi mener at andre som kan være rundt overdosen ikke er i stand til å gi samtykke på veiene av den som er inkludert.

Hvis REK ønsker det stiller noen fra rådet vårt gjerne opp på et møte med komiteen for å forklare nærmere og svare på spørsmål.

Med vennlig hilsen

Torstein Bjordal

Siv Løvland

Heidi Hansen

Fredrik Nilsson

Siri Sollie Getz

Bettina Blakstad

NTNU
Norwegian University of Science and Technology

Presentasjon av Brukerrådet

NTNU Intranasal naloxone trial, EudraCT:2016-004072-22

Mandat:

Mandatet til gruppa har utformet informasjonsmateriellet som skal gis til inkluderte deltagere i studien. Brukerrådet har vært med i protokollskrivingen og diskutert de forskjellige formene for samtykke som kan foreslåes i studien. Brukerrådet skal gi en uttalelse til studieteamet om hvilken metode de foreslår for samtykke i studien.

Etter oppstart har Brukerrådet mandat til å følge prosessen og være med sammen med forskerne å informere i brukermiljøet både i Oslo og i Trondheim om den pågående studien.

Etter studiens avslutning skal Brukerrådet være med å spre resultatene av studien i de samme miljøene.

Medlemmer:

Torstein Bjordal:
Nestleder, brukermedvirker og aktivist i Foreningen for human narkotikapolitikk (FHN). Han sier selv: *"… jeg er Semi aktiv bruker og for det meste oppholder meg i miljøer med flest aktive brukere og od'er (overdoser)?"*

Heidi Hansen:
jobber til daglig i Rusmisbrukernes interesseorganisasjon.

Siri Getz Sollie:
Styreleder i LAR Nett Norge, LAR- NETT NORGE (LNN). Jobber i 100 % stilling og sitter i ansvarsgrupper; følger pasienter til leger og ruskoordinatorer. Hun samarbeider med Pasient og brukerombudet; og Helse og Overdoseteamet i Trondheim. Sitter i Brukerrådet i Trondheim og jobber direkte mot enhetslederne inne rus og psykisk helse. Er medlem i Tenketanken Tyrili nasjonalt. Jeg holder foredrag og underviser. Det viktigste jeg gjør er likevel direkte møte med hvert eneste menneske i rus .

Siv Løvland: Styremedlem i porLAR- nasjonalt forbund for folk i LAR
Beskriver seg selv: *Jeg har vært rusmisbruker over halve livet mitt, men er nå rusfri. Jeg har hatt flere overdoser men er glad jeg lever. Jobber med brukermedvirkning og er veldig fornøyd med å få holde på med noe jeg har kompetanse på og kan få være med på å bidra muligheten til å forebygge og redde liv.*

Fredrik Nillson
Frivillig i RIO Rusmisbrukernes Interesseorganisasjon. Han beskriver bakgrunnen sin slik: *"Jag är iaf en man på 40 år. Började rusa mig på narkotika först när jag var ca 27. Men varit i kriminella och våldsamma miljöer sedan tidig tenåring. Varit rusfri nu ifrån narkotika i över 3.5 år. Sluta dricka alkohol helt sedan ca 6 månader. Varit i behandling på Renåvangen som är ett terapautiskt samfunn. Där jag på ett eftervärn mötte Kenneth Arctander då han var där och föreläste och tog efter det kontakt med RIO. Är frivillig arbetare där sedan det. Sitter även i BlåKors Öst brukarutvalg. Är med i flera olika projekt bland annat i Gamla Oslo där det ska startas ett Utvecklingscenter för psykriatri og rus."*

Bettina Blakstad fra Landsforbundet Mot Stoffmisbruk (LMS) er en organisasjon av og for pårørende av rusavhengige.
Bettina Blakstad har jobbet i LMS siden våren 2014. Bettina jobber innenfor LMS Pårørendesenter, som veileder for pårørende av rusavhengige. I tillegg arbeider hun med prosjektet 'tilbud til minoritetsetniske pårørende av rusavhengige', samt representerer LMS i en rekke brukerutvalg og ressursgrupper.

Arne Skulberg
Stipendiat på NTNU og spesialist i anestesiologi. Med i prosjektgruppen på dette studiet og jobber som lege i Ambulansetjenesten i Oslo og på Ullevål Sykehus.

Bjørn Loe
Paramedic i 18 år på Sentrum Ambulansestasjon i Oslo. Sitter som ambulansetjenestens representant i Arbeidsgruppen til Helsedirektoratets nasjonale overdose strategi

Prosjektmedarbeiderne **Anne Cathrine Braarud** og **Fridtjof Heyerdahl** har også møtt på noen av gruppas møter. **Erlend Paxal fra** gatemagasinet Sorgenfri i Trondheim møtte på første møte.

Møter:

Brukerrådet har hatt fast møteplass på Sentrum Ambulansestasjon i Storgata i Oslo.

Første møtet var 06.06 og etter sommeren to fulle møter den 14.09 og 04.10. I tillegg tok deler av gruppa med seg utkast til informasjonsmateriell på byvandring 03.10. Da snakket vi med tilfeldige rusbrukere i Brugata, ved Sprøyterommet og andre steder i sentrum. Studien ble presentert, forslag til infobrev ble vist fram og forklart. Det kom flere innspill på det forslaget som da ble lagt frem var for komplisert. I tillegg fikk vi bekreftet at alle vi snakket med hadde god tilgang på internett på daglig basis.

I tillegg til møtene har Brukerrådet mailet/ sendt SMS sammen. Referat fra alle møter er lagt i studiens Trial Master File jmf GCP regler.

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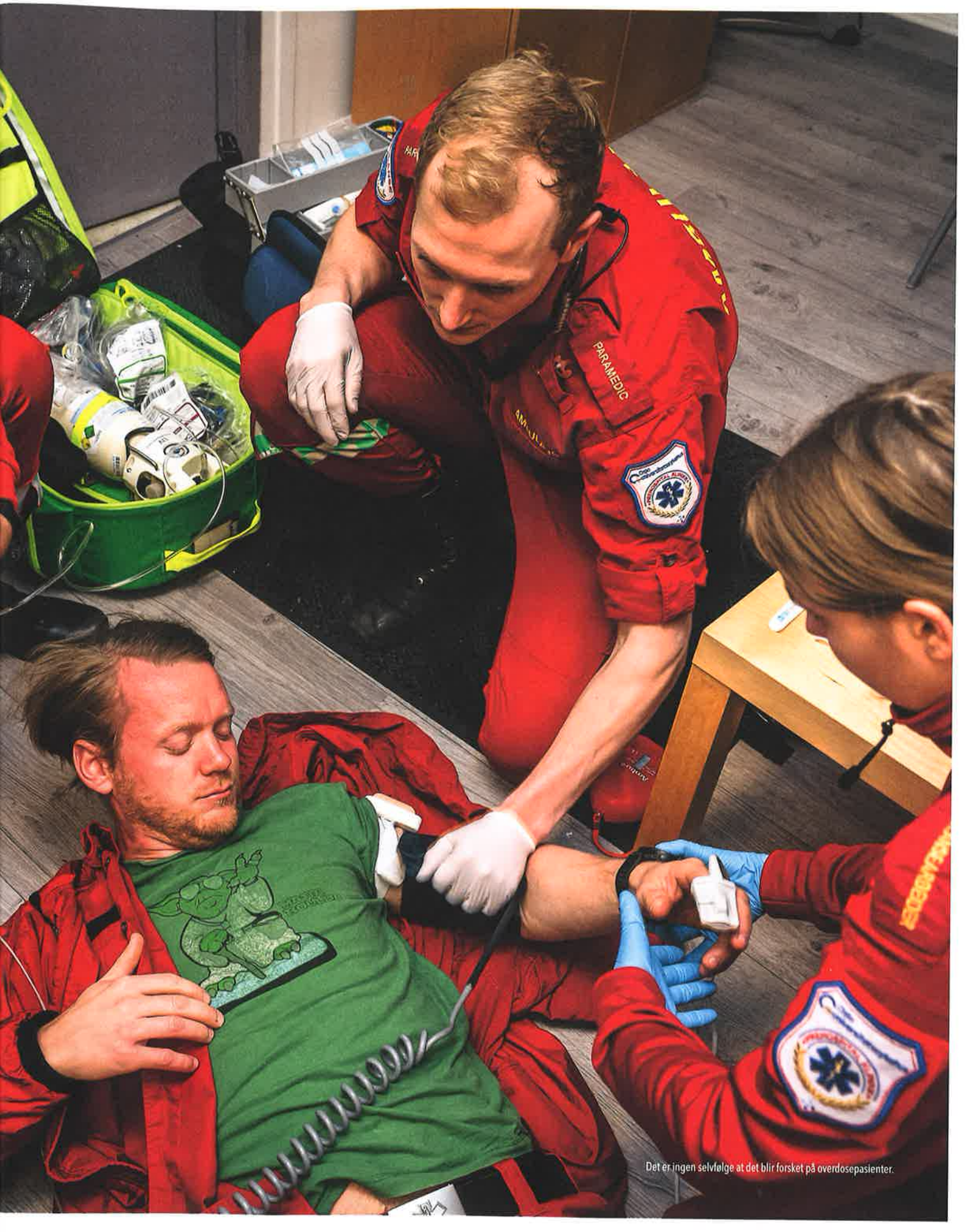
Unik norsk studie vil hjelpe overdoseofre

Nalokson har lenge vært brukt som motgift ved opioidoverdoser. Men ambulansepersonell kan enda ikke gi den i nesespray, som er mest skånsomt. Det kan snart endre seg, og vi ble med for å se hvordan.

Kari Bu Tommy Strømmen



Det er ingen selvfølge at det blir forsket på overdosepasienter.

En mann i tredveårene ligger utslått på en sofa med klærne på. Et team med ambulansefolk i røde dresser kommer inn i rommet. Monica Moen tar hånd om pasienten.

– Pulsen er godt følbar og regelmessig, men pusten er svak. Da ventilerer vi. Mistenker vi overdose?

Eivind Bru og Kristoffer Eppeland setter opp en monitor som blant annet viser puls, blodtrykk og oksygenmetning. Så setter den en maske på pasienten som gir ham pustehjelp.

– Respirasjonsfrekvens er under åtte. Glasgow Coma Scale er under tolv. Han lar seg ventilere greit. Er dere klare til å gi studiemedisin? spør Moen.

En pakke med nesespray, hetteglass, sprøyter, stoppeklokke og skjemaer blir åpnet. I pakker der nesesprayen inneholder nalokson, har hetteglasset til sprøyter kun sterilt saltvann, og omvendt. Pasienten får både nesespray og sprøyte.

– Heisann, er du våken? spør Moen mens hun rister litt i pasientens ene skulder. Han mumler at han har vondt i hodet. Han forstår ikke helt hva som har skjedd, men sier han har tatt heroin.

– Nå har vi prøvd noe nytt, fortsetter Moen. – Vi er med i en studie der vi gir motgiften din både i nesa og i armen. Vi vet ikke hvilken beholder som har nalokson i seg. Vi lurer på om du vil bli med i forskning der vi tar med navnet ditt?

– Hva er det dere forsker på?

– Om motgiften funker like bra i nesespray som i sprøyte.

– Ja, det burde vel gå bra.

Moen ber pasienten gjenta det hun har sagt. Han bekrefter at han har fått det med seg. Eivind Bru spør mannen hva han tenker seg videre. Han svarer at han har det ganske bra hjemme, men Bru synes han bør bli med på Legevakta eller Rusakuttmottaket. Moen gir ham et ark med mer informasjon om studien. Hun sier at han kan trekke seg senere hvis han vil, ved å melde fra på en nettside.

Arne Skulberg har observert hele seansen. Han er prosjektleder for en unik studie som NTNU i Trondheim har tatt ansvar for. Målet er å vise at like mange overdosepasienter kan puste selv etter ti minutter, enten de har fått nesespray med 1,4 milligram nalokson eller sprøyte med 0,8 milligram. Nalokson virker mot overdoser på opioider, det vil si stoffer som heroin, metadon, morfin, oksykodon og lignende. Studien foregår i ambulanser i Oslo og Trondheim, og involverer over 250 ambulansearbeidere.

Det vi har vært vitne til, var en øvelse på Ullevål sykehus. En ambulansearbeider spilte rollen som pasient. Han fylte kriteriene for en opioidoverdose: redusert bevissthet, redusert pust og små pupiller.

– Å se «narkoman» ut er ikke et kriterium for å diagnostisere overdose, sier Skulberg. – Vi vil oppleve overdoser utenfor den tradisjonelle gruppen. Jeg har vært på overdose hos kona til en politimann, og jeg vet om noen få tilfeller med eldre på sykehjem som har fått for mye smertestillende.

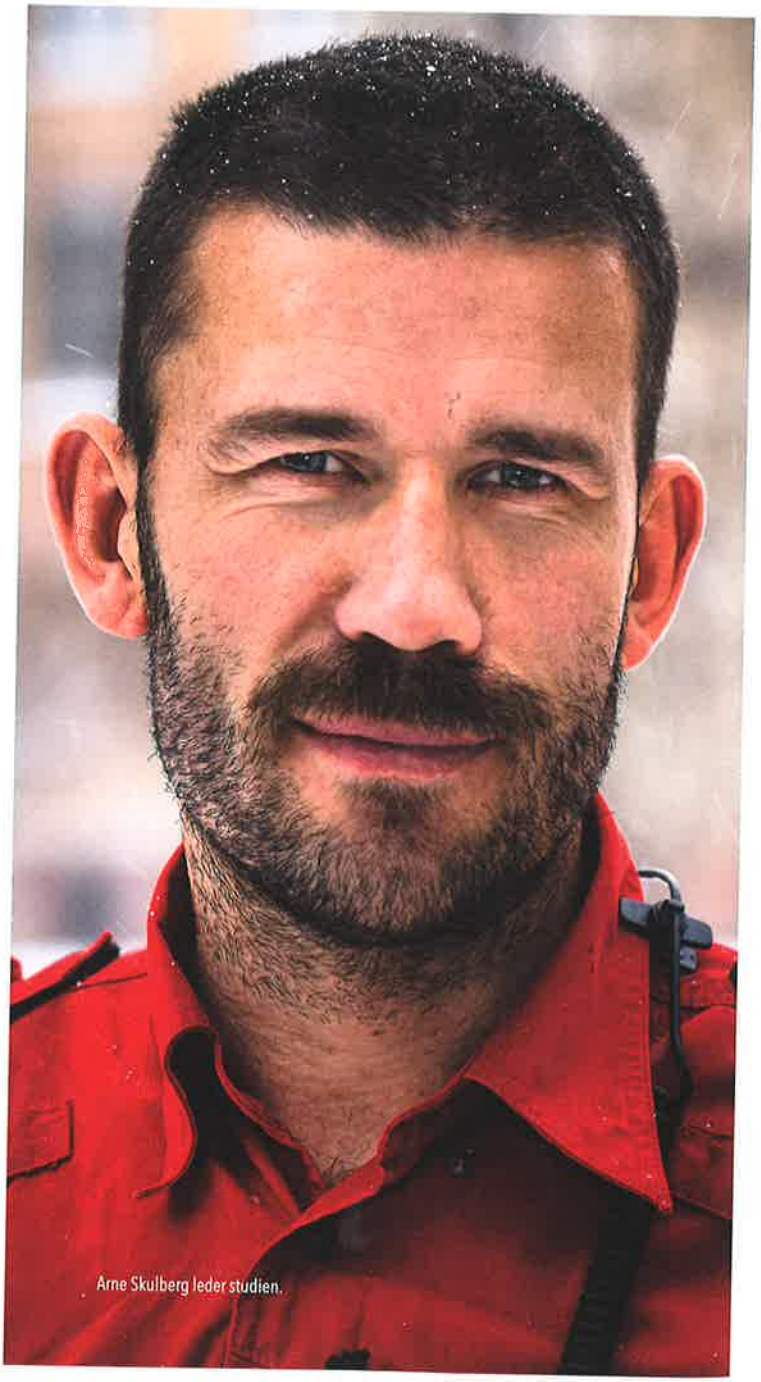
På sykehus eller lignende er det minimal sjanse for å få en overdose, selv om opioider brukes både mot smerter og ved bedøvelse og narkose. Men utenfor er det mer opioidlegemidler i omløp enn før. For mange er dette viktige medisiner. Som legemidler kan opioider ha navn som OxyContin og Tramadol. Noen tar for mye av medisiner de faktisk trenger, og folks respons på et legemiddel kan variere. Heroin rett fra gata er ikke lenger vanligste dødsårsak ved overdose. Flere dør av metadon og andre legemidler, gjerne i kombinasjon. Disse kan være forskrevet i Norge eller smuglet inn i landet.

– Det er økende bevissthet blant leger om at vi ikke skal ende opp som USA, med en opioidepidemi. Det er stadig mer kampanjer for riktig bruk av opioider i helsevesenet, sier Skulberg.

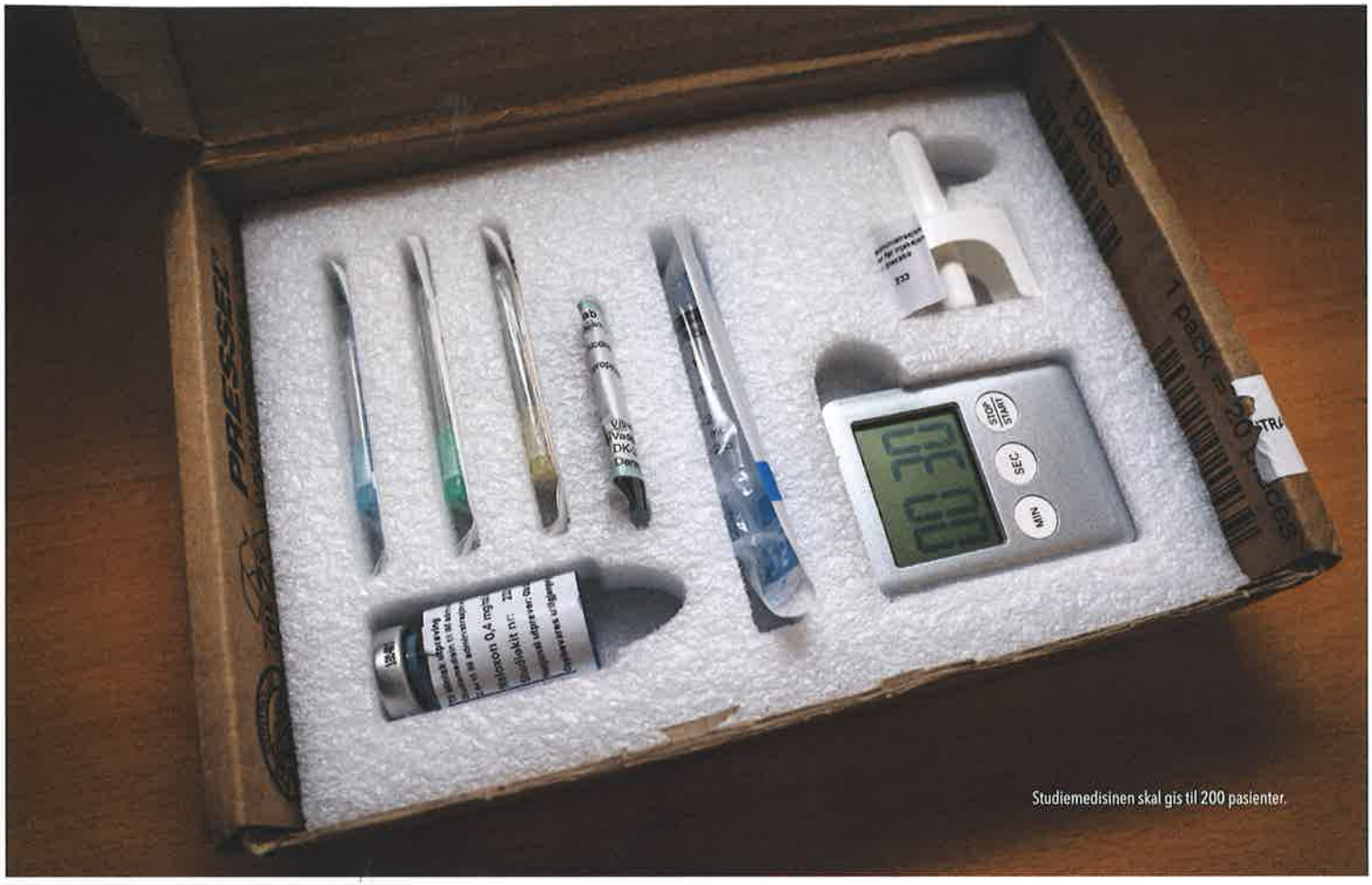
Naloksonstudien har foregått i halvannet år, og skal fortsette til 200 pasienter er inkludert. De aller fleste overdosepasienter blir ikke tatt med i studien. For det første vil forskerne bare ha med de aller sykeste. For det andre finns det en del kriterier som utelukker deltakelse. Blant annet blir du ikke med om du tar overdose i fengsel eller under arrest. Pasienter med hjertestans eller graviditet utelukkes. Det samme gjør personer under 18 år, men det er lenge siden ambulansen i Oslo har møtt mindreårige med opioidoverdoser. Snittalderen ved overdosene er 38 år.

I Norge har ambulanser brukt nalokson helt siden 1970-tallet, men bare i sprøyte. Nesesprayen brukes foreløpig kun som førstehjelp utenfor helsevesenet. Sprayen har flere fordeler fremfor en sprøyte med nalokson. Faren for stikkskader utelukkes, og motgiften bruker lengre tid på å virke, slik at pasienten får en mer behagelig oppvåkning med mindre abstinens. Derfor ønsker ambulansepersonell også å bruke den, men det er strengere krav når den skal brukes i helsevesenet.

– Vi vet at nesesprayen fungerer bra nok som førstehjelp, men vi vet ikke om den virker like bra som injeksjonen vår. Når vi finner pasienter som ikke vil bli med oss videre, må vi vite om det er trygt å forlate dem etter å ha gitt nesespray.

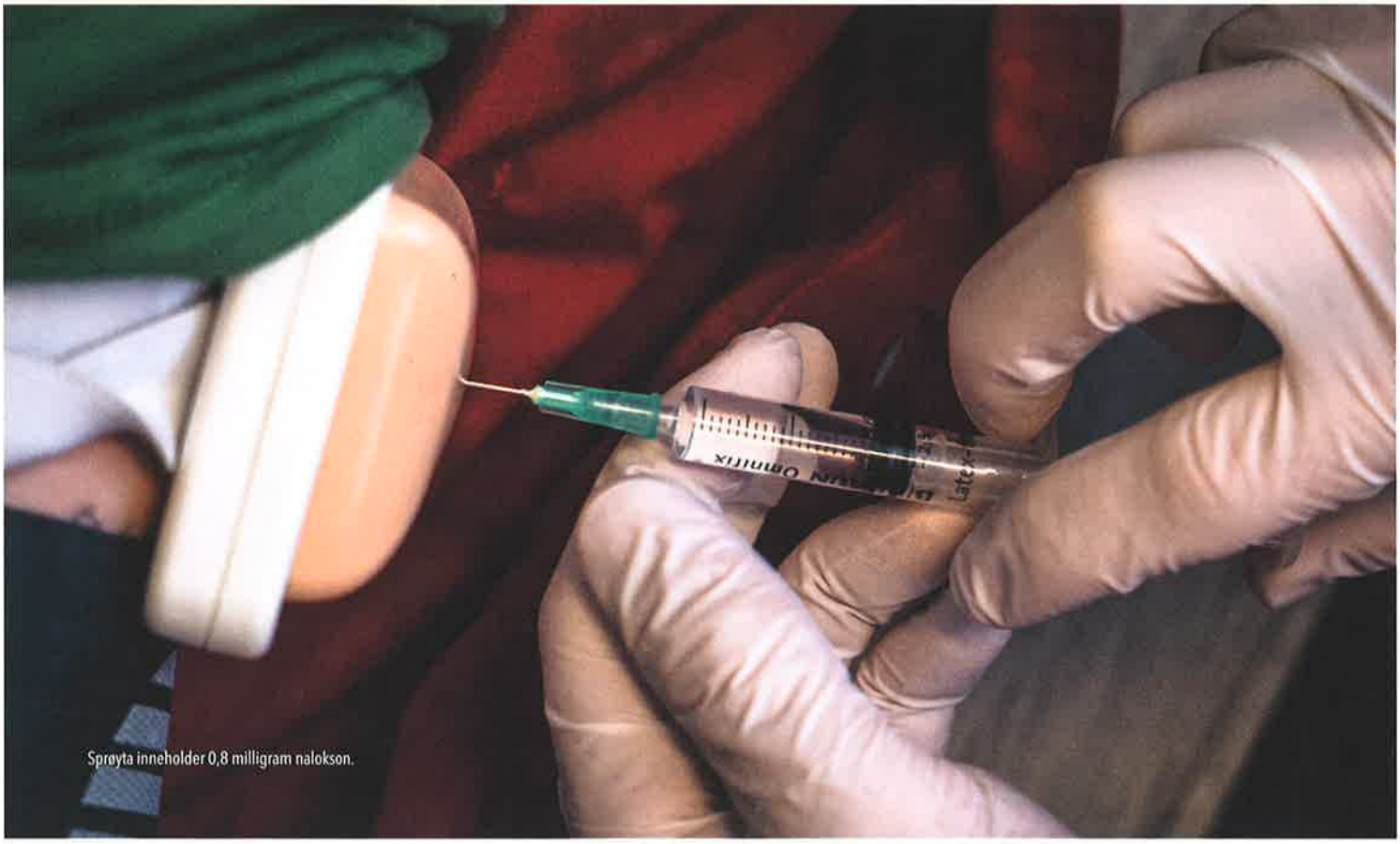


Arne Skulberg leder studien.



Studiemedisinen skal gis til 200 pasienter.

Puls, blodtrykk og oksygenmetning i blodet måles.



Sprøyta inneholder 0,8 milligram nalokson.

Skulberg minner om at alle skal ringe 113 når de møter noen med tegn til overdose. Selv om du gir førstehjelp med nalokson, er det ikke alltid nok hvis pasienten slutter å puste. Det kan trenges både ventilering og oppfølging. Når det gjelder forskning på nalokson, er Norge et foregangsland. Skulberg berømmer Helse Midt-Norge, som i mange år har finansiert slik forskning, og professor Ola Dale, som startet det hele. Det er ingen selvfølge at det blir gjort medisinske studier på overdosepasienter. Faktisk skjer det svært sjelden.

– Å bli forsket på er et gode som tidligere ikke har tilfalt ofre for overdose. Det skyldes både pasientenes ressurser, og hvilke legemidler industrien er interessert i å forske på. Når ingen studerer overdosepasienter, blir gruppen enda mer marginalisert. Her er det mye man kunne forsket på, for eksempel de andre helsebehovene til disse pasientene. Dette er en sårbar gruppe, så forskningen må ta særlige hensyn. Mange har ikke fast bopel, og må informeres på andre måter enn gjennom brev i posten, for eksempel.

Skulberg er forsiktig med å mene noe om ruspolitikk, men han ser en bedring i oppfølgingen av overdosepasienter.

– Ambulansetjenesten i Oslo har følt seg veldig alene i behandlingen av slike pasienter. I dag er det flere steder som tar dem imot. Det er viktig at det fins ulike tilbud for ulike pasienter. Nå skjer en tredjedel av alle opioidoverdoser i Oslo på Sprøyterommet. Der er det ingen som dør, og pasientene kan ofte bli værende der for videre oppfølging.

En annen fordel med Sprøyterommet, er at brukerne opplyser på forhånd om hva de skal innta. Dermed vet ambulansetjenesten hva slags stoff eller kombinasjon av stoffer de har tatt. Ambulansearbeider Monica Moen roser medarbeiderne på Sprøyterommet:

– Ofte er de godt i gang med å behandle pasienten før ambulansen kommer. Ellers er det mange overdoser på og rundt Oslo S. Vi prøver å gjøre det pasientene er mest fornøyde med. Vi gir ikke så mye nalokson at de får unødige abstinenser. Vi pleier ikke å ta vekk hele rusen, for da blir det fort svetting, skjelving og sinne. Noen overdoser er selvmordsforsøk. Da kan pasientene bli litt sinte når de overlever.

Moen gjør seg klar for en ny øvelse som skal forberede ambulansepersonell på naloksonstudien. Denne gangen spiller hun pasienten. Hun legger seg i en seng på et sted som skal forestille Adamstuen omsorgssenter. Overdoser skjer også på slike steder, der rusavhengige bor på eget rom. Denne gangen er det usikkert hva som har skjedd med pasienten. Ambulanseteamet blir tilkalt, og Eivind Bru trår til.

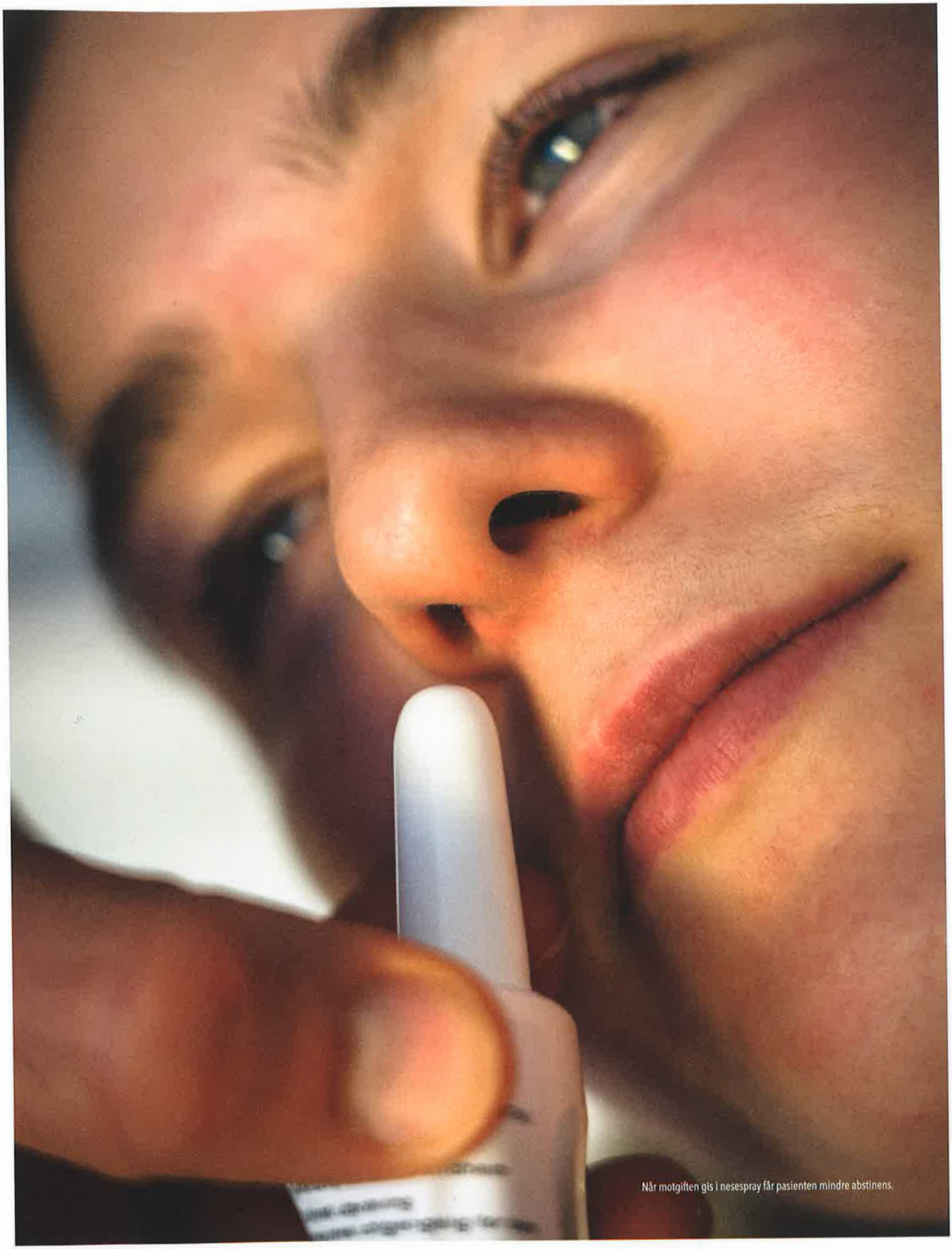
– Da har vi kontroll på luftveiene. Ikke noe helsepersonell har gitt opioider her. Er det noe historikk på pasienten?

Bru ringer Akuttmedisinsk kommunikasjonssentral (AMK). De kan fortelle at pasienten var på Sprøyterommet den 5. mars i fjor. Bru takker for informasjonen og melder fra til Lovisenberg sykehus om tilstanden.

– Pasienten ble observert før hun gikk og la seg. Hun er sløv og sluttet å puste en gang, så vi har maske-bag ventilert og gitt studiekit med medisin. Etter ti minutter gikk det over i genrealiserte kramper, ser det ut som. Etter fem milligram Stesolid intravenøst sluttet krampene. Fortsatt er det ingen respirasjon, men vitalia er fine.

Pasienten fyller kriteriene for overdose, men det er ikke sikkert hun har tatt en likevel. Det er viktig å ikke bli så opphengt i studiemedisinen at man slutter å tenke på resten av det medisinske fagfeltet, sier Skulberg. Kvinnen kan ha hatt et epileptisk anfall. De små pupillene kan skyldes at hun går på metadon. Når man jobber i livredningsbransjen, er det farlig å være forutinntatt.

Mer informasjon om studien finner du på nettadressen nalokson.no



Når motgiften gis i nesespray får pasienten mindre abstinens.

Institution: Oslo University Hospital and University of Oslo, OUS_UIO
Administrative unit: Division of Prehospital Services, PRE
Title of case study: The Norwegian Cardiac Arrest Registry as impact of cardiac arrest research and as prerequisite for further research and improvement
Period when the underpinning research was undertaken: 2003-2020
Period when staff involved in the underpinning research were employed by the submitting institution: 2003 – 2023, see list below
Period when the impact occurred: 2015-continuing

1. Summary of the impact

PRE has been studying out-of-hospital cardiac (OHCA) focusing on identifying possibilities for improvement throughout the chain of survival for cardiac arrest. Most OHCA patients die. Improving survival requires exploring new treatments, implementing scientific evidence, and addressing gaps in practice. The establishment of the cardiac arrest registry in Norway has provided valuable data for improvement processes, aiming to enhance cardiac arrest management and treatment, reducing mortality rates through research and quality efforts.

Our research has identified areas for improvement that has influenced international treatment guidelines, as well as national regulatory work. This has led to the establishment of the Norwegian AED-registry, increase in AED usage before ambulance arrival, evidence base for ethical challenges, as well as improved and timely recognition of cardiac arrest. All this is monitored through the OHCA registry.

2. Underpinning research

Cardiac arrest is a sudden collapse caused by extreme circulatory failure, such as pathophysiological processes including trauma, infection, or intoxication, but most often the aetiology is cardiac conditions such as acute coronary ischemia or arrhythmic diseases. When the heart stops ischemia quickly induces cell and organ death that becomes irreversible after few minutes. The brain is the most vulnerable organ, but by creating some circulation of oxygenated blood with chest compressions and ventilation (cardiopulmonary resuscitation; CPR), the process of death can be delayed until the heart can regain its function. Without treatment, cardiac arrest is fatal.

In Norway, approximately 40,000 deaths occur annually, with over 3,000 individuals receiving CPR from ambulance personnel. Through resuscitation and skilled care, around 400 lives are saved each year. (1) However, there is a need for further improvement in saving lives. This may be achieved through exploring new treatments (2) and implementing scientific evidence into society and healthcare. (3-4) Our research group has been involved in both strategies, as neither one is sufficient on its own.

Research into out-of-hospital cardiac arrest in the Oslo area has been ongoing for over 40 years. Prehospital anaesthesiologists in the physician-manned ambulance have played a crucial role in identifying research questions, translating them into animal experiments, and testing them in clinical trials. (2) Research at local, national, and international levels has demonstrates low and variable survival rates for cardiac arrest. (1) This indicates room for improvement throughout the entire care process. Identified gaps in practice have led to research and improvements in emergency medical communication centers (EMCC) (3), layperson training, (4) availability of defibrillators, resource allocation practices, (3) ambulance treatment, (2) and patient flow and care after resuscitation.

Our research group has provided evidence of potential improvements and the possibility for continuous measurement of improvement initiatives in EMCC (rate of cardiac arrest recognition, delay to first chest compression). (3) Ambulance dispatch (ambulance response interval) and patient treatment (effect of rapid defibrillation, effect of IV-access and medications, quality of CPR, pauses, chest compressions, ventilation, bypass-protocols to achieve more rapid access to invasive cardiac laboratories, and therapeutic hypothermia). (2)

In 2013, Norway established the world's first mandatory cardiac arrest registry, collecting data from all nineteen ambulance services. Since 2016, complete coverage has been achieved from ambulance services and hospitals receiving resuscitated patients. From 2021, nearly all hospitals also report in-hospital cardiac arrests, and thirteen of sixteen emergency medical communication centers systematically audit their cardiac arrest voice logs to capture quality indicators for the registry. (1)

In order for any registry to be valuable for improvement processes, it is crucial to ensure that the data collected is complete, accurate, and up-to-date. Our cardiac arrest registry has achieved a high level of inclusion and variable completeness, thanks to the implementation of strict protocols and routines that uphold its validity. (5) To address the barrier of timely data entry to the registry, we introduced collection of patient-reported outcome measures (PROMs) from surviving patients, which has significantly expedited the data entry process, improving the timeliness of the registry.

Participating researchers, positions, dates:

Lars Wik, senior researcher in the group from 2003
Jo Kramer-Johansen, PhD-student from 2003-2007, researcher from 2008-2013, professor and scientific head of the cardiac arrest registry from 2013
Theresa M Olasveengen, PhD-student from 2006-2009, researcher from 2011-2013
Camilla Hardeland, PhD-student 2012-2017, researcher 2017-2023
Andres Neset, Medical School Research Program 2008-2011, PhD-student 2012-2013
Tonje Birkenes, PhD-student 2009-2014
Ingvild Tjelmeland, Head of the cardiac arrest registry from 2010, PhD-student from 2019
Kristin Alm-Kruse, Master-student 2013-2014, PhD-student from 2017-2024
Astrid Karina Valås Harring, Master-student from 2016-2018
Polina Petrovich, Medical School Research Program, 2019-2020
Inga Katherina Kelpanides, PhD student from 2022.

3. **References to underpinning research:**

(1) Tjelmeland IBM, Alm-Kruse K, Andersson LJ, Bratland S, Hafstad AK, Haug B, Langørgen J, Larsen AI, Lindner TW, Nilsen JE, Olasveengen TM, Soreide E, Skogvoll E, Kramer-Johansen J. Cardiac arrest as a reportable condition: a cohort study of the first 6 years of the Norwegian out-of-hospital cardiac arrest registry. BMJ Open. 2020 Jul 8;10(7):e038133. doi: 10.1136/bmjopen-2020-038133. PMID: 32641339; PMCID: PMC7348469.

(2) Olasveengen TM, Sunde K, Brunborg C, Thowsen J, Steen PA, Wik L. Intravenous drug administration during out-of-hospital cardiac arrest: a randomized trial. JAMA. 2009 Nov 25;302(20):2222-9. doi: 10.1001/jama.2009.1729. PMID: 19934423.

(3) Hardeland C, Skåre C, Kramer-Johansen J, Birkenes TS, Myklebust H, Hansen AE, Sunde K, Olasveengen TM. Targeted simulation and education to improve cardiac arrest recognition and

telephone assisted CPR in an emergency medical communication centre. Resuscitation. 2017 May;114:21-26. doi: 10.1016/j.resuscitation.2017.02.013. Epub 2017 Feb 21. PMID: 28236428. Hardeland (EMCC)

(4) Neset A, Birkenes TS, Furunes T, Myklebust H, Mykletun RJ, Odegaard S, Olasveengen TM, Kramer-Johansen J. A randomized trial on elderly laypersons' CPR performance in a realistic cardiac arrest simulation. Acta Anaesthesiol Scand. 2012 Jan;56(1):124-31. doi: 10.1111/j.1399-6576.2011.02566.x. Epub 2011 Oct 19. PMID: 22092097.

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4. **Details of the impact**

Our research of out-of-hospital cardiac arrest has had an impact on **treatment guidelines** internationally for improved training (A), recognition that **quality of CPR** is an important factor for survival, and possible confounder in clinical interventional trials (B), increased awareness of the **important role of EMCC in recognition and CPR instructions** (C). Others have described the utilisation of lay people or other emergency services to bring easy-to-use defibrillators to the patient even before the ambulance arrives, leading to the start of **the Norwegian AED-registry** (D) and regulatory work to formalize all aspects of non-medical personnel aiding the emergency medical response (E). The complexity of all possible interventions in a country with huge differences in geography, climate, and demography make monitoring and registering this condition a natural follow-up.

Research of out-of-hospital cardiac arrest always aims to improve survival with good function and quality of life. Out-of-cardiac arrest is a dreaded and dramatic condition which no-one survives without treatment started within a very limited timeframe. Each study and project will at best be a small contribution, but the development of **a national, population-based registry provides the fundamental prerequisite for further improvement of care and outcomes**.

Our research describing the registry and proving its quality and completeness, makes it an important member of the family of Norwegian medical quality registries. Unlike most such registries, the Cardiac Arrest Registry considers the whole system of care in the patient perspective – from alarming the EMCC, recognition and encouragement to start CPR, via ambulance and hospital treatment, to the follow-up and the patients' own perception of health-related quality of life.

From 2017 to 2022 a **nation-wide collaborative effort** aimed to address the early phase of life-threatening conditions, including cardiac arrest by coordinating education and training across different non-governmental organisations, schools, and workplaces. The possibility to measure effects by registries was important for the choice of conditions.

The strategy (F) of this collaborative effort described how improving the public preparedness could improve outcome for four life-threatening emergencies. Many of the planned actions were more based on stakeholders' interests than thorough analyses of gaps in treatment and realistic aims. (G) Nevertheless, the impact of this collaborative effort has been better communication amongst the non-governmental organisations involved in first aid, professional services and user/patients.

A commonality of the successful projects seems to be governmentally mandated changes in public structures and regulations, e.g., as seen for the public AED-registry and in the formalisation of use of other emergency services to improve local preparedness for medical emergencies. We will continue to monitor the effect of these projects through the registry. We have seen an increase in the proportion of out-of-hospital cardiac arrest patients who have an AED attached before ambulance arrival from 13 to 16 % during the years 2017-2022.

Ethical challenges are common in cardiac arrest treatment. Most patients are elderly, and many are at the end of their natural life. This creates ethical dilemmas of patient autonomy in acute settings, resource allocation to futile cases, and availability of medical information and advanced care decisions to front line personnel. A study from our registry confirms that some patients receive resuscitation efforts although previous medical and ethical decisions have been made to not provide resuscitation in case of cardiac arrest (DNAR). The same study also demonstrated that age or residential status (home or healthcare institutions) do not predict survival with good neurologic outcomes. This publication caused widespread debate among care providers and increased awareness of possibilities to share and make critical decisions known in emergency situations. (H)

Cardiac arrest is a highly time-critical condition where the EMCCs are essential key-holders to recognise and initiate telephone-guided CPR within the shortest possible timeframe, in order to increase the likelihood for survival with good neurologic results. One of our studies increased the ability to recognise cardiac arrest, and at the same time decrease the time to recognition in Norwegian EMCCs. The collaboration between European registries further enabled comparison between countries, and discovered ample grounds for improvement both for recognition and time to recognition, based on the method developed. (C)

5. Sources to corroborate the impact

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(B) Perkins GD, Jacobs IG, Nadkarni VM, Berg RA, Bhanji F, Biarent D, Bossaert LL, Brett SJ, Chamberlain D, de Caen AR, Deakin CD, Finn JC, Gräsner JT, Hazinski MF, Iwami T, Koster RW, Lim SH, Huei-Ming Ma M, McNally BF, Morley PT, Morrison LJ, Monsieurs KG, Montgomery W, Nichol G, Okada K, Eng Hock Ong M, Travers AH, Nolan JP; Utstein Collaborators. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update of the Utstein Resuscitation Registry Templates for Out-of-Hospital Cardiac Arrest: a statement for healthcare professionals from a task force of the International Liaison Committee on Resuscitation (American Heart Association, European Resuscitation Council, Australian and New Zealand Council on Resuscitation, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Southern Africa, Resuscitation Council of Asia); and the American Heart Association Emergency Cardiovascular Care Committee and the Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation. Circulation. 2015 Sep 29;132(13):1286-300. doi: 10.1161/CIR.0000000000000144. Epub 2014 Nov 11. Erratum in: Circulation. 2015 Sep 29;132(13):e168-9. PMID: 25391522.

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(D) The Norwegian AED registry with overview over registred AED's in Norway (in Norwegian)

(E) Helsedirektoratet (2023). Ny rettleiar for akutthjelparar. Oslo: Helsedirektoratet. (National Guidelines for the Emergency Helper Program) https://www.helsedirektoratet.no/nyheter/ny-veileder-for-akutthjelpere

(F) Saving lives together in sport (in Norwegian)

(G) Saving lives together– a master thesis evaluating the achievement of the campaigns goals

(H) Harring AKV, Kramer-Johansen J, Tjelmeland IBM. Resuscitation of older adults in Norway; a comparison of survival and outcome after out-of-hospital cardiac arrest in healthcare institutions and at home. Resuscitation. 2023 Aug;189:109871. doi: 10.1016/j.resuscitation.2023.109871. Epub 2023 Jun 14. PMID: 37327851.

Oslo university hospital (OUS), The Division of Technology and Innovation (TIK). Case 1

Institution: OUS
Administrative unit: TIK
Title of case study: OSLO-COMET
Period when the underpinning research was undertaken: 2012-2016
Period when staff involved in the underpinning research were employed by the submitting institution: 1996-dd (PI, Edwin) 2011-dd (co-PI, Fretland)
Period when the impact occurred: 2018-2024

1. **Summary of the impact** (indicative maximum 100 words)

As the first randomized controlled trial (RCT) in the field, OSLO-COMET contributed to worldwide implementation and an increased level of evidence of minimally invasive liver surgery for malignant liver tumours. The study found that minimally invasive liver surgery causes less complications and pain to patients, has improved quality of life, and is cost-effective, compared to the traditional open surgery. The main impact was achieved in 2019 when the results were presented as part of the official press release program at the annual meeting of the American Society of Clinical Oncology (ASCO), with 40 000 delegates including a broad media coverage.

2. Underpinning research (indicative maximum 500 words)

OSLO-COMET was the first randomized controlled trial to compare laparoscopic (keyhole) liver surgery to the standard open liver surgery. The trial was performed at Oslo University Hospital between February 2012 and February 2016, and provided data from the entire 3 million population of South-East Norway.

The primary outcome of OSLO-COMET was postoperative complications. The study used a value-based health care approach, examining a range of secondary outcomes, including health related quality of life, health economy, pain management, long term recurrence and survival.

The key findings of OSLO-COMET was that laparoscopic liver surgery had a lower rate of postoperative complications [1], improved quality of life [2], and was cost-effective, compared to open liver surgery [1]. The long-term cancer results were similar for both methods, with 5-year overall survival of 57% and 56%, respectively[3]. The study got a significant impact in medical journals, press and social media, with the selection to the official press conference at ASCO 2019 as the most important impact event[4]. Following the study, both training and use of laparoscopic liver surgery increased worldwide.

OSLO-COMET was led by professor Bjørn Edwin, head of clinical research at the Intervention Centre (IVC). Dr. Åsmund Avdem Fretland was employed at IVC as a Ph.D. candidate from February 2012 and was responsible for the daily operations during the entire study period. Dr. Vegar Dagenborg (Ph.D. candidate) participated in patient inclusion from 2014, while Dr. John Hausken (researcher) and Gudrun M.W. Bjørnelv (Ph.D. candidate) collected data for pain management [5]and health economy, respectively. The study was assessor blinded, meaning that the patients and hospital personnel were aware of what operation was used while the person registering the complications was not. The core study group consisted of personnel from the Intervention Centre, the Department of Hepato-Pancreato-Biliary surgery, the Division of Emergency and Critical Care, Centre of Biostatistics and Epidemiology, Oslo University Hospital, and the Institutes of Health and Society, and Clinical Medicine, University of Oslo.

Until 2012, most experts considered that a RCT of laparoscopic vs open liver surgery would not be possible to perform. A main impact of OSLO-COMET was that this deadlock was broken, and a total of 4 RCTs have been published since, and a similar number in the closely related field of pancreas surgery. Thus, it paved way for the creation of level 1 evidence for the use of laparoscopic liver surgery, supporting its widespread implementation worldwide. The research group has participated in two of the new RCTs and is currently leading a new RCT exploring ablation (an even less invasive treatment method) versus laparoscopic resection.

Liver surgeons increasingly use a liver parenchyma sparing technique when removing liver cancer. An ongoing impact of OSLO-COMET is that the data collected has been made available for research on artificial intelligence. The researchers have focused on two topics, prognostic AI (clinical data, images and genomics), and AI-assisted surgical planning. The latter work has resulted in a startup, Holocare, that recently received CE mark for their liver surgery planning application.

- Names of the key researchers and what positions they held at the administrative unit at the time of the research (where researchers joined or left the administrative unit during this time, these dates must also be stated).
- Any relevant key contextual information about this area of research.

2. **References to the research**

1. Fretland, Å. A. *et al.* Laparoscopic Versus Open Resection for Colorectal Liver Metastases: The OSLO-COMET Randomized Controlled Trial. *Annals of Surgery* **267**, 199–207 (2018).

2. Fretland, Å. A. *et al.* Quality of life from a randomized trial of laparoscopic or open liver resection for colorectal liver metastases. *British Journal of Surgery* **106**, 1372–1380 (2019).

3. Aghayan, D. L. *et al.* Long-Term Oncologic Outcomes After Laparoscopic Versus Open Resection for Colorectal Liver Metastases: A Randomized Trial. *Ann Intern Med* (2020) doi:10.7326/m20-4011.

4. Fretland, Å. A., Aghayan, D., Edwin, B. & Group, O.-C. T. Long-term survival after laparoscopic versus open resection for colorectal liver metastases. *J Clin Oncol* **37**, LBA3516–LBA3516 (2019).

5. Hausken, J. *et al.* Intravenous patient-controlled analgesia versus thoracic epidural analgesia after open liver surgery: a prospective, randomized, controlled, noninferiority trial. *Annals of Surgery* **270**, 193–199 (2019).

4. Details of the impact (indicative maximum 750 words)

Randomized controlled trials are difficult to perform in surgery, due to the individual nature of many surgical procedures, and the difficulty of standardizing skill dependent interventions. Most high impact RCTs are based on the comparison of drugs, where delivery of interventions can be standardized and placebo controlled. For these and other reasons, development in surgery is more often based on evolution of techniques rather than high level evidence. Because of this, the impact of surgical RCTs can be large.

The primary publications from OSLO-COMET reached a high attention score (98th percentile attention score at Altmetric) and is heavily cited (633 citations). The long-term outcome data received massive publicity following the press conference at ASCO 2019. Following this the diffusion of laparoscopic liver surgery increased further worldwide [1], including the formation of the International Laparoscopic Liver Surgery association, that currently has members from 86 countries.

Regarding the societal impact, a 12% points reduction in postoperative complications and a 2 days reduction in hospital stay is significant, given that liver surgery is increasingly performed as a consequence of improved diagnostics and oncologic treatment. Similarly, a quality of life improvement lasting up to 4 months after surgery will have an impact of patient's ability to go back to work, care for family members and perform other daily activities.

As laparoscopic liver surgery now expands from developed to developing countries, this impact can be strengthened as patients undergoing liver surgery in developing countries will be younger and more likely to be caregivers.

The Intervention Centre has since the 1990s run teaching courses in laparoscopic liver surgery, both locally and internationally, and surgeons more than 100 surgeons have been trained. International courses have been held in Hamburg and Saarbrucken (Germany), Turin (Italy), Uppsala (Sweden) Yerevan (Armenia), Moscow (Russia), Vilnius (Lithuania), Oulu (Finland) amongst others.

The final impact of OSLO-COMET is contribution to the development of artificial intelligence research in liver cancer. The most prominent impact is the creation of HOLOCARE AS, a startup that currently holds CE mark and awaits FDA approval for its application for liver surgery planning. The software was developed in parts on data from OSLO-COMET. Further research is ongoing, its impact underlined by two successful EU grant applications (HiperNav (Horizon 2020) and HoloSurg (Horizon 2023).

Translational research projects were also performed, as a study of activation of the immune system following the two operations, and a biobank study examining genetic alterations in tumours. The study has contributed to a range of research projects, at the moment counting 13 PhDs (9 completed) in and 5 Post Docs in total.

5. Sources to corroborate the impact (indicative maximum of ten references)

1.Ratti, F. *et al.* Ten years of Italian mini-invasiveness: the I Go MILS registry as a tool of dissemination, characterization and networking. *Updat. Surg.* **75**, 1457–1469 (2023).

Oslo university hospital (OUS), The Division of Technology and Innovation (TIK)

Case 2

Institution: OUS
Administrative unit: TIK
Title of case study: Technology for Surgical Planning and Navigation
Period when the underpinning research was undertaken: 2012 to 2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2012 to 2022
Period when the impact occurred: 2013 to 2022

1. Summary of the impact (indicative maximum 100 words)

Our developments on cutting-edge technologies in surgery planning and navigation, highlighted by automatic patient-specific models and innovative mixed reality tools, can dramatically transform surgical practices, and improve surgical precision and patient outcomes. Moreover, our mixed reality-based navigation methods can potentially improve diagnostic accuracy and provide better learning conditions for surgeons in training. All these new advancements led to the establishment of HoloCare AS, representing a landmark collaboration between the public and private sectors, setting new standards in medical technology. Finally, HoloCare AS has obtained a CE mark for its liver surgery planning, demonstrating a tangible, regulated application of these innovations.

2. Underpinning research (indicative maximum 500 words)

The research unit's journey in surgical planning and navigation came out of a long-term close collaboration between laparoscopic surgeons and technology researchers at The Intervention Centre (IVS) already back from early 2000. It began with one of our laparoscopic surgeons who requested a 3D liver model with tracked instruments like in a navigation system. In 2012, the Oslo-CoMet study (NCT01516710) began to compare laparoscopic and open liver resection outcomes for colorectal metastases, providing foundational research data invaluable for further technological research. The technical development in the period began with novel semi-automatic methods for 3D patient-specific model (PSM) creation, which was a significant advancement over traditional techniques and offered greater speed and efficiency [1]. Later the unit developed a novel surgical planning method for liver resection using 3D PSM using deformable surfaces, marking a substantial progression in surgical planning techniques [2]. These developments were achieved and also implemented in opensource software 3DSlicer (www.slicer.org) through multiple international (IIIOS (EU: 238802)) and national projects (HepaNavi (HSØ: 2014117), NorMIT (RCN: 226140, www.normit.no) during the period 2012-2019. The NorMIT financed new hybrid operating theatres with DynaCT (Artis Pheno) and intra-operative CT at the unit. Thus, establishing a new umbrella agreement with SEIMENS. After identifying major bottlenecks in automated surgery planning and navigation for minimally invasive surgeries, the unit coordinated the HiPerNav Project (EU: 722068, www.hipernav.eu), where SEIMENS is also a partner, during 2016-2021, to develop methods toward this goal. The wide utilization of AI in image analysis led to the development of methods for automatic 3D PSM creation [3]. Through the project, the unit could also emphasize the importance of intraoperative imaging for accurate surgical navigation

particularly in minimally invasive surgery [4]. The developments in 3D PSM creation, planning, and navigation led to the need for innovative visualization methods leading to the development of mixed reality-based solutions. Initially through innovation projects during 2017-2019 (HoloViz & HoloNav (HSØ innovation)), the unit pioneered on first mixed reality-based surgery planning solutions for the liver and heart together with the contractor company SopraSteria [5]. Furthermore, novel tools were developed for diagnostic and surgical navigation using mixed reality, enhancing both diagnostic accuracy and surgical precision [6]. The innovations in mixed reality led to the HoloCare Cloud project (RCN: 296570, Project Owner: SopraSteria, Project lead: IVS), during 2019-2023, which involved the clinical validation of new mixed reality solutions and the development of cloud-based AI solutions for 3D PSM model creation. The research efforts culminated in the creation of HoloCare AS in 2019 - a public-private partnership that integrated the results of the HoloCare Cloud project. Later, HoloCare AS obtained the first CE-marked medical product for liver surgery planning. This venture marked a significant milestone in practical application of research.

Key Researchers:
Ole Jakob Elle (Leader of the Section for Technology Research(2012-...))
Bjørn Edwin (Project manager (2012), Leader of the Section for clinical research (2013-...))
Åsmund Fretland (PhD(2012-18),ConsultantSurgeon(2018-...))
Rahul Prasanna Kumar (PhD(2010-2014)-PostDoc(2015-2019)-Researcher(2019-2023)-SeniorEngineer(2023-...))
Rafael Palomar (SoftwareDeveloper(2010-2013)-PhD(2013-2016)-Researcher(2016-2018)-ResearchScientist(2018-…))
Egidijus Pelanis (PhD(2017-2023),SpecialAdvisor(2023-...))
Andrea Teatini (PhD(2017-2020))
Pravda Jith Ray(PhD(2017-2021))

3. References to the research (indicative maximum of six references)

[1] R. P. Kumar, F. Albregtsen, M. Reimers, B. Edwin, T. Langø, and O. J. Elle, 'Three-Dimensional Blood Vessel Segmentation and Centerline Extraction based on Two-Dimensional Cross-Section Analysis', *Ann Biomed Eng*, vol. 43, no. 5, pp. 1223–1234, May 2015, doi: 10.1007/s10439-014-1184-4.

[2] R. Palomar, F. A. Cheikh, B. Edwin, Å. Fretland, A. Beghdadi, and O. J. Elle, 'A novel method for planning liver resections using deformable Bézier surfaces and distance maps', *Computer Methods and Programs in Biomedicine*, vol. 144, pp. 135–145, Jun. 2017, doi: 10.1016/j.cmpb.2017.03.019.

[3] P. J. R. Prasad *et al.*, 'Numerical Evaluation on Parametric Choices Influencing Segmentation Results in Radiology Images—A Multi-Dataset Study', *Electronics*, vol. 10, no. 4, p. 431, 2021.

[4] A. Teatini *et al.*, 'The effect of intraoperative imaging on surgical navigation for laparoscopic liver resection surgery', *Sci Rep*, vol. 9, no. 1, pp. 1–11, Dec. 2019, doi: 10.1038/s41598-019-54915-3.

[5] R. P. Kumar *et al.*, 'Use of mixed reality for surgery planning: Assessment and development workflow', *Journal of Biomedical Informatics: X*, vol. 8, p. 100077, Dec. 2020, doi: 10.1016/j.yjbinx.2020.100077.

[6] A. Teatini, R. P. Kumar, O. J. Elle, and O. Wiig, 'Mixed reality as a novel tool for diagnostic and surgical navigation in orthopaedics', *Int J CARS*, vol. 16, no. 3, pp. 407–414, Mar. 2021, doi: 10.1007/s11548-020-02302-z.

4. Details of the impact (indicative maximum 750 words)

The research journey in surgical planning and navigation has been marked by significant achievements and recognitions, each contributing materially to the field's transformation.

The semi-automatic method for PSM creation was recognized with the Inven2 Idea award in 2013, highlighting its breakthrough in speeding up PSM creation and enabling a more efficient approach to patient care. Later the novel liver surgery planning method was released as an extended module in 3DSlicer, making it accessible worldwide [a]. This open-source availability has democratized access to advanced surgical planning tools, allowing medical professionals globally to benefit from this innovation.

Later the HiPerNav project pushed the research frontier in AI for image analysis, and soft-tissue navigation for minimally invasive surgery, leading to significant developments in the domain. The project led to 13 finalized PhDs, 24 peer-reviewed articles, 22 conference proceedings, 3 book chapters, 2 public datasets, and also multiple popular science dissemination fields [b].

The advancements resulted in the need for improved 3D visualization tools, leading to significant progress in the field of mixed reality for medicine. This development has been recognized and honored with prestigious awards such as the Microsoft Global Innovation Award 2017 and the Computer World E-Health Award 2017 [c]. Furthermore, it has received an Inven2 Idea award, highlighting the revolutionary nature of the research.

The novel developments utilizing mixed reality not only garnered acclaim but also directly influenced the medical field. These advancements set the stage for more immersive and precise surgical planning and navigation, significantly enhancing both the surgeon's capabilities and patient outcomes. The culmination of these efforts through the HoloCare Cloud project led to the formation of HoloCare AS (www.holocare.com) in 2019 [d]. This step marked a pivotal moment in transitioning from research to practical application, allowing for the direct utilization of these groundbreaking results in the healthcare industry.

1. Beneficiaries of the Research:
    - Medical Professionals: Surgeons and healthcare practitioners have gained advanced tools, enhancing their capabilities in surgical planning and execution.
    - Patients: Benefited from more personalized, precise, and safer surgical interventions.
    - Global Medical Community: With tools like the 3D Slicer module and products from HoloCare AS, the global medical community has access to state-of-the-art surgical planning technology.
2. Evidence of Impact:
    - Awards and Recognition: The various awards and honors received by the research projects testify to their significance and impact in the field.
    - Global availability: By making research results available through open-access publications and as open-source software, researchers and users globally can further develop methods.
    - Commercial Exploitation and Success: The collaboration established with SEIMENS resulted in a successful EU project and helped start other projects, such as AbdoNav, with a private-public partnership. Also, the formation of HoloCare AS demonstrates the commercial viability and real-world application of the research. In 2023, HoloCare AS achieved a remarkable milestone by receiving the first CE-marked medical application for mixed reality-based liver surgery planning, paving the way for a new era.
3. Collaborative Impact:

- The impacts are a result of multiple research projects with some having larger collaborative efforts by national and international collaborators, including industrial collaborators, from our network, with the research unit (IVS) significantly contributing to advancements.
- HiPerNav was an Innovative Training Network (ITN) funded through a Marie Skłodowska-Curie grant, with 9 beneficiaries and 5 partner organizations across the EU. There were 14 fully funded and 2 partially funded Ph.D.s working on the project [e].
- HoloCare Cloud was a national project funded by the Research Council of Norway, which was driven by user innovation. The unit led the project, which had both private and public partners across the country, including SopraSteria, OUS, Microsoft, and HoloCare AS [f].

5. Sources to corroborate the impact (indicative maximum of ten references)

[a] 'Slicer-Liver'. ALive, Nov. 16, 2023. Accessed: Jan. 18, 2024. [Online]. Available: https://github.com/ALive-research/Slicer-Liver

[b] 'HiPerNav: Publications and Dissemination', HiPerNav | High Performance soft tissue Navigation. Accessed: Jan. 18, 2024. [Online]. Available: https://hipernav.eu/publications-and-dissemination/

[c] 'HoloViz - from 2D to 3D'. Accessed: Jan. 18, 2024. [Online]. Available: https://www.oslo-universitetssykehus.no/om-oss/nyheter/holoviz-fra-2d-til-3d/

[d] 'HoloCare | Who we are'. Accessed: Jan. 18, 2024. [Online]. Available: https://www.holocare.com/who-we-are#:~:text=HoloCare%20began%20in%202016%20as,was%20formed%20as%20a%20company.

[e] 'HiPerNav: Network', HiPerNav | High Performance soft tissue Navigation. Accessed: Jan. 18, 2024. [Online]. Available: https://hipernav.eu/network/

[f] 'HoloCare Cloud'. Accessed: Jan. 18, 2024. [Online]. Available: https://prosjektbanken.forskningsradet.no/en/project/FORISS/296570?Kilde=FORISS&distribution=Ar&chart=bar&calcType=funding&Sprak=no&sortBy=date&sortOrder=desc&resultCount=30&offset=60&Fag.2=Medisinsk%20teknologi

Oslo University Hospital (OUS), The Division of Technology and Innovation (TIK). Case 3

Salveo Solutions AS is in the process of securing funds for additional patents and IPR rights from IVS. In this regard, this impact case cannot be made public due to confidentiality.

If relevant, describe any reason to keep this case confidential:

Institution: OUS
Administrative unit: TIK
Title of case study: Wireless Capsule Video Endoscopy
Period when the underpinning research was undertaken: 2012-2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2012-2022
Period when the impact occurred: The whole period

1. Summary of the impact

Our research has contributed to the design, development, and establishment of a novel batter-free wireless data transmission method integrated with artificial intelligence demonstrated for automatically investigating the entire gastrointestinal tract by the user. The technology enables a cost-effective, user-friendly, population-based colon cancer screening method.

2. Underpinning research

Colon polyps can become malignant (cancerous). Multiple studies show that colon cancer is the second deadliest cancer for both men and women**.** Early detection of polys means survival. Therefore, population-based screening has been introduced in many Western countries, including Norway, since 2022. There are two methods to examine the colon to detect polyps – colonoscopy and wireless capsule colon video, where the colonoscopy is the gold standard. However, a standard colonoscopy examination can be expensive (e.g., approximately $ 4500 in the US in 2013). This means colonoscopy cannot be considered a standard diagnostic tool for population-based screening programs due to cost and lack of healthcare personnel.

Given Imaging Inc. initially proposed wireless capsule video endoscopy in 2002 for the investigation of the small bowel. The swallowable pill comprises an image sensor, LED lights, batteries, a digital signal processor, and a wireless transmitter. Such pills have been developed further to have two image sensors at both ends to be considered for investigating the big bowel – colon. Unfortunately, none has been used routinely since they produce low-quality images, which require manual inspection by trained physicians.

Our research unit has performed research and development in developing new CMOS high-resolution image sensors and a new wireless technology that does not require battery power for video transmission. This means the wireless capsule will have high-quality images that can be transmitted to an external device or cloud service for automatic processing for polyp detection and classification into three main cancer classes such as hyperplastic (normal polyps), adenoma (needs to be followed-up), and malignant (cancer). One notable innovation was using a deep learning method applied in the

cloud to the visible light video images to classify them into those three classes without using a narrow band image sensor, the standard method integrated into the colonoscopy device. This means only those users/patients classified with adenoma need to be followed up. In this way of diagnosing becomes timely, cost-effective, and patient-friendly.

Our research has developed a complete prototype, tested it in phantoms and preclinical models such as animals, and demonstrated the technology with a plan to bring it forward to the market in collaboration with a startup company.

The following provides a list of projects and activities:

1) Wireless capsule video endoscopy was part of the research project Medical Sensing, Localization and Communication using Ultra Wideband Technology (MELODY I and MELODY II) funded by NFR's StorIKT:IKTpluss (large scale ICT research program) program with 7 (4+3) years of funding with 49 MNOK in 2008. The project was led by Professor Ilangko Balasingham, where in the project's second phase (MELODY II) 2012-2015, studied ultra-wideband technology for high-definition video transmission from inside the gut to an on-body receiver and had a PhD student and a postdoc. This project gave us the opportunity to become the first group in the world to demonstrate the use of ultra-wideband technology to stream high quality video from inside the gut to an off-body personal computer.

1) An industrial PhD program jointly funded by NFR and OmniVision AS (5.5 MNOK), a world-leading manufacturer of CMOS camera technology with an R&D office in Oslo, in 2015-2020. Two PhD students were hired. The first PhD student developed an ultralow-power CMOS camera chip with HD quality. The second PhD student studied a deep learning (AI) method for automatically detecting polyps with an accuracy of 88%. The grant allowed us to start working with PhD programs in microchip design and the use of deep learning for video processing. The PhD work led to machine learning and artificial intelligence becoming focus areas at IVS. This project was essential for the subsequent development of our backscatter technology and its commercial developments.

2) Wireless capsule video endoscopy was one of two major research topics in the H2020:MSCA:ITN project Wireless In-body Environment (WiBEC) funded by the EU in 2016 – 2019 with 3.957 M€. The project coordinated by Professor Ilangko Balasingham had 16 PhD students and 8 partners, including three companies. One of the company partners was the German Ovesco Endoscopy AG, which studied a wireless capsule video robotic endoscopy controlled by a magnet to be used in the hospital. The device is a small pill-shaped device inserted through. It had more than 6 degrees of freedom than a classical colonoscopy, which made it easy to maneuver for investigating different folders with a joystick and was less painful to the patient than the colonoscopy.

3) A verification project of 5 MNOK funded by the NFR (FORNY program) and the German company Ovesco Endoscopy AG. Inven2 TTO led the project with the help of Balasingham's team. The backscatter wireless video transmission prototype was tested in Ovesco's platform, where the performance was positively evaluated.

4) In the Horizon Europe ICT project 5G Heart, Balasingham's group implemented wireless capsule endoscopy with backscatter technology and transmitted the video data to a cloud using a 5G mobile network. The group implemented a deep learning method in the cloud to

detect polyps automatically in real-time. We then sent the signal back to wireless capsule endoscopy to adjust the camera parameters for lighting conditions for high-quality imaging in real time while the capsule was moving. This demonstration showed the potential use of the technology in the user's home environment, where the user swallows the capsule, and the video data can automatically be analyzed with a report indicating the detected polyps classified into three major cancer classifications according to the guidelines.

5) Based on the results obtained through the abovementioned projects and patents, a spin-off company, Salveo Solutions AS, was established in 2022 to bring the technology into the market.

- The research led by Professor Ilangko Balasingham (2002 – present) is still working as Head of Medical ICT Research, whereas Ali Khaleghi (2017 – present) and Jacob Bergsland (2002 – present) are presently working as senior scientists. Our main collaborator, Professor Lars Aabakken, Head of the Gastroenterology laboratory, still works at OUS.
- Hemin Qadir, an Industry PhD student in the OmniVision project, was hired as a permanent researcher at IVS in 2021 to advance the use of artificial intelligence in medical applications.
- Several master's students, PhD students, and postdocs were involved in different projects mentioned previously.

3. References to the research (indicative maximum of six references)

- A. Khaleghi and I. Balasingham, On-body antenna for wireless communication of medical implant, GB1913086.3, 2019
- A. Khaleghi and I. Balasingham, Implantable Antenna, 136303 62159-17139, 2018
- A. Khaleghi, I. Balasingham, and J. Bergsland, Medical Implant with Wireless Communication,62201-15239-GB-1, 2016.
- R. Noormohammadi, A. Khaleghi, and I. Balasingham. Galvanic Impulse Wireless Communication for Biomedical Implants. IEEE Access, 2021;9:38602-38610.
- A. Khaleghi, A. Hasanvand, and I. Balasingham. Radio Frequency Backscatter Communication for High Data Rate Deep Implants. IEEE Transactions on Microwave Theory and Techniques, 2019;67(3):1093-1106.
- A. Khaleghi, A. Hasanvand, and I. Balasingham. Coherent Query Scheme for Wireless Backscatter Communication Systems with SingleTag. EURASIP Journal on Wireless Communications and Networking, 2018;184:1-14.

4. Details of the impact

The impact of IVS's decision to establish a research focus on the use of microwaves and advanced signal processing in medicine has been shown to be a good one over the last 20 years. Although we will focus here on the period 2012-2022 and the so-called wireless capsule video endoscopy (camera pills), it is necessary to include the MELODY project, supported by NFR in 2008 – 2015. The project had research partners such as the Dept. of Electronics Systems at NTNU, the Dept of Informatics at UiO and the Defense Research Institute (FFI) on microwave medical radars. The investigators at FFI and the medical and engineering team at IVS developed a method for cardio-respiratory monitoring using ultrawideband (UWB) microwave radar (2008-2015). The impact of the effort by the IVS has been extensive, but we limit this document to a description of the capsule endoscopy. The MELODY project was the backbone of the pan-European project, WiBEC (2016 – 2019), which included NTNU, OUS/IVS, Technical University of Dresden in Germany, Universitat Politècnica de València in Spain, Liva Nova in France, Ovesco Endoscopy in Germany, ValoTec in France, and Lafe hospital in Spain. The WiBEC project expanded greatly in the interphase between electronic engineering and medicine, studying intra-and extra-body communication with medical sensor devices. In addition, the WIBEC program made it possible to

improve signal- and image processing by utilizing machine learning and artificial intelligence. The WiBEC project also helped to obtain other grants.

Our research at the IVS has demonstrated accuracy for polyp detection at 88%, where we are still working to improve this above 95% using novel deep learning algorithms with augmentation and false positive discrimination. *The technology submitted as a DOFI aims to reduce the examination viewing time with high-accuracy detection by providing overlay video information of polyps and other anomalies in a cost-effective manner in 2020.*

To summarize, the impact of the research performed by IVS's researchers and supported by NFR, EU and other funding agencies in Norway like HSØ innovation grant has had several important developments and discoveries. Several spin-off research and innovation activities have led to other new avenues within molecular biology and nanotechnology. One example is integrating synthetic bacteria in wireless capsule endoscopy to study the gut for various diseases. This research has been supported with a 16 MNOK grant awarded by NFR for "CLIPEUS: Internet of Bio-NanoThings for Prediction and Prevention of Infectious Diseases" in 2020.

The successful establishment of a commercial entity, Salveo Solutions AS, represent a promising commercial impact. Salveo Solutions is developing the next-generation wireless capsule video endoscopy, which may revolutionize gastrointestinal diagnosis using backscatter data transfer technology and data transfer to cloud-based use of artificial intelligence, resulting in earlier and better therapy of this important field of medicine that affects 40% of the global population.

5. Sources to corroborate the impact (indicative maximum of ten references)

1. Soon you'll be able to examine your gut from home (norwegianscitechnews.com) , 2022
2. Camera pill for screening colorectal cancer using 5G networks and real time AI - a research prototype shown in the Norwegian State Broadcaster, NRK Samarbeid mellom NTNU, Telenor og Rikshospitalet om nytt pillekamera som skal oppdage tarmkreft – NRK Trøndelag – Lokale nyheter, TV og radio
3. Getting a wireless network under the skin to talk to the brain (norwegianscitechnews.com), 2022
4. Engineers will replace clinicians (teknologer vil frigjøre medisinere) Dagens Medisin, 2017. 1bb05483-6ac7-4652-af12-fdfffb0badf1 (ntnu.edu)

Impact case guidelines

Each case study should include sufficiently clear and detailed information to enable the evaluation committee to make judgements based on the information it contains, without making inferences, gathering additional material, following up references or relying on members' prior knowledge. References to other sources of information will be used for verification purposes only, not as a means for the evaluation committee to gather further information to inform judgements.

In this evaluation, impact is defined as an effect on, change or benefit to the economy, society, culture, public policy or services, health, the environment or quality of life, beyond academia.

Timeframes

- The impact must have occurred between 2012 and 2022
- Some of the underpinning research should have been published in 2012 or later
- The administrative units are encouraged to prioritise recent cases

Page limit

Each completed case study template will be limited to **five pages** in length. Within the annotated template below, indicative guidance is provided about the expected maximum length limit of each section, but institutions will have flexibility to exceed these so long as the case study as a whole remains no longer than **five pages** (font Calibri, font size 11). Please write the text into the framed template under the sections 1–5 below. The guiding text that stands there now, can be deleted.

Maximum number of cases permitted per administrative unit

For up to 10 researchers: one case; for 10 to 30 researchers: two cases; for 30-50 researchers: three cases; for 50-100 researchers: four cases, and up to five cases for units exceeding 100 researchers.

Naming and numbering of cases

Please use the standardised short name for the administrative unit, and the case number for the unit (1,2,3, etc) in the headline of the case. Each case should be stored as a separate PDF-document with the file name: [Name of the institution and name of the administrative unit] [case number]

Publication of cases

RCN plans to publish all impact cases in a separate evaluation report. By submitting the case the head of the administrative units consents to the publication of the case. Please indicate below if a case may not be made public for reasons of confidentiality.

If relevant, describe any reason to keep this case confidential:

Please write the text here

[Pilar, RBUP] [1]

Institution: PILAR
Administrative unit: RBUP Eastern and Southern Norway
Title of case study: Mamma Mia
Period when the underpinning research was undertaken: August 2012 – December 2022 (still ongoing)
Period when staff involved in the underpinning research were employed by the submitting institution: August 2012 – December 2022 (and ongoing)
Period when the impact occurred: 2013 - ongoing

1. Summary of the impact

Mamma Mia is an internet intervention for perinatal depression and subjective well-being. This case describes the impact of the RCN and Norwegian Women's Public Health Association (NKS) funded research project, Mamma Mia, on perinatal mental health care practices. This case has provided a highly scalable intervention, licensed to the Directorate of Health, and provided to all pregnant and postpartum women in Norway. Approximately 11.000 women have thus far used Mamma Mia. Through our research, more than 30 municipalities (59 well-baby clinics; WBC) and 2.000 women have used Mamma Mia. Publications show that Mamma Mia prevents and reduces depression, enhances well-being, and appears promising as a guided and unguided intervention. As a direct consequence of our publications, Mamma Mia has been exported internationally (e.g., the US and UK).

2. Underpinning research

The Mamma Mia research project comprises two randomized controlled trials (RCTs). The first RCT (2012–2017) included 1.342 women and 305 men, and we compared Mamma Mia without guidance to treatment as usual. A subset of women was interviewed about their experiences and perceptions of the intervention. In addition, we conducted a pilot study of Mamma Mia in 14 WBCs (2014–2016). The second trial (2020–ongoing) is a cluster randomized trial (cRCT) with 31 municipalities, 182 midwives and public health nurses, and 774 women to date (recruitment still ongoing) where we evaluate the effect of Mamma Mia with guidance from health personnel compared to Mamma Mia without guidance. The intervention consists of 44 sessions that span from gestational week (gw) 21 until 6 months after birth. The development and content of Mamma Mia are described in detail by Drozd and colleagues (2015). Participants in both RCTs were monitored individually at baseline, gw37, 6 weeks, 3, 6, and 12 months postpartum. The principal investigators are researchers Silje Marie Haga (2012–ongoing) and Filip Drozd (2013–ongoing) from RBUP. Project members include Patricia Kinser, VCU, and Vidar Halsteinli, NTNU. Results have been published in international peer-reviewed journals, peer-reviewed books, and presented at international and national conferences both for practitioners and researchers and media aimed at the public. The RCT comprised Drs. Haga and Drozd's post-doctoral fellowships, while the cRCT employs two PhD candidates to finish by the end of 2024 and in 2025.

Main findings and insights from the study:

<u>Findings:</u>

- The first RCT showed (Haga et al., 2019; 2020):
    - The Mamma Mia group displayed fewer depressive symptoms than participants in the control group during follow-up.

- The prevalence of women with EPDS-score ≥ 10 was lower in the Mamma Mia group at all follow-up measurements.
- The effect of Mamma Mia was moderated by EPDS score at baseline, and more women with lower educational levels dropped out.
- There were no differences in life satisfaction and positive affect between groups. However, the Mamma Mia group showed less negative affect during follow-up.

- Interview data indicated that:
  - The program and content were considered accessible and helpful in their transition to motherhood but had limitations that could be solved through guidance (Drozd et al., 2017).
  - Women with elevated depressive symptoms found Mamma Mia to be credible and a helpful tool for self-care, but it should be optimized by personalized support from health personnel (unpublished).
- Early piloting showed that the program could be implemented in WBCs but identified several barriers and facilitators (Drozd et al., 2018).

Insights:

- Mamma Mia reduces depressive symptoms and negative affect, but the most vulnerable women had a higher tendency to drop out (Haga et al., 2019).
- Some level of support would seem beneficial to accommodate the lack of program flexibility and adapt contents to women's situations (Drozd et al., 2017)
- Mamma Mia should be integrated into regular perinatal healthcare.
- The cluster RCT will implement and test the cost-effectiveness of Mamma Mia with guidance compared to Mamma Mia as a stand-alone program (https://doi.org/10.1186/ISRCTN11387924).

Key contextual information

In Norway, 51.500 children were born in 2022. Nearly all attend the WBC's infant health care program during the first year of life. About 10-15% of perinatal women experience mild-to-moderate depression, in which about one-third of cases begin in pregnancy. More recent studies seem to suggest that prevalence rates have increased. This has implications for both the mother, partner, and child. According to National guidelines, health personnel in WBCs are supposed to promote and prevent perinatal mental health and well-being. However, it is not specified how this should be done, and no evidence-based model on how to accomplish this goal existed for the Norwegian context at that time, which is why Mamma Mia was developed.

3. References to the research

1] Haga, S. M., Drozd, F., Brendryen, H., & Slinning, K. (2013). Mamma Mia: A feasibility study of a web-based intervention to reduce the risk of postpartum depression and enhance subjective well-being. JMIR Research Protocols, 2(2), e29. http://www.researchprotocols.org/2013/2/e29/

[2] Drozd, F., Haga, S. M., Brendryen, H., & Slinning, K. (2015). An Internet-based intervention (Mamma Mia) for postpartum depression: Mapping the development from theory to practice. JMIR Research Protocols, 4(4), e120. https://doi.org/10.2196/resprot.4858

[3] Drozd, F., Andersen, C. E., Haga, S. M., Slinning, K., & Bjørkli, C. A. (2017). User experiences and perceptions of internet interventions for depression. In S. U. Langrial (Ed.), Web-based behavioral therapies for mental disorders (pp. 27–52). IGI Global. https://doi.org/10.4018/978-1-5225-3241-5.ch002

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[5] Haga, S. M., Drozd, F., Lisøy, C., Wentzel-Larsen, T., & Slinning, K. (2019). Mamma Mia – A randomized controlled trial of an internet-based intervention for perinatal depression. Psychological Medicine, 49(11), 1850–1858. https://doi.org/10.1017/S0033291718002544

[6] Haga, S. M., Kinser, P., Wentzel-Larsen, T., Lisøy, C., Garthus-Niegel, S., Slinning, K., & Drozd, F. (2021). Mamma Mia – A randomized controlled trial of an internet intervention to enhance subjective well-being in perinatal women. The Journal of Positive Psychology, 16(4), 446–454. https://doi.org/10.1080/17439760.2020.1738535

Processes that lead to impact:

We collaborated closely with experts in the field, end-users (perinatal women, midwives, and public health nurses), and Changetech (program developers) to ensure Mamma Mia would accommodate the needs of perinatal women. According to the feasibility study, Mamma Mia was considered a high-quality and credible program that users found acceptable and would recommend to others (Haga et al., 2013). A mapping of the intervention that linked theories and empirical evidence to the contents and materials of the program was developed (Drozd et al., 2015). This provided a foundation for the first RCT in which the effect of Mamma Mia was compared to treatment as usual (Haga et al., 2019; Haga et al., 2021). In parallel to the RCT, we invited participants who stopped using the program for an interview. A key insight was that women started using the program once we got in touch, and many continued using it after the interview. In addition, a central theme in interviews was the desire to receive support from health personnel, with WBCs being the most prominent. Based on these insights, we developed an implementation guide for Mamma Mia, piloted in 14 WBCs with 24 health personnel (Drozd et al., 2017). Findings showed that the program was implementable, but we identified several barriers and facilitators (Drozd et al., 2018). Findings from the RCT and the implementation pilot attracted the interest of national and international health authorities and research communities, resulting in research collaborations and licensing to national authorities.

Further dissemination and research collaborations:

Days after the first RCT was published online, we were contacted by researchers and stakeholders from abroad. By the end of 2018, we applied for funding from the RCN for a collaborative project with a research partner in the U.S. Funding was conditional on our partner (i.e., Virginia Commonwealth University (VCU) and Arizona State University (ASU)) receiving funding in the U.S. Funding was acquired in 2019 such that our cluster-RCT could start in 2020 where we would examine the effect of Mamma Mia with professional support from the WBCs (2020–2025). To this end, we revised the implementation guidelines and devised new guidelines for training, supervision, and clinical work at the WBCs (Olavesen et al., 2021a; 2021b; 2022). Our partner in the U.S. is currently investigating the effect of Mamma Mia in a three-armed RCT (treatment as usual vs. Mamma Mia unguided vs. Mamma Mia guided; Kinser et al., 2021) and recently completed recruitment. Later in 2020, we were invited to become a partner in the RCN-financed Center for Research-driven Innovation (SFI) “Forhelse” (2020–2029; https://app.cristin.no/projects/show.jsf?id=2522829), which Helse-Bergen owns. This partnership allows us to make an economic evaluation and examine the cost-effectiveness of Mamma Mia, led by Prof. Halsteinli and Ph.D. candidate Khan.

During COVID-19, the Government implemented several measures to counteract the effects of the pandemic. One of these was to allocate additional funds for digital health services. In 2021, the

Norwegian Directorate of Health announced the acquisition of digital mental health services licenses. Changetech and N.K.S. acquired one of these bids, and Mamma Mia became freely available to all pregnant women in 2022 via the national online health service in Norway – HelseNorge. In 2023, with the license expiring, there was no more funding to continue Mamma Mia as the pandemic had subsided. The partnership with Forhelse allowed us to make a preliminary cost evaluation which showed that the Mamma Mia app costs of providing universal access had been considered low compared to potential lifetime savings (i.e., savings from preventing one mother from perinatal depression) and that the number of women needed to use Mamma Mia, to prevent one case of depression, was 32 (Haga et al., 2023). Given the approx. 11.000 users during the licensing year contributed to securing additional funds and a new 3–year license with the option of a 1–year extension. Furthermore, the partnership with Forhelse led to the development of a program costs framework for digital health interventions that were applied to Mamma Mia (Khan et al., in revision).

During all this, we were approached by Drs. Garthus-Niegel and Baumann in Germany applied for research funding (2019-2021) with the aim of including partners in the Mamma Mia program. Although we were unsuccessful in securing funding, it resulted in several joint publications (e.g., Garthus-Niegel et al., 2019, 2020; Valla et al., 2023). In 2023, Dr. Hare from Vanderbilt University, USA, also approached us who has applied for funding to modify and adapt Mamma Mia to mothers with a history of neglect and early adversity and run a small-scale RCT.

This body of work has also had several business impacts for Changetech:

- Ongoing trialing of Mamma Mia at three hospitals in The Midlands, UK.
- Trialing soon to convene in Slovenia. Final translations and adaptations are underway.
- Dialogue with the Egmontfonden in Denmark about possible financing of Mamma Mia in Denmark and Sweden.
- Dialogue with the Maternity Hospital Foundation in Latvia.

Competence building:
As a direct consequence of the Mamma Mia study, RBUP has strengthened its competence in implementing an evidence-based intervention for perinatal mental health in WBCs. Likewise, health personnel have received training and supervision in implementing a new intervention systematically using an implementation guide. The guide is a flexible framework that can be applied to various contexts and interventions. Health personnel in WBCs have strengthened their competence in detecting and early intervention of perinatal depression. To ensure the continued implementation of Mamma Mia, we plan to integrate Mamma Mia into the Early-in program. This program aims to identify children who need extra support because their parents are struggling.

Conclusive remarks:
To summarize, Mamma Mia is an evidence-based internet intervention that reduces perinatal depression and enhances subjective well-being. Both perinatal women and health personnel perceive Mamma Mia as a useful tool to address mental health during pregnancy and postpartum. Preliminary analyses suggest that Mamma Mia is a cost-effective intervention. Through the ongoing cluster randomized controlled trial, Mamma Mia is implemented in 31 municipalities across Norway. Half of the municipalities have received training and supervision in systematically implementing an intervention using an implementation guide, a flexible framework that can easily be adapted to other interventions, etc. Thus, Mamma Mia and the implementation guide are important tools for working evidence-based and systematically in health services. The beneficiaries of the study are, first and foremost, perinatal women and health personnel in WBCs, but also service leaders, as they have either been part of the study or received support from RBUP in their

quality work. Quality building is mandatory in the sector, but a research-based model for doing it has largely been lacking.

5. Sources to corroborate the impact

[1] Valla, L., Haga, S. M., Niegel, S. G., & Drozd, F. (2023). Dropout or drop-in experiences in an internet-delivered intervention to prevent depression and enhance subjective well-being during the perinatal period: Qualitative study. JMIR Pediatrics and Parenting, 6, e46982. https://doi.org/10.2196/46982

[2] Haga, S. M., Drozd, F., Khan, Z. A., & Halsteinli, V. (2023). En fortsatt bred tilgang på Mamma Mia-app'en vil gi verdifull ny kunnskap og erfaring [Cost-effectiveness considerations of Mamma Mia in a Norwegian context]. Bergen, Trondheim, & Oslo: ForHelse – Forskningssenter for digitale helsetjenester & Regionsenter for barn og unges psykiske helse, Helseregion Øst og Sør.

[3] Kinser, P., Jallo, N., Huberty, J., Jones, E., Thacker, L., Moyer, S., Laird, B., Rider, A., Lanni, S., Drozd, F., & Haga, S. M. (2021). Study protocol for a multisite randomized controlled trial of an internet and mobile-based intervention for preventing and reducing perinatal depressive symptoms. Research in Nursing & Health, 44(1), 13–23. https://doi.org/10.1002/nur.22092

[4] Olavesen, E. S., Sundrehagen, T., Haga, S. M., & Drozd, F. (2022). Mamma Mia – Veileder for opplæring og veiledning [Mamma Mia – A practical guide to training and supervision]. Regionsenter for barn og unges psykiske helse, Helseregion Øst og Sør.

[5] Olavesen, E. S., Sundrehagen, T., Haga, S. M., & Drozd, F. (2021a). Mamma Mia – En veileder for implementering [Mamma Mia – A practical guide to implementation]. Regionsenter for barn og unges psykiske helse, Helseregion Øst og Sør.

[6] Olavesen, E. S., Sundrehagen, T., Haga, S. M., Hartmann, K., Randen, I., Staksrud, G. H., & Drozd, F. (2021b). Mamma Mia – En veileder for det helsefremmende og forebyggende arbeidet [Mamma Mia – A practical guide for health promotion and prevention]. Regionsenter for barn og unges psykiske helse, Helseregion Øst og Sør.

[7] Garthus-Niegel, S., Staudt, A., Kinser, P., Haga, S. M., Drozd, F., & Baumann, S. (2020). Predictors and changes in paternal perinatal depression profiles — Insights from the DREAM study. *Frontiers in Psychiatry*, *11*, 563761. https://doi.org/10.3389/fpsyt.2020.563761

[8] Garthus-Niegel, S., Horsch, A., von Soest, T., Haga, S. M., Drozd, F., Ayers, S., & Eberhard-Gran, M. (2019). Posttraumatic stress symptoms following childbirth: Associations with prenatal attachment in subsequent pregnancies. *Archives of Women's Mental Health*, *23*, 547–555. https://doi.org/10.1007/s00737-019-01011-0

[9] Drozd, F., Haga, S. M., & Slinning, K. (2017). From science to practice: Implementation and clinical guidelines for an internet intervention for postpartum depression. In S. U. Langrial (Ed.), Web-based behavioral therapies for mental disorders (pp. 79–110). IGI Global. https://doi.org/10.4018/978-1-5225-3241-5.ch004

All other publications from the project can be found at:
https://app.cristin.no/projects/show.jsf?id=413655
https://app.cristin.no/projects/show.jsf?id=416722
https://app.cristin.no/projects/show.jsf?id=2471826

[Pilar, RBUP] [2]

Institution: Pilar
Administrative unit: RBUP Eastern and Southern Norway
Title of case study: Thrive by three
Period when the underpinning research was undertaken January 2017 – December 2022
Period when staff involved in the underpinning research were employed by the submitting institution: January 2017 - December 2022
Period when the impact occurred: 2018 - ongoing

1. Summary of the impact

This case describes the impact of the RCN-funded research project Thrive by three (Tb3) on the development of process quality in Early Childhood Education and Care (ECEC) in Norway. The study has provided a highly applicable system for quality building through professional development named the Tb3. The Tb3 has been scaled up and/or sustained within all the 7 municipalities that participated in the original research and has spread to other municipalities in Norway. Publications show that ECEC professionals find Tb3 to be useful in their work with process quality, that process quality is enhanced, and that child outcomes are impacted.

2. Underpinning research

The Thrive by three research project was a cluster randomized controlled trial, with 7 participating municipalities from Eastern- and Mid- Norway, 78 ECEC centers, 187 toddler classrooms, 1561 toddlers (1-3 years) and their parents, and 794 ECEC professionals. The study had a waitlist-control design. The intervention group received the Thrive by three (Tb3) intervention in the school year 2018/2019. The control group received Tb3 the year after. The intervention was a 10-month in-service professional development model to promote the quality of caregiver-child interactions (i.e., process quality). The model is based on the Classroom Assessment Scoring System (CLASS; La Paro et al., 2012) and previous research on professional development. The tb3 consists of 4 main components:

1) Quality assessment and feedback (based on CLASS)
2) Supervision and reflection
3) Child development and mental health seminars.
4) Manuals, booklets, posters, and website.

A secondary research aim was to investigate the impact on child mental health, well-being, and development and if the model proved efficient in enhancing quality. There were four data collection time points: pre- (Sept./Oct. 2018), mid- (January 2019), post-intervention (June 2019), and one-year follow-up (June 2020). The study was a joint effort between the project owner RBUP, RKBU Mid Norway, and the Norwegian Business School (BI, Nydalen). The principal investigators were Professor Turid Suzanne Berg-Nielsen (2017 – 2018) and researcher Elisabet Solheim Buøen, PhD (2018-2022), both from RBUP. Project members were Professor May Britt Drugli (RKBU Mid Norway) and associate Professor Ratib Lethal (BI). The results that underpin the impact were from analyses conducted on the pre-, mid-, and post-data. Multi-informant, multimethod data was gathered by means of observations, interviews, and questionnaires. Results have been published in peer-reviewed journals and presented at international and national conferences both for practitioners and researchers, and the Tb3 and its implementation have been described in a peer-reviewed book to be published in January 2024. Two PhD candidates were employed. They received their Ph.D. degree in 2023, according to plan.

Main findings and insights from the study:

Findings:

- The process quality increased in the intervention group and slightly decreased in the control group.
- The intervention did not impact mental health, possibly due to the low prevalence of mental health problems in the study population of 1-3-year-olds and the universal preventive nature of Tb3 (unpublished).
- The intervention positively impacted girls' language development.
- Interview data indicated that:
    - The ECEC professionals report greater professional awareness around their daily work in ECEC due to the Tb3. They highlight the use of observation (CLASS), reflection in groups, and feedback as the most important components.
    - They also report that the quality of the caregiver-child interactions has improved and that the operationalization of high quality through CLASS has been especially useful as a basis for their daily work.
    - They highlight that support for the ECEC leaders is key to success and that lack of time is the most important threat to sustainment.

Insights:

- ECEC centers quickly adopted Tb3, and ECEC leaders in the participating municipalities reported that they found the intervention useful.
- All 7 municipalities continued to implement the Tb3 model after the research project ended. 6 scaled up to all or most of the ECEC centers in the municipality. Most of the municipalities included preschool classrooms.

Key contextual information:

In Norway, as much as 87% of 1- and 2-year-olds are in ECEC, most attending for long hours. Childcare quality is of great importance for all these young children, both in the short and long run. Yet, recent evidence from both international and Norwegian studies finds quality typically to be in the low-medium range, especially when it comes to stimulating children´s learning and development. Moreover, caregiver-toddler interactions vary in quality both between and within centers. At the initiation of Tb3, studies with sufficiently rigorous designs to study the effects of professional development programs on process quality were lacking for toddlers (ages 1 to 3 years) in ECEC. Moreover, and according to the Framework Plan for Kindergartens (udir.no/rammeplan), continuous quality building, to ensure that children's needs are met in good ways, is a core task for the ECEC-centers. Nonetheless, no evidence-based model for accomplishing this goal exists in the Norwegian context.

3. References to the research

Buøen, E. S., R. Lekhal, S. Lydersen, T. S. Berg-Nielsen, and M. B. Drugli (2021). "Promoting the Quality of Teacher-Toddler Interactions: A Randomized Controlled Trial of "Thrive by Three" In-Service Professional Development in 187 Norwegian Toddler Classrooms." *Frontiers in Psychology*, https://doi.org/10.3389/fpsyg.2021.778777

Buøen, E.S., Drugli, M.B. og Lekhal (2024). *De yngste i barnehagen: Bedre samspillskvalitet*. CAPPELEN DAMM AS.

Drugli, M.B., Lekhal, R. og Buøen, E.S. (2023). Erfaringer med Trygg før 3 – profesjonsutvikling på småbarnsavdelinger - en kvalitativ studie. *Paideia*, 26, 20–31.

Lekhal,R., Drugli, M.B., Karlsen, L., Lydersen, S. & Buøen, E.S. (2023) Does *thrive by three*, a quality-building intervention in childcare centres, strengthen children's language skills?, *European Early Childhood Education Research Journal*, DOI: 10.1080/1350293X.2023.2260131

Patras, J.S., Drugli, M.B., Follestad, I.B., Brenne, A.S., & Buøen, E.S. *Implementation of a Professional Development Model in Early Childhood Education and Care (ECEC)*. Poster at European Implementation Event, Basel, June 8. -9., 2023.

4. Details of the impact (indicative maximum 750 words)

Processes that lead to impact:

At the outset of the Tb3 study, we collaborated closely with head teachers, ECEC leaders, and leaders of the ECEC in the municipalities to make sure that the Tb3 intervention would be an answer to some of the needs in the field and everyday work of ECEC professionals. The Tb3 model was also piloted in one municipality, where more than 200 ECEC classrooms participated. This provided a solid foundation for our randomized controlled trial (RCT) study, as we already had preliminary indications that the proposed quality-building model would align well with the preferences and needs of practitioners in a Norwegian context. Further, as a part of the study setup, we invited ECEC leaders at the municipality level to join an extended project group, with regular meetings from 2012 - 2020. This group was used to adjust along the way and to keep an open communication with the study participants. By the end of the school year 2019/2020, the control group had also been given the Tb3, and we started to see preliminary positive results (Buøen et al., 2021). Based on this, the extended project group discussed how the model could be implemented and sustained in the municipalities´ standard practices for building quality in ECEC. These discussions resulted in a pamphlet with recommendations given to the municipalities to guide their implementation process. Another strength of the Tb3 model that most likely contributed to its impact is that we trained childcare teachers to become CLASS observers and supervisors. In that way, we ensured that important knowledge was kept in the municipalities after the research project ended. In addition, the mentors supervising the teachers were selected from facilities in the municipality that were already responsible for supervising the childcare centers. In cooperation with the center leaders, we also made sure that supervision and workshops were scheduled during already planned non-contact time. This enhanced the model's sustainability and strengthened the applicability of the findings in a real-world setting.

Further implementation and upscaling:

After it became clear that 6 out of 7 municipalities wanted to continue with the Tb3 model and scale up in various ways (i.e., include both toddler and preschool groups, include most ECEC centers, add seminars, expand the implementation period), both RKBU Midt and RBUP provided support in that process. Both provided implementation support, and RBUP provided CLASS training and seminars to new participating ECEC centers. Thus, one striking evidence of Tb3's impact is the mere fact that this way of working with quality building in ECEC is now implemented in 6 of the original Tf3 municipalities, with a total of 170 ECEC centers, 867 classrooms, 3498 ECEC caregivers, and 14330 children. Some municipalities have provided extra funding to the ECEC sector to support the continuous quality building within the ECEC centers. However, most are implemented within the normal ECEC budget. The municipalities have made some adjustments but kept the four main components at the core of their work. The project's web page, www.tf3.no, was made publicly available in August 2020 and is being used by the municipalities in their further implementation.

Competence building:

As a direct consequence of the Tb3 study, RBUP and RKBU Midt have strengthened their competence in promoting quality in ECEC and supporting the implementation of the Tb3 model. The centers offer CLASS training so that ECEC professionals and others can use CLASS as a basis for their municipality's quality work in ECEC. These trainings are offered four times a year and are fully booked every time.

The results from Tb3 and the knowledge gained from the study have been disseminated in various ways:

- The closing conference of the Thrive by 3 December 2020
- Day seminars with ECEC professionals at RBUP 2020- ongoing
- Digital seminars, webinars 2020 – ongoing
- Part of the curriculum at the leader programs for pedagogical leaders and ECEC leaders (styrere) at the Norwegian Business School BI, campus Oslo. 2018 – ongoing

It has mainly been the researchers in Tb3 that have disseminated the results and the knowledge. In 2021, RBUP developed a new strategy for quality-building in ECEC and schools, which the Tb3 study paved the way for. With the new strategy, two RBUP employees, not originally in the study, are now contributing to the dissemination. RBUP is also supporting other municipalities that have contacted us because they want to use the Tb3 model as the basis of their quality work in ECEC. RBUP currently supports three non-Tb3 municipalities in their training, competence-building, and implementation. Quality building is now an important part of the RBUP portfolio. To further corroborate the impact, two of Norway's largest private ECEC chains have adopted a slightly modified version of the Tb3 in all their ECEC centers, 2019 – to date.

Other impact:
The Tb3 study established a national network for municipalities working with quality building in ECEC based on the Classroom Assessment Scoring System (CLASS) in 2022. The network is coordinated from RBUP and meets two times a year. The participants (approx. 40) are from 10 different municipalities from different parts of Norway.
Tb3 also paved the way for the study Implementation of a Professional Development Model in Early Childhood Education and Care (IMBA). In IMBA, four municipalities that upscaled the Tb3 were assessed in terms of implementation quality in the school year of 2022/2023. Data collection has just finished, but preliminary results show that implementation quality is generally high and that all the municipalities have kept the four components of the Tb3.

Conclusive remarks:
To summarize, the Tb3 model is implemented broadly in several municipalities. The beneficiaries are, first and foremost, ECEC professionals and their leaders in the municipality. They have been impacted either because they were part of the Tb3 study, part of the broader implementation after the tb3 study, or because they have attended seminars/workshops at RBUP/RKBU Midt, leader programs at BI, or received support from RBUP or RKBU Midt in their quality work. The children of the centers that participated in the Tb3 have benefitted and continue to do so in all the ECEC centers that have implemented the model. The Tb3 has become an important tool for the ECEC leaders of centers and at the municipality level to implement a systematic approach to quality-building in ECEC. Quality building is mandatory in the sector, but a research-based model for doing it has largely been lacking. Moreover, staff in the services supporting ECEC, like pedagogical-psychological services (PPT) and other services for special education, have also been impacted by being included in the quality work in new ways.

5. Sources to corroborate the impact (indicative maximum of ten references)

All publications from the study can be found at: https://tf3.no/publications/
More information can be found at: https://app.cristin.no/projects/show.jsf?id=536641

Impact case guidelines

Each case study should include sufficiently clear and detailed information to enable the evaluation committee to make judgements based on the information it contains, without making inferences, gathering additional material, following up references or relying on members' prior knowledge. References to other sources of information will be used for verification purposes only, not as a means for the evaluation committee to gather further information to inform judgements.

In this evaluation, impact is defined as an effect on, change or benefit to the economy, society, culture, public policy or services, health, the environment or quality of life, beyond academia.

Timeframes

- The impact must have occurred between 2012 and 2022
- Some of the underpinning research should have been published in 2012 or later
- The administrative units are encouraged to prioritise recent cases

Page limit

Each completed case study template will be limited to **five pages** in length. Within the annotated template below, indicative guidance is provided about the expected maximum length limit of each section, but institutions will have flexibility to exceed these so long as the case study as a whole remains no longer than **five pages** (font Calibri, font size 11). Please write the text into the framed template under the sections 1–5 below. The guiding text that stands there now, can be deleted.

Maximum number of cases permitted per administrative unit

For up to 10 researchers: one case; for 10 to 30 researchers: two cases; for 30-50 researchers: three cases; for 50-100 researchers: four cases, and up to five cases for units exceeding 100 researchers.

Naming and numbering of cases

Please use the standardised short name for the administrative unit, and the case number for the unit (1,2,3, etc) in the headline of the case. Each case should be stored as a separate PDF-document with the file name: [Name of the institution and name of the administrative unit] [case number]

Publication of cases

RCN plans to publish all impact cases in a separate evaluation report. By submitting the case the head of the administrative units consents to the publication of the case. Please indicate below if a case may not be made public for reasons of confidentiality.

If relevant, describe any reason to keep this case confidential:

Please write the text here

St. Olavs hospital Impact Case #1

Institution: NTNU- Norwegian University of Science and Technology + St.Olavs Hospital
Administrative unit: Institute of NeuroMedicine and Movement Science (INB) + NeuroClinic
Title of case study: Candesartan as a migraine prophylactic treatment
Period when the underpinning research was undertaken: 2003 + 2013 - 2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2003-2022
Period when the impact occurred: 2013 - 2022

1. Summary of the impact (indicative maximum 100 words)

The headache research group has through drug- repurposing brought a new (off-label) indication to an existing drug (candesartan) to be used as a migraine prophylactic treatment. Today this drug is being used for migraine treatment by millions of migraineurs all over the world, and it is also included as **first-line treatment** in current international treatment guidelines and consensus statements.

2. Underpinning research (indicative maximum 500 words)

The importance of clinical observations cannot be underestimated. In this case, prof. Harald Schrader at INB, NTNU/ St.Olavs Hospital, started on an anti-hypertensive medication, lisinopril, and noticed that his migraine disappeared. A few of his patients then tried this in clinical practise and responded. This clinical observation led to a small placebo-controlled study showing efficacy of the ACE- inhibitor lisinopril in patients with episodic migraine that was published in BMJ in 2001 (Schrader H et al). The downside was that many patients experienced cough as a side effect due to accumulation of bradykinin. The headache research group found theoretical grounds for an angiotensin II receptor antagonist to have a potential similar, and maybe even better, effect; without the risk of cough as a side effect (no accumulation of bradykinin). Candesartan was selected to be tested out in a clinical trial. A placebo- controlled crossover study on n=60 patients with episodic migraine found candesartan to be effective as a migraine prophylactic drug. The results were published in JAMA in 2003 (Tronvik E et al).
Even though this study was meticulously performed and published in a high-ranking journal, not much happened on the impact front internationally for the next 10 years.
The research group then decided to do a head-to- head study with the first-line prophylactic agent in migraine, propranolol. A randomised, triple-blind, placebo-controlled, double cross-over study comparing candesartan to both propranolol and placebo was published in Cephalalgia in 2013 (Stovner LJ et al). This study showed that candesartan had a similar effect size as propranolol but with different adverse effects. It was also shown that non-responders to one of the drugs could be a responder to the other. Both drugs were superior to placebo. This study triggered increased interest for candesartan as a migraine prophylactic drug internationally.

<u>Key researchers for this case study.</u>
Harald Schrader (2001 – 2009) – Prof, MD
Lars Jacob Stovner (2001 -) – Prof, MD
Erling Tronvik (2001 -) - PhD -> Prof, MD
Trond Sand (2001 -) - Prof, MD

3. References to the research (indicative maximum of six references)

1. Schrader H, Stovner LJ, Helde G, Sand T, Bovim G. Prophylactic treatment of migraine with angiotensin converting enzyme inhibitor (lisinopril): randomised, placebo controlled, crossover study. BMJ. 2001 Jan 6;322(7277):19-22. doi: 10.1136/bmj.322.7277.19. PMID: 11141144; PMCID: PMC26600.
2. Tronvik E, Stovner LJ, Helde G, Sand T, Bovim G. Prophylactic treatment of migraine with an angiotensin II receptor blocker: a randomized controlled trial. JAMA. 2003 Jan 1;289(1):65-9. doi: 10.1001/jama.289.1.65. PMID: 12503978.
3. Stovner LJ, Linde M, Gravdahl GB, Tronvik E, Aamodt AH, Sand T, Hagen K. A comparative study of candesartan versus propranolol for migraine prophylaxis: A randomised, triple-blind, placebo-controlled, double cross-over study. Cephalalgia. 2014 Jun;34(7):523-32. doi: 10.1177/0333102413515348. Epub 2013 Dec 11. PMID: 24335848.

4. Details of the impact (indicative maximum 750 words)

Until the first anti-CGRP drug (erenumab) was FDA approved in 2018, there were few options for migraine prophylactic treatment available, and for all existing drugs the anti-migraine effect had been discovered by serendipity. Available options were betablockers, flunarizine (available only in some countries), amitriptyline and antiepileptics (valproate and topiramate); and botulinum toxin from 2010 (chronic migraine only). The oral drugs had a side-effect profile that was not compatible with an on average young migraine population, and 40% of discontinuations were due to side-effects (Blumenfeld et al 2013 doi: 10.1111/head.12055). Late 2023 the European Medicine Agency (EMA) issued a warning against use of topiramate in fertile women and in 2024 a warning against use of valproate in fertile men (+ women). This reduces the number of available low-cost effective alternatives for migraine prophylactic treatment.
Since the candesartan paper was published in 2013, use of the drug has increased internationally. Real-world studies have confirmed clinical efficacy (Sánchez-Rodríguez C et al 2021 doi: 10.1038/s41598-021-83508-2;; Messina R et al doi: 10.1007/s00415-020-09989-9).

Candesartan is now included as **first-line treatment** in most updated international guidelines or consensus statements e.g:

- **European:** Eigenbrodt AK et al. Diagnosis and management of migraine in ten steps. Nat Rev Neurol. 2021 Aug;17(8):501-514. doi: 10.1038/s41582-021-00509-5.
- **US:** Ailania J et al. The American Headache Society Consensus Statement: Update on integrating new migraine treatments into clinical practice. Headache. 2021 Jul;61(7):1021-1039. doi: 10.1111/head.14153.
- **Danish:** Schytz H et al. Reference programme: diagnosis and treatment of headache disorders and facial pain. Danish Headache Society, 3rd edition, 2020. J Headache Pain. 2021 doi: 10.1186/s10194-021-01228-4
- **Brazilian:** Santos PSF et al. Consensus of the Brazilian Headache Society (SBCe) for prophylactic treatment of episodic migraine: part II. Arq Neuropsiquiatr. 2022 Sep;80(9):953-969. doi: 10.1055/s-0042-1755320.
- **Greek:** Kouremenos E et al. Consensus of the Hellenic Headache Society on the diagnosis and treatment of migraine. J Headache Pain. 2019 Dec 13;20(1):113. doi: 10.1186/s10194-019-1060-6.

- **Candadian:** Pringsheim T et al. Canadian Headache Society Prophylactic Guidelines Development Group. Canadian Headache Society guideline for migraine prophylaxis. Can J Neurol Sci. 2012 Mar;39(2 Suppl 2):S1-59.

Unfortunately, many countries, including Norway, have refused to reimburse candesartan due to the fact that the two clinical trials from our group were of cross-over and not parallel design. In addition, we saw that we lack knowledge on whether a lower dose than 16 mg could be sufficient for effect. The headache research group therefore in 2020 initiated a placebo controlled three-armed parallel study comparing candesartan 8 mg to candesartan 16 mg to placebo (NCT04574713). The study ended inclusion in des-23 (**n = 450 patients**) and results will be published in 2024. A positive result on efficacy, dose-finding and safety will further advocate the use and impact of this research, as this is a drug that is cheap (patent expired), has an acceptable side-effect profile and is a drug suitable for use in both primary- and secondary care.

5. Sources to corroborate the impact (indicative maximum of ten references)

Main sources for impact would be the international guidelines, consensus statements and real-world evidence referenced above.

Impact case guidelines

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In this evaluation, impact is defined as an effect on, change or benefit to the economy, society, culture, public policy or services, health, the environment or quality of life, beyond academia.

Timeframes

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Publication of cases

RCN plans to publish all impact cases in a separate evaluation report. By submitting the case the head of the administrative units consents to the publication of the case. Please indicate below if a case may not be made public for reasons of confidentiality.

If relevant, describe any reason to keep this case confidential:

Please do not publicly disclose the sources to corroborate the impact (point 5).

St. Olavs hospital Impact Case #2

Institution: St. Olavs hospital
Administrative unit: St. Olavs hospital
Title of case study: Effect of spinal cord burst stimulation vs placebo stimulation on disability in patients with chronic radicular pain after lumbar spine surgery: A randomized clinical trial
Period when the underpinning research was undertaken: 2018 - 2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2018 - 2022
Period when the impact occurred: 2022

1. Summary of the impact (indicative maximum 100 words)

This section should briefly state what specific impact is being described in the case study.

Around 30% of patients undergoing spine surgery experience persistent or even worse radicular pain after their surgery. Spinal cord stimulation (SCS) for this type of chronic pain is a growing and lucrative market, but there is not much convincing evidence of its benefits. In this randomised trial of 50 people, two three-month periods of bursts of SCS using a subcutaneous implantable pulse generator with leads into the epidural space, resulted in no difference in disability related to back pain, leg and back pain, quality of life, or physical activity levels compared with placebo. The placebo effect was powerful, highlighting the need to treat claims based on open label trials with caution if not scepticism.

2. Underpinning research (indicative maximum 500 words)

Key researchers:

Consultant neurosurgeon and professor of neurosurgery Sasha Gulati (principal investigator)
Consultant neurosurgeon Sozaburo Hara
Trial nurse and MSc Hege Andresen

Underpinning research:

The use of spinal cord stimulation for chronic pain following lumbar spine surgery is increasing, yet rigorous evidence of its efficacy is lacking. The objective of this trial was to investigate the efficacy of spinal cord burst stimulation, which involves the placement of an implantable pulse generator connected to electrodes with leads that travel into the epidural space posterior to the spinal cord dorsal columns, in patients with chronic radiculopathy after surgery for degenerative lumbar spine disorders. This industry independent, placebo-controlled, crossover randomized clinical trial in 50 patients was conducted at St. Olavs University Hospital, Norway, with study enrollment from September 5, 2018, through April 28, 2021, and the date of final follow-up was May 20, 2022. Patients underwent two three-month long periods with spinal cord burst stimulation and two three-month periods with placebo stimulation in a randomized order. Burst stimulation consisted of closely spaced, high-frequency electrical stimuli delivered to the spinal cord. The stimulus paradigm consisted of a 40 Hertz burst mode of constant-current stimuli with four spikes per burst and an amplitude corresponding to 50–70% of the paresthesia perception threshold. The primary outcome was difference in change from baseline in the self-reported Oswestry disability index (ODI; range, 0 [no disability] to 100 [maximum disability]; minimal clinically important difference, 10 points) score between periods with burst stimulation and placebo stimulation. Secondary outcomes were leg and back pain, quality of life, physical activity levels, and adverse events. Among 50 patients who were randomized (mean age, 52.2 years; 27 [54%] women), 47 (94%) had at least one follow-up ODI score and 42 (84%) completed all randomization periods and ODI measurements. The mean ODI at baseline was 44.7 points and the mean changes in ODI were -10.6 points for burst stimulation and -9.3 points for placebo stimulation, resulting in a mean difference in change in ODI of -1.3 points (95% CI, -3.9 to 1.3, P=0.32). Of four prespecified

secondary endpoints, none showed a significant difference. Nine patients (18%) experienced adverse events, including four (8%) that required surgical revision of the implanted system. Among patients with chronic radicular pain after lumbar spine surgery, spinal cord burst stimulation, compared with placebo stimulation, after placement of a spinal cord stimulator resulted in no significant difference in the change from baseline in self-reported back pain-related disability.

3. References to the research (indicative maximum of six references)

1. Effect of Spinal Cord Burst Stimulation vs Placebo Stimulation on Disability in Patients With Chronic Radicular Pain After Lumbar Spine Surgery: A Randomized Clinical Trial
Sozaburo Hara, Hege Andresen, Ole Solheim, Sven M. Carlsen, Terje Sundstrøm, Greger Lønne, Vetle V. Lønne, Kristin Taraldsen, Erling A. Tronvik, Lise R. Øie, Agnete M. Gulati, Lisa M. Sagberg, Asgeir S. Jakola, Tore K. Solberg, Øystein P. Nygaard, Øyvind O. Salvesen, and Sasha Gulati;
JAMA, 2022
URL: https://jamanetwork.com/journals/jama/fullarticle/2797419
PMID: 36255427

2. Spinal Cord Burst Stimulation vs Placebo Stimulation for Patients With Chronic Radicular Pain After Lumbar Spine Surgery-Reply
Sasha Gulati, Sozaburo Hara, and Øyvind O Salvesen
https://jamanetwork.com/journals/jama/article-abstract/2802320
DOI: 10.1001/jama.2022.24755
PMID: 36917052

3. Six-Month Follow-up of a Trial of Spinal Cord Burst Stimulation vs Placebo Stimulation and Disability in Patients With Chronic Radicular Pain After Lumbar Spine Surgery
Sozaburo Hara, Hege Andresen, Ole Solheim, Sven M. Carlsen, Asgeir S. Jakola, Øyvind O. Salvesen, and Sasha Gulati;
JAMA, 2023
URL: https://jamanetwork.com/journals/jama/fullarticle/2805915
PMID: 37314281

4. Details of the impact (indicative maximum 750 words)

Results from the trial were published in 2022 in one of the world's leading medical journals, JAMA, and continues to receive widespread attention both by national and international media channels as well and in the medical community. The results from the trial have been widely disseminated, also to patients with chronic pain, and continues to receive a lot of attention in social media. Top-tier medical journals such as JAMA only publish novel research with rigorous scientific methods and great clinical relevance to a large group of patients. In wake of the publication of the trial, there has been an ongoing debate about both the trial and treatment of chronic back pain with spinal cord stimulation. As an example, the trial results made a great impact on the latest Cochrane systematic review on spinal cord stimulation for back pain. Spinal cord stimulation remains a controversial treatment and following the publication of the results there are now ongoing reviews in Australia on the efficacy and safety of this treatment and whether the treatment should be reimbursed by the public health care system. The trial is frequently cited in reviews and discussions about spinal cord stimulation. A continuous overview of the attention the study receives is provided by Altmetric (https://jamanetwork.altmetric.com/details/137354916). The trial is in the top 5% of all research outputs scored by Altmetric and is on the 99th percentile compared to outputs of the same age.

This trial underlines the powerful placebo effect of invasive neuromodulation therapies and inherent weaknesses of open label studies. The clinically significant placebo effect should therefore be considered when interpreting results from open-label studies. The placebo effect in surgery may be augmented by patient expectations of highly specialized and expensive technology and surgical interventions, repeated visits, attentive patient and care provider interactions, and lack of other treatment options. The evidence supporting spinal cord stimulation has received increased scrutiny because of concerns regarding equipoise, bias, lack of placebo-control, and blinding. Many trials have close ties with spinal cord stimulation industry which might explain favourable reports, the absence of replication studies, and emphasis on testing novel stimulation parameters instead of confirming efficacy. Considering limited high-quality evidence for benefits and increasing costs associated with its use, spinal cord stimulation for chronic radicular pain outside well-designed clinical trials is hard to defend and must be weighed against the common incidence of device-related complications.

The trial is also of great importance in the discussion about corporate influences on science and health. The reception of the trial results clearly demonstrates the tactics that are used by corporations and clinicians with vested interests to undermine independent medical research when results do not play in their favour (https://jamanetwork.com/journals/jamainternalmedicine/article-abstract/2812937).

5. Sources to corroborate the impact (indicative maximum of ten references)

Adrian Traeger PhD
Principal investigator of the latest Cochrane review on spinal cord stimulation for back pain
The University of Sydney, Faculty of Medicine and Health, School of Public Health, Institute for Musculoskeletal Health, Australia
E-mail: adrian.traeger@sydney.edu.au

Vinay Prasad MD PhD
Oncologist and professor at UCSF, USA
Currently one of the most authoritative figures in the US on academic medicine and health policy.
The trial is reviewed and discussed in detail on his freely available podcast “Plenary session” episode 5.25 (from 35:30 min and onwards).

St. Olavs hospital Impact case #3

Institution: St. Olavs hospital
Administrative unit: St Olavs hospital, Trondheim University Hospital (St Olav)
Title of case study: Improving healthcare delivery by targeting sleep and circadian systems
Period when the underpinning research was undertaken: 2012-2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2012-2022
Period when the impact occurred: 2012-2022

1. Summary of the impact

The last decades, patients in somatic medicine has benefitted from technological advances. However, these advances have had a limited impact on mental healthcare. We explore how technology may be used to target the sleep-wake system and improve the delivery and outcomes across diagnoses in the general public and secondary care settings. We embed digital interventions for insomnia and chronotherapy into regular secondary care and test if these interventions can improve patient outcomes. These approaches can potentially change the delivery of mental healthcare services and accelerate symptom relief for patients.

2. Underpinning research

1: Digital Cognitive Behavioral Therapy for Insomnia: Evidence indicates that providing cognitive behavioral therapy for insomnia (CBT- I) to patients with comorbid mental or physical disorders not only improves sleep-wake disruption but has effects on daytime fatigue and psychological distress. Clinical implementation of the treatment is hampered due to the cost of treatment and the lack of trained staff. Thus, regardless of evidence supporting the benefits of CBT-I and its rating as the treatment of choice, it is rarely offered to patients. Instead, most patients are treated using pharmacological interventions despite the well-known risks of developing tolerance and/or addiction over time. To meet these challenges, our research group has been studying the effectiveness of a fully automated *digital* intervention, based on CBT-I (dCBT-I). During the past few years, we have started five randomized controlled trials, of which two are completed. Thus far our results point toward dCBT-I as being highly effective in the general population, with about every third participant achieving symptomatic remission within 9 weeks, and the positive effects seem to persist for at least 18 months after the intervention.

2: Chronotherapy: The Trondheim Sleep and Chronobiology Research group (SACR, ntnu.no/sleep) has integrated a set of interventions that act on the circadian system in order test if it can produce rapid effects on mental disorders for patients typically seen in mental healthcare. These interventions are called ‘chronotherapy’ and can be used in both outpatients and inpatients. The interventions include morning bright light therapy, evening dark-therapy, wake-therapy, and sleep-wake phase stabilization. Our approach is based on recent findings from basic physiology and treatment research that have elucidated how light at specific frequencies and specific times of day can impact sleep-wake disruption and arousal. Moreover, blocking specific light frequencies may be an effective treatment for the early improvement of symptoms in severe mental disorders. This is a potential breakthrough in our understanding of how severe mental disorders are maintained and offers the opportunity to develop innovative non-pharmacological interventions with little side-effects. Based on this, we have incorporated new light- and radar technologies into the acute psychiatric inpatient unit at St. Olavs hospital. This can be used to modify the light

environment in a hospital unit according to chronobiological principles. We also designed the hospital unit for randomized trials with two identical wards with different light environments, with radar technology installed in all patient rooms in both wards. We hypothesize that our strategy will improve sleep-wake disruption and improve the clinical condition. Further, the new radar technology in the ward allows for non-invasive, real-time observation of patients at night, allowing more accurate monitoring of sleep-wake cycles and symptom improvement while avoiding frequent staff interruptions. We have initiated three RCTs to test the effectiveness of chronotherapies; results from one trial are published and results from the second trial are submitted.

3: Artificial intelligence (AI): In collaboration with Prof. Kerstin Bach at the Data and AI group (https://www.ntnu.edu/health/machine-learning-to-tailor-treatments-in-mental-health) we are developing new machine-learning methods to find patterns characterizing non-responding patient groups using *all our existing data* (N ≥ 3000). These models will provide predictions for (a) whether a patient will respond to the treatment or not, and (b) whether a patient will complete or drop out of the intervention, and (c) what characterizes patients who need face-to-face therapy CBT-I rather than dCBT-I.

Radar technology and movement analyses: We have shown that radar-based movement analyses from contact-free radar assessment of the sleep-wake phase is possible using simple mathematical models. The accuracy of the prediction model could be improved using deep learning models. Moreover, while the radar was originally intended to assess sleep, we are set to develop models to predict future aggressive behavior and changes in clinical state as well.

SACR is part of the research and innovation plan of the St. Olavs hospital, Clinic of Mental Healthcare. Our approach is met with enthusiasm in the field. The group has extensive experience in performing high-quality clinical trials and includes experts across different clinical specialties and research fields (psychiatry, clinical psychology, sleep medicine, neurology, neurophysiology, neuroscience, addiction medicine) and related scientific fields (computer science, cybernetics, neuropsychology, health economy, biostatistics, and epidemiology). The group consist of senior members:

- *Håvard Kallestad,* PI, researcher, senior clinical psychologist (NTNU/St Olav,) 2012 -
- *Knut Langsrud,* MD, PhD, head of Acute Department (St Olav, Østmarka), 2012 -
- *Gunnar Morken,* Professor, senior consultant (NTNU/St Olav), 2012 -
- *Simen Saksvik,* PhD, researcher (NTNU), 2020 -
- *Ingvild Ulsaker-Janke,* PhD, researcher (NTNU), 2021 -

Key members

- *Kerstin Bach*, Professor in Artificial Intelligence (NTNU), 2022 -
- *Trond Sand*, Professor (NTNU/St Olav), 2012-2023
- *Terje Torgersen*, Head of research and innovation dept (Mental health care, St Olav), 2022-
- *Øystein Vedaa*, Department Director, Norwegian Institute of Public Health, 2012 -
- *Børge Sivertsen*, Professor, Senior researcher, Norwegian Inst. of Public Health, 2012 -
- *Morten Engstrøm*, Associate Professor and leader of Neuroclinic (St Olav), 2012 -
- *Joar Øveraas Halvorsen*, Associate Professor and senior clinical psychologist (NTNU/St Olav), 2022 -
- *Vidar Halsteinli*, PhD, health economist (St Olav), 2023-

Associated members

- *Elin Ulleberg*, Head of clinic for Mental Health Care (St Olav)
- *Vegard Vestvik*, Head of clinic for Mental Health Care (St Olav)
- *Lars Bø*, Professor, leader of Norwegian Multiple Sclerosis Competence Centre and Research Group (University of Bergen/Haukeland University Hospital)
- *Kjell Morten Myhr*, Professor Clinical Medicine (University of Bergen/Haukeland University Hospital)
- *Alexander Olsen*, Associate Professor, leader Clinical Neuroscience Laboratory, Dept of Psychology (NTNU/St Olav)
- *Rajeevkumar R. Nair*, Senior research scientist/leader Viral Vector Core, Kavli Institute for Systems Neuroscience (NTNU)
- *Roshan Das Nair*, Senior research scientist, SINTEF Digital

International collaboration:

- *Jan Scott*, Professor, Newcastle University, UK, and Adjunct Professor at NTNU 2018-2023
- *Lee Ritterband*, Professor and Director of the Center for Behavioral Health & Technology, University of Virginia, USA
- *Allison Harvey*, Professor of psychology, University of California, Berkeley, USA

Established regional, national, and international collaborations have been ongoing, highly positive, and productive. There are established meetings and contacts with members of the group and partners. Since 2023, the group and extended regional network was awarded Clinical Academic Group status from the Central Norway Regional Health Authority (https://www.helse-midt.no/samarbeidsorganet/clinical-academic-groups-cag/)

3. References to the research

Main publications

- **Øystein Vedaa**, **Håvard Kallestad, Jan Scott**, Otto R F Smith, Ståle Pallesen, **Gunnar Morken**, **Knut Langsrud**, Philip Gehrman, Frances P Thorndike, Lee M Ritterband, Allison G Harvey, Tore Stiles, **Børge Sivertsen,** *Effects of digital cognitive behavioural therapy for insomnia on insomnia severity: a large-scale randomised controlled trial,* Lancet Digit Health. 2020 Aug;2(8):e397-e406, doi: 10.1016/S2589-7500(20)30135-7.

- **Håvard Kallestad, Jan Scott, Øystein Vedaa,** Stian Lydersen, **Daniel Vethe, Gunnar Morken**, Tore Charles Stiles, **Børge Sivertsen, Knut Langsrud,** *Mode of delivery of Cognitive Behavioral Therapy for Insomnia: a randomized controlled non-inferiority trial of digital and face-to-face therapy, Sleep*, Volume 44, Issue 12, December 2021, zsab185, doi: 10.1093/sleep/zsab185

- **Daniel Vethe, Jan Scott,** Morten Engstrøm, Øyvind Salvesen, Trond Sand, Alexander Olsen, **Gunnar Morken, Hanne S Heglum, Kaia Kjørstad, Patrick M Faaland, Cecilie L Vestergaard, Knut Langsrud, Håvard Kallestad,** *The evening light environment in hospitals can be designed to produce less disruptive effects on the circadian system and improve sleep,* Sleep, Volume 44, Issue 3, March 2021, zsaa194, doi: 10.1093/sleep/zsaa194

- **Hanne Siri Amdahl Heglum, Håvard Kallestad, Daniel Vethe, Knut Langsrud**, Trond Sand, Morten Engstrøm, *Distinguishing sleep from wake with a radar sensor: a contact-free real-time sleep monitor,* Sleep. 2021 Aug 13;44(8):zsab060. doi: 10.1093/sleep/zsab060.

4. Details of the impact

Trondheim Sleep and Chronobiology Research Group has gradually gained experience with different treatment interventions and new methods of observation and diagnostics in close connection with the clinics of mental healthcare at St Olav Hospital and user organizations. In the last years the group has expanded their efforts by including participants in studies both from the rest of St Olav and from mental healthcare clinics all over Norway (≥ 20). At NTNU the group has, in addition to Dep of Mental Health, developed close cooperation with Department of Psychology, Department of Computer Science and the clinic of neurophysiology at St. Olavs Hospital, with PhD students employed in all four departments. SACR has established a national and international research network which has previously conducted several RCTs, including researchers from the Norwegian Institute of Public Health and international collaboration with the University of Virginia and University of California, Berkeley. This research network has been essential in the setup of the previously described trials on dCBT-I and will be important for planned future trials. The results from completed, ongoing, and planned trials has the potential of being highly relevant for patients and their next of kin, in addition to having clear scientific impact. Due to the novelty and scope of the projects, publications in high impact international journals are likely. The main publication from the RCT of dCBT-I in the general population was published in The Lancet Digital Health (Impact factor: 36.615). Through the established collaborations, our group is key for the implementation of recommended treatments for sleep and chronobiology across Norway.

The research group's societal contribution, including user-oriented publications:

No.	Name of publication	Date	Link to the document
1	Helautomatisk måling og behandling av søvn i Trondheim	18.03.2022	https://www.helse-bergen.no/nasjonal-kompetansetjeneste-for-sovnsykdommer-sovno/tidsskriftet-sovn/
2	Kan nett-terapi mot søvnløshet hjelpe mot psykisk sykdom?	08.10.2020	https://forskning.no/psykiske-lidelser-sovn/kan-nett-terapi
3	Søvnproblemer under radaren	01.12.2012	https://www.forskning.no/psykiske-lidelser-sovn/sovnproblemer-under-radaren/667633
4	Slik vil forskerne hjelpe søvnløse	15.02.2017	https://www.forskning.no/psykologi-sovn/slik-vil-forskerne-hjelpe-sovnlose/365014
5	Kan oransje lys hjelpe psykisk syke?	09.11.2017	https://www.forskning.no/ntnu-partner-psykiske-lidelser/kan-oransje-lys-hjelpe-psykisk-syke/311226

5. Sources to corroborate the impact

- Sean W Cain, Andrew J K Phillips, *Do no harm: the beginning of the age of healthy hospital lighting,* Sleep, Volume 44, Issue 3, March 2021, zsab016, https://doi.org/10.1093/sleep/zsab016

- Annemieke van Straten, Jaap Lancee, *Digital cognitive behavioural therapy for insomnia: the answer to a major public health issue?* Lancet Digit Health. 2020 Aug;2(8):e381-e382. doi: 10.1016/S2589-7500(20)30167-9.

- Eva Charlotte Winnebeck, Dorothee Fischer, Tanya Leise, Till Roenneberg, *Dynamics and Ultradian Structure of Human Sleep in Real Life,* Curr Biol. 2018 Jan 8;28(1):49-59.e5. doi: 10.1016/j.cub.2017.11.063. Epub 2017 Dec 28.

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For up to 10 researchers: one case; for 10 to 30 researchers: two cases; for 30-50 researchers: three cases; for 50-100 researchers: four cases, and up to five cases for units exceeding 100 researchers.

Naming and numbering of cases

Please use the standardised short name for the administrative unit, and the case number for the unit (1,2,3, etc) in the headline of the case. Each case should be stored as a separate PDF-document with the file name: [Name of the institution and name of the administrative unit] [case number]

Publication of cases

RCN plans to publish all impact cases in a separate evaluation report. By submitting the case the head of the administrative units consents to the publication of the case. Please indicate below if a case may not be made public for reasons of confidentiality.

If relevant, describe any reason to keep this case confidential:

Please write the text here

[Name of the institution and name of the administrative unit] [case number]

Institution: NTNU
Administrative unit: Faculty of Medicine and Health Science
Title of case study: High-dose, twice-daily thoracic radiotherapy prolongs survival in limited stage small cell lung cancer
Period when the underpinning research was undertaken: 2014-2020
Period when staff involved in the underpinning research were employed by the submitting institution: 2007-
Period when the impact occurred: 2020-

1. Summary of the impact (indicative maximum 100 words)

SCLC is the most aggressive lung cancer and causes 4% of cancer deaths. Treatment for limited stage SCLC is concurrent chemo- and radiotherapy. Twice-daily (BID) thoracic radiotherapy (TRT) is recommended, but poorly implemented due to concerns about toxicity. We were the first to show that BID TRT is more effective than hypofractionated TRT and does not cause more toxicity. Subsequent implementation of BID TRT in Norway led to improved survival. We then showed that high-dose BID TRT almost doubles survival time and 40% more patients are cured. This is the first positive randomized trial in this setting for >25 years.

2. Underpinning research (indicative maximum 500 words)

Concurrent chemo- and radiotherapy has been standard treatment for limited stage (LS) SCLC since the early 1990's. A trial published in 1999 showed that BID TRT of 45 Gy in 30 fractions was superior to QD TRT of 45 Gy in 25 fractions. However, the BID schedule caused more toxicity and logistical challenges, and although BID TRT has been recommended in international guidelines, population-based studies show that only a minority actually receive such TRT.

Once-daily (QD) hypofractionated TRT was still standard schedule in Norway and other countries (especially UK and Canada). Survival for LS SCLC was much lower in Norway in the 1990's than in international trials (median overall survival 14.5 months, 5-year survival 10%). We performed the first randomized trial comparing hypofractionated QD with BID TRT (HAST-trial, enrolled patients from 2005-11, published in 2015). Numerically, BID TRT prolonged median overall survival (25.1 vs. 18.8 months) and did not cause more toxicity. These data supported the assumed superiority of BID TRT and we implemented the BID schedule as the new standard in Norway in 2012 when the first results were presented.

Using data from the Norwegian Cancer Registry, we evaluated the impact of implementing BID TRT on a population level (published in 2021). We found that the proportion who received BID TRT increased from 1.8% to >90% during the study period, and a clinically relevant improvement in median survival time similar to in our trial (26.2 vs. 19.6 months) and a doubling in 5-year survival (33% vs. 16%). The implementation rate of BID TRT (>90%) was the highest ever seen in a population based study (typically 15-35%).

Still, there was a need for better treatment. It had been hypothesized that higher TRT doses might improve local control and thus survival. However, large phase III trials have failed to show a survival benefit of high-dose QD TRT. We performed a randomized phase II trial comparing high-dose BID TRT of 60 Gy in 40 fractions with the 45 Gy in 30 fractions (patients enrolled 2014-18, first results presented 2020, first publication 2021). Median overall survival in the high-dose group was almost twice as long as in the control arm (43.6 vs. 22.6 months) and 5-year survival increased with 40% (40.4% vs. 28.4%). Notably, the higher dose did not

cause more toxicity. This is the first positive randomized trial in this setting for more than 25 years.

We have implemented 60 Gy as our standard schedule and will evaluate the impact using data from the Norwegian Cancer Registry (similar to our evaluation of the 45 Gy schedule). We were also the first to report patient-reported outcomes in this setting. These data show that severe radiotherapy esophagitis, considered to be the most dose-limiting toxicity, is transient and that almost all patients recover within a few weeks after completing TRT. Thus, the clinical impact is less and more transient than previously believed.

Population based studies show that older patients and those with comorbidity are less likely to receive standard chemoradiotherapy. Thus, we investigated whether outcomes differ among patients with severe comorbidity or old age compared with younger and more fit, and conclude that also these patients should receive standard chemoradiotherapy. This is important since a majority of LS SCLC patients are >70 years and have a history of heavy tobacco smoking which causes significant comorbidity.

- Names of the key researchers and what positions they held at the administrative unit at the time of the research (where researchers joined or left the administrative unit during this time, these dates must also be stated).
- Any relevant key contextual information about this area of research.

3. References to the research (indicative maximum of six references)

Grønberg, B. H. et al. Randomized phase II trial comparing twice daily hyperfractionated with once daily hypofractionated thoracic radiotherapy in limited disease small cell lung cancer. Acta oncologica (Stockholm, Sweden) 55, 591–597 (2016)

Halvorsen, T. O. et al. Comorbidity and outcomes of concurrent chemo- and radiotherapy in limited disease small cell lung cancer. Acta oncologica (Stockholm, Sweden) 1–9 (2016) doi:10.1080/0284186x.2016.1201216.

Graabak, G., Grønberg, B. H., Sandvei, M. S., Nilssen, Y. & Halvorsen, T. O. Thoracic Radiotherapy in Limited-Stage Small-Cell Lung Cancer – a Population-Based Study of Patterns of Care in Norway from 2000 until 2018. JTO Clin Res Reports 100270 (2021) doi:10.1016/j.jtocrr.2021.100270

Grønberg, B. H. et al. High-dose versus standard-dose twice-daily thoracic radiotherapy for patients with limited stage small-cell lung cancer: an open-label, randomised, phase 2 trial. Lancet Oncol 22, 321–331 (2021)

Killingberg, K. T. et al. Patient-reported health-related quality of life from a randomized phase II trial comparing standard-dose with high-dose twice daily thoracic radiotherapy in limited stage small-cell lung cancer. Lung Cancer 166, 49–57 (2022).

Killingberg, K. T., Grønberg, B. H., Slaaen, M., Kirkevold, Ø. & Halvorsen, T. O. Treatment outcomes of older participants in a randomized trial comparing two schedules of twice-daily thoracic radiotherapy in limited stage small-cell lung cancer. J Thorac Oncol (2023) doi:10.1016/j.jtho.2023.01.012.

4. Details of the impact (indicative maximum 750 words)

Even if guidelines have recommended BID TRT since the publication of the results of the Intergroup 0096 trial in 1999, a minority of patients actually receive such TRT. Most patients receive QD schedules that have never been compared with the recommended schedules, and it appears that clinical practice to a large extent is opinion driven rather than evidence based.

This was also the case for the former Norwegian standard, hypofractionated QD schedule. According to calculations of biological effective dose, it should actually be slightly more effective than the BID 45 Gy schedule, and older colleagues were convinced that it was better tolerated, illustrating the need to perform comparisons through randomized controlled trials.

However, we know that patients eligible for clinical trials on average have less comorbidity, are younger and more fit than the average patient. Consequently, it is of essential to evalute the effect of new interventions on a population level. Supported by our subgroup analyses of patients with comorbidity, we have documented an implementation level that by far exceeds any other international population based study. More importantly, the implementation of BID TRT led to a survival improvement which mirrors the data from our trial.

Our trial demonstrating that BID TRT of 60 Gy prolongs survival represent the largest improvement in this setting for more than 25 years. Most notably, the higher dose did not cause more toxicity, and subgroup analyses show that also older patients tolerate this treatment, supported by patient reported health related quality of life data.

Since the presentation of the primary results of this trial in 2020, the 60 Gy schedule has been standard in Norway, and implementation has been easy. The exact implementation rate and impact on survival will be evaluated in 2025 using the same methods as when we evaluated implementation of the 45 Gy schedule. The Norwegian Cancer Registry has excellent data to identify LS SCLC patients and full overview over all radiotherapy administered to each individual patient.

Results have been presented at the largest cancer conferences in the world (oral presentations at ASCO and ESMO, invited speaker at WCLCs and ESMO) and published in the highest ranking oncology journal (Lancet Oncology, IF 51 in 2023). They have been cited in review articles and recommended by key opinion leaders, and we know from personal communication that it is standard in Scandinavian hospitals and implemented also internationally.

All trials have been designed, organized, and performed by our study group. The group leader is also the chairman of the Norwegian Lung Cancer Study Group which developed and updates Norwegian guidelines for diagnosis and treatment lung cancer and thus, he has been essential in the implementation of our research results. The trials have been conducted in collaboration with colleagues in Norway and abroad through a network that he has established for this purpose.

Lung cancer is one of the areas in oncology in which most progress has been seen the last decades, but unfortunately, not much improvement has been seen for SCLC and the prognosis for these patients have been unchanged. Thus, the research activity addresses large unmet needs, and has resulted in a most welcome treatment improvement for a largely neglected subgroup of patients with cancer.

5. Sources to corroborate the impact (indicative maximum of ten references)

The most important is the already mentioned article reporting the improvement in survival in Norway due to the implementation of BID TRT:

Graabak, G., Grønberg, B. H., Sandvei, M. S., Nilssen, Y. & Halvorsen, T. O. Thoracic Radiotherapy in Limited-Stage Small-Cell Lung Cancer – a Population-Based Study of Patterns of Care in Norway from 2000 until 2018. JTO Clin Res Reports 100270 (2021) doi:10.1016/j.jtocrr.2021.100270

The article reporting the results of the high-dose BID TRT is currently cited 80 times. The final survival analyses will be published Q1 2024, and since these numbers are even better (median was not reached in the primary analysis), we expect even more citations.

Some examples of citations of our results:

https://dailynews.ascopubs.org/do/podcast-asco23-novel-therapies-lung-cancer?cid=DM13647&bid=273135954

https://register.gotowebinar.com/register/6062998916380287066

Bogart JA, Waqar SN, Mix MD. Radiation and Systemic Therapy for Limited-Stage Small-Cell Lung Cancer. J Clin Oncol. 2022 Feb 20;40(6):661-670. doi: 10.1200/JCO.21.01639. Epub 2022 Jan 5. PMID: 34985935; PMCID: PMC10476774.

Dumoulin DW, Bironzo P, Passiglia F, Scagliotti GV, Aerts JGJV; ERN-LUNG Core Network Mesothelioma. Rare thoracic cancers: a comprehensive overview of diagnosis and management of small cell lung cancer, malignant pleural mesothelioma and thymic epithelial tumours. Eur Respir Rev. 2023 Feb 7;32(167):220174. doi: 10.1183/16000617.0174-2022. PMID: 36754434; PMCID: PMC9910338.

St. Olavs hospital Impact Case #5

Center for Medical devices, technology, and innovation

Case: Fraxinus

Institution: St. Olavs hospital
Administrative unit: St. Olavs hospital
Title of case study: Fraxinus – Open Source Software for planning bronchoscopy in lung cancer diagnostics
Period when the underpinning research was undertaken: 2016-2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2016-2022
Period when the impact occurred: 2018-2022

1. Summary of the impact (indicative maximum 100 words)

Fraxinus is a decision support software-only platform for planning and guidance in bronchoscopy and will be able to increase the success rate of biopsy sampling. Systems for navigation are available in the market, but these are expensive, have high running costs, and complex to take into clinical use. Only a few specialised centres can make the necessary investments. Our solution can be used in any clinic performing lung cancer diagnostics. By integrating available radiological information (mainly CT and PET), Fraxinus will automatically segment all relevant structures and suggest a path to the target lesion. The current open-source software is in early stage clinical testing at five Norwegian hospitals.

The platform has been used to attract international research and innovation projects from Eureka, EEA (Romania-Norway), and national/regional funding, including pre-commercial projects. The software has also been tested and used in research and product development in Chine, Russia, Australia, India, in addition to Norway.

2. Underpinning research (indicative maximum 500 words)

The research team started in 2008 with a PhD project linked to the national advisory unit for ultrasound and image guided therapy at St. OLavs hospital. From this work our research group in collaboration with Norwegian and European industry and clinical end-users have developed an early prototype of a navigation system based on electromagnetic tracking (Eurostars Eureka project MARIANA). Further, we pursued and investigated the possible commercialization of a software-only system for planning and guiding bronchoscopy. Such a system would have very low running costs and the investments would be minute compared to full-fledged navigation systems with advanced (single use) instruments with integrated electromagnetic tracking and steering capabilities. For most cases, we believe that such a software-only system, would increase the success rate of tissue sampling to a significantly higher level. Furthermore, we have conducted a 1-year innovation project on the user interface and set-up of the software (2019-20). Recently, we have implemented a state-of-the-art machine learning algorithm for nodule detection in CT scans,

a method that reduces the efforts needed by radiologists/pulmonologists in the preparatory phase. Our research in this field includes publications such as:

- **Navigation and guidance platform**: preclinical and clinical feasibility testing of guidance technology, including human trials at TRL5-6. This includes the work from 3 PhD projects (1-3)
- **Basic technological components development and demonstration**:
  - Automatic registration of preoperative images to the patient (4-5)
  - Segmentation of airway structures (6-9), including a Master thesis report on AI techniques for automatic segmentation of nodules (10)
  - Decision support software platform (11, 12)
  - Visualization techniques (13-16)
  - Electromagnetic tracking system development (17, 18)
- **Clinical demonstration of prototypes (19-21)**

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2. Sorger H. Clinical PhD, NTNU, Trondheim, Norway, 2018. Development of navigated US bronchoscopy.
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4. Hofstad EF, Sorger H, Leira HO, Amundsen T, Langø T. Automatic registration of CT images to patient during the initial phase of bronchoscopy: a clinical pilot study. Med Phys. 2014, Apr;41(4):041903. doi: 10.1118/1.4866884. PubMed PMID: 24694134.
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Håkon O. Leira, MD, PhD, Senior Consultant, Dept. Thoracic Medicine, St. Olavs hospital, Trondheim University Hospital
Hanne Sorger, MD, PhD, Senior Consultant, Dept. Thoracic Medicine, Levanger hospital
Arne Kildahl Andersen, MD, PhD candidate, Dept. Thoracic Medicine, St. Olavs hospital
Erlend F Hofstad, MSc, Technological Project leader, SINTEF, Medical technology
Thomas Langø, PhD, Chief Scientist, Medical technology, SINTEF
Ole Vegard Solberg, PhD, Senior Software developer, SINTEF, Medical technology
David Bouget, PhD, Senior researcher, AI in medical image analysis, SINTEF, Medical technology

3. References to the research (indicative maximum of six references)

See reference list in section 2 above. The technology (Fraxinus) is in early-stage clinical testing at five Norwegian hospitals. The software is open access and can be downloaded from here: https://github.com/SINTEFMedtek/Fraxinus

The basis of the software is CustusX; https://github.com/SINTEFMedtek/CustusX and also the NorMIT platform: https://normit.no/en/downloads/

4. Details of the impact (indicative maximum 750 words)

Studies are currently underway to provide data to document impact of the software for planning and guiding bronchoscopy for lung cancer diagnostics.

5. Sources to corroborate the impact (indicative maximum of ten references)

Kjetil Roth, Ålesund hospital
Hanne Sorger, Levanger hospital
Astrid Kravdal, Gjøvik hospital
Vibeke Melby, Bærum hospital
Arve Sundset, Oslo University hospital
Anders Bugge, Oslo University hospital
Fabian Kirchner, Akershus Univerisy hospital, Oslo

National Institute of Occupational Health, STAMI - Case no. 1

Institution: STAMI
Administrative unit: STAMI
Title of case study: THE NEW WORKPLACE
Period when the underpinning research was undertaken: 2012-2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2012-2022
Period when the impact occurred: 2012-2022

1. Summary of the impact

Common mental disorders and musculoskeletal disorders are leading causes of reduced work ability, increased sick leave, and disability pension. The knowledge derived from this project has proven crucial in highlighting that a substantial proportion of common health problems among employees can be attributed to specific psychosocial risks in the workplace. This project has introduced psychosocial work factors as identifiable and measurable entities that can serve as objects for mapping, risk assessment, and preventive measures in the workplace. Advocating for the survey-feedback model, the project raised awareness of psychological and social factors crucial to well-being, health, and function, promoting the use of scientifically based survey data to enhance the psychosocial work environment. Furthermore, the project has contributed to the revision of the content of labor inspections and has raised awareness of the potential for prevention through improved systematic health and safety management of psychosocial risks in the workplace. Finally, the project has led to investigative efforts aimed at strengthening and clarifying legal requirements for the psychosocial work environment.

2. Underpinning research

Context: This research emerged in response to the Research Council of Norway's call for prospective studies of the impact of psychosocial work factors on health, absenteeism, and workforce exit in Norway. In the early 2000s, the relevant knowledge base was predominantly shaped by a few theoretical models, most evidently the Demands-Control model. While it had contributed valuable insights, its prominence had resulted in a selective focus, limiting the general applicability of the knowledge base. It was most often studied in terms of two factors – "job demands" and "job control" – which are rather general and combine several specific concepts. For instance, "job demands" subsumes amount of work, time pressure, and conflicting demands (role conflict). These are distinct, specific concepts that may operate by different psychological processes and have differential health effects.

Project Information: The study was designed to explore the relationship between various specific psychosocial factors and health, while offering practical insights for companies and policymakers. We conducted a survey covering a comprehensive array of specific, modifiable work factors to operationalize "the psychosocial work environment". Some important features were i) Mapping a wide range of specific factors enabled simultaneous comparison of their effects within the same work environments. Practical significance could be compared, providing practitioners with valuable advice on what to prioritize. ii) Repeated participation from organizations resulted in most publications being based on prospective analyses. iii) The comprehensive approach included gathering data on multiple outcomes, potential moderators, and mediators at each time point. This enabled nuanced examinations of potential processes involved. For instance, it allowed comparison of hypothesized effects with alternative explanations such as reverse causality (e.g. health influences reporting of work factors). iv) Data were gathered at multiple levels of the

organizations. This allowed multilevel examinations, for instance of average work unit levels of work factors on individual employees' health. Among other things, this addresses biases associated with individual self-report.

Further enhancing the practical significance of the project, participating organizations received feedback reports along with guidance for interpretation, so they could identify and address challenges specific to their work environment.

Key Research Insights: So far, more than 40 peer-reviewed scientific articles from this project have revealed critical and nuanced insights about psychosocial work characteristics and health. We discovered that some factors which are often subsumed under broader dimensions are more significant risk factors when considered independently. We identified role conflict as one of the most consistent risk factors overall. However, amount of work (quantitative workload), which is often combined with role conflict in measuring "job demands", seemed much less important. Similar insights were gained for other factors.

Specific Findings with Societal Impact: Documenting effects of specific work factors provide practical information for businesses. For instance, advice to "remove role conflict by clarifying, synchronizing, and harmonizing expectations from different levels of management" is more actionable than "reduce job demands and stress". We documented the relative importance of several other factors, e.g., fair and empowering leadership, emotional dissonance, and positive workplace challenges. Our studies also showed that shared or open-plan offices are associated with higher risks of absence and disability than cellular offices. Specific modifiable factors can be targeted in improvement efforts. Hence, knowledge from this project should contribute to improving occupational health substantially.

Names of the key researchers

Name	Position	Period
Knardahl, Stein. MD. PhD.	Research Director	2012 – 2022
Christensen, Jan Olav. PhD.	Research Professor	2012 – 2022
Nielsen, Morten B. PhD.	Lead Research Professor	2012 – 2022
Finne, Live Bakke. PhD.	Research Associate Professor	2012 – 2022

3. References to the research

1. **Christensen, J. O., Knardahl S**. Work and headache: a prospective study of psychological, social, and mechanical predictors of headache severity (2012). PAIN 153(10) :s. 2119-2132. Impact factor (IF): 7.9
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2. **Finne LB, Christensen JO, Knardahl S:** Psychological and social work factors as predictors of mental distress: a prospective study (2014). PLoS ONE, 9:e102514
   Impact factor (IF): 3.7
   https://doi.org/10.1371/journal.pone.0102514

3. **Christensen, J. O., Nielsen, M. B., Finne, L. B., & Knardahl, S.** Comprehensive profiles of psychological and social work factors as predictors of site-specific and multi-site pain. Scandinavian journal of work, environment & health (2018) 44(3): s.291-302.
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Impact factor (IF): 3.0.
https://doi.org/10.1007/s00420-019-01463-y

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Impact factor (IF): 6.3
https://doi.org/10.5271/sjweh.3859

6. **Finnanger G.B, Knardahl S, Emberland JS, Skare Ø, Johannessen HA.** Effects of the Labour Inspectorate Authority's regulatory tools on psychosocial and biomechanical work factors in Norwegian home care services: a cluster randomised controlled trial. Occupational and Environmental Medicine (2022). 79(12), s. 807-815 Impact factor (IF): 4.9
https://doi.org/10.1136/oemed-2022-108470

4. Details of the impact

This project provided new insights into the relationship between various aspects of the psychosocial work environment and prevalent health issues among employees, including musculoskeletal and mental disorders. Defining and operationalizing psychological, social, and organizational work factors, the project introduced measurable entities for mapping, risk assessment, and preventive measures. The project illuminated both factors contributing to ill health, such as high psychological demands and role conflicts, and factors promoting health, such as aspects of job autonomy and positive challenges at work. Moreover, the project shed light on a comprehensive set of factors that can mitigate the impact of risk factors on health, such as empowering, supportive, and fair leadership.

The new knowledge has been applied and disseminated in courses for health, safety, and occupational health practitioners at STAMI, a key institution for training such professionals in Norway[4]. Additionally, the insights from the project have been shared through lectures at universities and businesses. The impact has further extended to a broader audience through extensive coverage in mass media channels.

Advocating for the survey-feedback model, the project aimed to improve work conditions by surveying work characteristics, presenting results to organizational units for discussion and acceptance of risk factors, and planning interventions. Implemented in participating organizations, this model raised awareness of psychological and social factors crucial to well-being, health, and function, promoting the use of scientifically based survey data to enhance the psychosocial work environment.

The survey-feedback model and research insights formed the basis for the scientifically based employee survey, "The State Survey of Employees (MUST)[1]", introduced for all governmental employees. With 70 entities conducting the MUST survey and over 33,000 participants as of November 2023, this initiative has gained significant traction, providing a science-based system for mapping the work environment.

The project's findings played a pivotal role in enhancing STAMI's surveillance system, contributing to the development of new indicators for assessing the psychosocial work environment. Validated questions on psychosocial risk factors were added to the national representative survey, "Working Environment: Survey on Living Conditions," conducted every third year by Statistics Norway[3]. This

survey serves as a primary data source for monitoring the work environment and health in Norway. Based on new psychosocial indicators and this representative sample of the working-age population, it was possible to estimate the amount of ill health and sickness absence attributable to psychosocial work factors. These estimates demonstrated that a considerable proportion of prevalent health issues and instances of sickness absence could be attributed to various psychosocial factors in the workforce. For instance, an estimated 40 percent of lower back pain cases, 25 percent of mental distress cases, and 15 percent of doctor-certified long-term sick leave cases were found to be attributable to adverse working conditions. This new knowledge has raised awareness of the potential for prevention through improved systematic health and safety management of psychosocial risks in the workplace. It has prompted stakeholders, including employers and policymakers, to recognize the importance of proactive measures in addressing psychosocial factors that can impact employee health.

Awareness and knowledge derived from the project contributed to redefining the content of the "Inclusive Work Agreement" (IA) (2019-2024)[4], a tripartite cooperation for a more inclusive working life in Norway. The agreement aims to achieve high employment and mobilize the workforce by preventing and reducing sick leave and withdrawal from working life. The revision placed increased focus on preventing working conditions scientifically documented to have effects on sick leave and withdrawal, including musculoskeletal and common mental disorders typically associated with sick leave. The project's research and indicators were central to providing enterprises with updated knowledge, facts, and user-oriented tools[6], facilitating a systematic and knowledge-based approach to managing their work environment[7].

Furthermore, the project played a pivotal role in the revision of the content of labor inspections. The insights influenced the focus and scope of inspections, placing greater emphasis on assessing and addressing psychosocial risks alongside traditional safety concerns. Additionally, the project prompted a call for research to assess whether the Labour Inspection Authority possessed efficient regulatory tools to guide enterprises in providing psychosocial and ergonomic working conditions in accordance with Occupational Safety and Health (OSH) legislation and regulations.

The findings from these studies contributed to the Labour Inspection Authority initiating investigative efforts aimed at strengthening and clarifying legal requirements for the psychosocial work environment. The resulting report concluded that current regulations are insufficient, underscoring the need to improve legal texts specifically addressing the psychosocial work environment[2].

In essence, the project expanded the societal understanding of the relationship between psychosocial work factors and employee health, catalyzing practical changes in policies and practices, fostering a healthier and more supportive work environment for employees.

5. Sources to corroborate the impact

1. The Working Conditions Survey for Governmental Agencies (MUST)
   The State Survey of Employees (MUST) - STAMI

2. Technical Report. Investigation by the Labour Inspection Authority 2023. "Need for improved regulation of the requirements of the Working Environment Act for psychosocial work environment". Behov for bedre regulering av arbeidsmiljølovens krav til psykososialt arbeidsmiljø (arbeidstilsynet.no)

3. Working environment, survey on living conditions https://www.ssb.no/en/arbeid-og-lonn/arbeidsmiljo-sykefravaer-og-arbeidskonflikter/statistikk/arbeidsmiljo-levekarsundersokelsen

4. The Governmental Agreement for an Inclusive work place 2019-2024: The IA Agreement 2019–2024 - regjeringen.no

5. The educational courses for occupational health and safety personnel Educational Activites - STAMI

6. A tool to improve the work environment A Great Day at Work - STAMI

7. The working Environment Programme The Working Environment Programme - STAMI

National institute of occupational health, STAMI - Case no. 2

Institution: STAMI
Administrative unit: STAMI
Title of case study: Occupational Cancer
Period when the underpinning research was undertaken: 2012-2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2012-2022
Period when the impact occurred:2012-2022

2. Summary of the impact

STAMI provides knowledge relevant for human carcinogenesis for the purpose of advising regulatory bodies, enterprises, employees and the society about occupational cancer risk assessment and to improve risk management. STAMI contributes to knowledge dissemination regarding occupational cancer through contributions to the International Agency for Research on Cancer (IARC) Monographs, Nordic Expert Group (NEG) documents, STAMI-reports, EU projects and regulatory toxicology on a national level for the setting and revision of occupational limit values. STAMI develops exposure assessment methods to enable compliance with lowered limit values and provided knowledge needed for medico-legal approval of occupational cancer compensation and for prevention of occupational cancer by exposure reduction activities.

3. Underpinning research

At the start of the evaluation period both Norwegian and international working life stood on the threshold of major transitions increasing the need for knowledge on cancer risks in changing industrial processes and work organisation. Worldwide, occupational cancer constitutes about three percent (2-8 percent) of all cancer cases, indicating approximately 1.000 cases annually in Norway. During the period 2012-2022, STAMI has published more than 180 scientific papers related to occupational cancer using different methodology such as cancer epidemiology, exposure assessment of potential carcinogens, and toxicology and mechanisms of carcinogenesis.

STAMI has performed human observational studies of cancer incidence in national cohorts of fire fighters, petroleum exploitation and refinery workers, metal smelter workers, laboratory workers exposed to benzene, workers exposed to diesel exhaust, respirable crystalline silica, silicon carbide, night shift workers, farmers, and among workers exposed to electromagnetic fields. Some examples are the Agricultural Cohort Consortium (agricoh.iarc.fr) led by the International Agency for Research on Cancer (IARC), were STAMI performed analysis of lymphomas according to agricultural production for the international pooling of result in the consortium, identifying associations of glyphosate exposure with a subtype of lymphoma[1]. STAMI is also a partner in the Nordic cooperation network in Occupational Cancer (NOCCA). In this joint effort STAMI studied occupational risk variation of nasopharyngeal cancer by grouping the Nordic population by industry[2]. Furthermore, STAMI developed a study-specific job exposure matrix (JEM) relevant for epidemiologic studies on occupational cancer, which have been used in a range of studies, including a study on rock drillers exposed to crystalline silica[3].

STAMI has additionally performed exposure assessment studies of potential carcinogens among employees exposed to diesel exhaust in underground engine-powered production, mining, tunnel production, asbestos in demolition work, wood dust during manufacturing of building materials, respirable crystalline silica in rock drilling operations, and to ultrafine particles in smelters, welding, and laser cutting operations. Furthermore, biological monitoring of benzene-exposed employees[4] and exposure assessments to metals including chromium among welders have been performed.

Finally, STAMI has performed toxicological studies relevant for the exposure of cultured cells to welding fumes, nanoparticles including carbon nano tubes, titanium oxide, silica and silicomanganese particles, polyaromatic hydrocarbons (PAH), persistent organic pollutants, diesel exhaust and exposure to electromagnetic fields. In a study of mechanisms relevant for cancer development among tunnel-finishing workers exposed to diesel exhaust particles, levels of PAH-adducts to DNA and altered micro-RNA expression and lipid profiles was included[5]. Furthermore, STAMI has characterised lung cancer susceptibility according to genetic and epigenetic patterns. Further, mechanisms of disruption of diurnal rhythms by night shift, relevant for breast cancer risk, were studied using epigenetic methods. For example, a study on night shift work as a mechanisms of breast cancer development by identifying key pathways of mechanisms that support the observed association in human studies[6].

In sum, STAMI contributes to the identifications of new cancer risks, tools for risk assessment, refined exposure assessment methods for epidemiology and regulatory purposes, updated regulatory actions, and to the identification of mechanisms by which observed increases of cancer incidence rates in working populations can develop.

Names of the key researchers

Name	Position	Period
Ellingsen, Dag. MD. PhD.	Lead Research Prof. /Research Director	2012 – 2022
Zienolddiny (Narui), Shan. PhD.	Lead Research Prof./Head, Research Field	2012 – 2022
Skaug, Vidar. MD.	Head Physician	2012 – 2021
Mollerup, Steen. PhD.	Lead Research Professor	2012 – 2022
Samulin-Erdem, Johanna. PhD.	Research Associate Professor	2013 – 2022
Wallin, Håkan. PhD.	Lead Research Prof./Head, research Field	2017 – 2022
Skaugset, Nils Petter. PhD.	Researcher/Group Leader	2012 – 2022
Ervik, K. Torunn. PhD.	Research Professor	2017 – 2022
Olsen, Raymond. PhD.	Research Professor	2012 – 2022
Nordby, Karl-Christian. MD. PhD.	Research Professor/Head, Research Field	2012 – 2022
Ingrid, Mehlum S. MD. PhD.	Lead Research Professor	2012 – 2022
Bugge, Merete D. MD. PhD.	Head Physician	2012 – 2022
Lie, Jenny-Anne S. PhD.	Research Professor	2012 – 2022
Alfonso, Jose H. MD, PhD.	Research Professor	2014 – 2022
Kristensen, Petter. MD, PhD.	Lead Research Professor	2012 – 2022
Ulvestad, Bente. MD, PhD.	Lead Research Professor	2012 – 2022

4. References to the research (STAMI-researchers in bold typing)

1. Leon M.E., Schinazi L.H., Lebailly P., Freeman L.E.B., **Nordby K.-C**., Ferro G., Monnereau A., Brouwer M., Tual S., Baldi I., Kjærheim K., Hofmann J.N., **Kristensen P**., Koutros S., Straif K., Kromhout H., Schüz J. Pesticide use and risk of non-Hodgkin lymphoid malignancies in agricultural cohorts from France, Norway and the USA: a pooled analysis from the AGRICOH consortium. Int J Epidemiol (2019) 48(5) s.1-17. Impact factor 7.70 http://dx.doi:10.1093/ije/dyz017

2. Carpen T., Gille E., Hammarstedt-Nordenvall L., Hansen J., Heikkinen S., Lynge E, Selander J., **Mehlum I.S.**, Torfadottis J.E., Makitie A., Pukkala E. Occupational risk variation of nasopharyngeal cancer in the Nordic countries. BMC Cancer (2022) 22:1130. Impact factor (IF): 3.80 https://doi.org/10.1186/s12885-022-10209-y

3. **Ulvestad B, Skaugset NP**, Aaløkken TM, Günther A, **Clemm T**, Lund MB, **Ellingsen DG**. Pulmonary function and high-resolution computed tomography in outdoor rock drillers exposed to crystalline silica. Occupational and Environmental Medicine (2020) 77, s. 611–616. Impact factor 4.95 https://doi.org/10.1136/oemed-

4. **Rosting C, Olsen R**. Biomonitoring of the benzene metabolite s-phenylmercapturic acid and the toluene metabolite s-benzylmercapturic acid in urine from firefighters. Toxicology Letters (2020) 329, s.20-25. Impact factor 4.27 https://doi.org/10.1016/j.toxlet.2020.04.018

5. **Rynning I**, Volker M A, Vrbova K, Neca J, Rossner P, Klema J, **Ulvestad B, Petersen E, Skare Ø, Haugen Aa**, Phillips DH, Machala M, Topinka J, **Mollerup SK**. Bulky DNA adducts, microRNA profiles, and lipid biomarkers in Norwegian tunnel finishing workers occupationally exposed to diesel exhaust. Occupational and Environmental Medicine (2019) 76 (1) s. 10-16. Impact factor 4.95 http://dx.doi.org/10.1136/oemed-2018-105445

6. **Samulin Erdem J., Notø H.Ø., Skare Ø., Lie J.S.,** Petersen-Øverleir M., Reszka E, Pepłońska B, **Zienolddiny S**. Mechanisms of breast cancer risk in shift workers: association of telomere shortening with the duration and intensity of night work. Cancer Medicine. (2017) 6(8) s. 1988-1997. Impact factor (IF): 4.71 https://pubmed.ncbi.nlm.nih.gov/28707432/

4. Details of the impact

During 2012-2022 STAMI's research on occupational cancer has contributed scientific knowledge on the associations between occupational exposure and cancer outcomes in many reports and documents used by the Ministry of Labour and Social Inclusion, industries, businesses and workers to identify workers at risk and thereby helping to target systematic risk assessment and preventive measures in the workplace. Additionally, STAMI's occupational cancer research has provided

scientific knowledge used as foundation for the labour inspectorates in the decisions on setting occupational exposure limit values. This is of great importance for a safe and healthy working life and to the benefit of workers exposed to carcinogenic substances in their occupation. Finally, the research and expertise built up on the occupational cancer field is used in consultation statements and in participation in different committees set up by authorities related to activities and societal efforts on the prevention of occupational cancer at large.

Influence on policy and regulatory decision-making: STAMI's research has had an impact on regulatory activity related to occupational cancer risk on a societal level both nationally and internationally. For example, STAMI's research into the mechanisms of potential breast cancer risk among female workers engaged in night shift work has been used for the regulatory decisions necessary to limit the risk of night shift work. This contributes and impact policy as the International Agency for Research on Cancer (IARC) presently has classified night shift work with disruption of circadian rhythms as probably carcinogenic to humans (2A)1. Furthermore, STAMI's research on lung cancer risk (and other respiratory health hazards) of respirable crystalline silica (RCS) exposure 2,3 has contributed to a risk assessment document from the Toxicological Expert Group at STAMI, that was the basis of a decision to lower the Occupational Exposure Limit of respirable crystalline silica (RCS) exposure to 0.05 mg/m3.
STAMI's Toxicological Expert Group (TEG) has had an important impact on regulatory decision-making as documents regarding chemical exposures such as respirable crystalline silica (2021), diesel exhaust particles (2021), benzene (2021), polyaromatic hydrocarbons (2021) have been prepared with scientific advice from STAMI researchers[2-4].

Impacts on the understanding on cancer risk assessment and cancer management.
STAMI has been a long-time partner in the Nordic Occupational Cancer study (NOCCA), joining Nordic studies on work and cancer. A recent update investigated occupational variation of nasopharyngeal cancer, identifying groups of workers with increased risk of these cancers. This Nordic initiative enables the detection of important associations, which are crucial for the awareness of needs for exposure reduction within the industries focusing on jobs categorised with increased risk. This work is also available to the enterprises to inform and increase understanding of risk levels, and the need for prevention to address the need for exposure control measures in the workplace.

STAMI's research also impacts cancer risk assessment and risk management on company level, as we develop new methods for evaluating compliance with the lowered occupational exposure, such as the limit of benzene (0.2 ppm) from 2021[2]. STAMI performed research to validate exposure assessment of benzene exposure using biomonitoring techniques in parallel with personal sampling of airborne benzene concentrations in the workplace atmosphere among firefighters and upstream oil workers. The method enables the surveillance of exposure levels to compare with new suggested limit values and for the evaluation of historic exposure levels[5,6]. For example, elementary carbon method to assess exposure to diesel exhaust is performed at STAMI as the only available national facility for this analysis[4].

Strengthen the national and international capacity and expertise on occupational cancer.

STAMI has an important advisory role to the Ministry of Labour and Social Inclusion and to the Labour Inspectorates and drafts documents needed for the legal approvement of occupational diseases that impacts the decision on compensation claims, and we also appear before the courts as expert witnesses to provide the present knowledge status regarding causal effects from exposure to carcinogens. STAMI's research and knowledge dissemination increases the awareness and highlights the potential for prevention of occupational cancer by means of reduced exposure to occupational carcinogens. STAMI contributes to this work by nominating researchers with expertise in the field to several bodies that compile the knowledge status enabling prevention and regulatory activities, such as the Scientific Committee on Occupational Exposure Levels[2], IARC Monographs[1,7] and Nordic Expert Group (NEG)[8,9].

5. Sources to corroborate the impact

1. The IARC Monograph, 2020 Volume. 124- Night Shift Work https://www.iarc.who.int/news-events/iarc-monographs-volume-124-night-shift-work/

2. List of documents with contributions from STAMI to set limit values for chemicals https://arbeidstilsynet.no/tema/kjemikalier/grenseverdier-for-kjemisk-pavirking/grunnlagsdokumenter-for-grenseverdier-for-kjemikalier/

3. STAMI-report; 2014;15 (3) Dust exposure during rock drilling during the day. http://hdl.handle.net/11250/2411023

4. STAMI-report; 2015;16 (2) Mapping of exposure to diesel exhaust particles in Norwegian working life http://hdl.handle.net/11250/284998

5. STAMI-report; 2015;16 (4) Lymph-hematologic cancer among employees and students at Rosenborg laboratories http://hdl.handle.net/11250/285065

6. Official Norwegian Report (NOU): NOU 2022:19 Chemical exposure in the upstream oil industry and compensation for work-related disease NOU 2022: 19 - regjeringen.no

7. The IARC Monograph, 2017 Volume. 111- Some Nanomaterials and Some Fibres IARC Monographs Volume 111: Some Nanomaterials and Some Fibres – IARC (who.int)

8. Work and Health report; 2018;52 (1) The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals. Document no. 150 Silicon Carbide https://gupea.ub.gu.se/handle/2077/56006

9. Work and Health report; 2023;57 (2) The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals. Document no. 155 Occupational chemical exposures in combination with unusual working hours https://gupea.ub.gu.se/handle/2077/78758

National Institute of Occupational Health, STAMI - Case no. 3

Institution: STAMI
Administrative unit: STAMI
Title of case study: Prevention potential for the working environment in Norway
Period when the underpinning research was undertaken: 2012 - 2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2012 - 2022
Period when the impact occurred: 2012 - 2022

5. Summary of the impact

STAMI uses national surveillance data and scientific analyses to identify work-related risk factors and estimate the proportion of cases of disease or ill health that can be attributed to specific risk factors in the workplace and are amenable to interventions. Research impact unfolds through a systematic and well-coordinated approach, disseminating findings widely to authorities, employer and employee organisations, businesses, media and the general public. Updates to the "Factbook on working conditions and health", along with a web-based surveillance system, ensure wide accessibility beyond academic circles. The resulting knowledge has guided decision-making through collaboration with the Norwegian Labour Inspection Authority, targeting industries with elevated exposure and health risks. Under the inclusive working life (IA) agreement, STAMI developed "A Great Day at Work," using our national surveillance statistics to map crucial work factors tailored to different branches and sectors. This tool promotes a knowledge-based approach to mitigate health problems, reduce sick leave, and address withdrawal from work life.

6. Underpinning research

Context of the research: The research carried out is integral to STAMIs goals of developing reliable and valid indicators that describe the status and trends in national occupational health and working environment. At the beginning of the evaluation period, we observed a lack of occupational health research based on representative and national data, notably in Norway.

Content of the research: The research grounded in nationwide and representative data is anchored in the "Survey of Level of Living-Working Conditions". This representative and longitudinal survey of about 11,200 employed Norwegian residents aged 18 to 66 years is conducted every third year by Statistics Norway. STAMI has contributed to the survey by ensuring the quality of the questionnaire content. This research carried out as part of the surveillance of work conditions and health has two primary objectives: to identify specific work factors that increase health risks and sick leave, and to estimate the population attributable risk (%) reflecting the proportion of cases of disease or ill health that can be attributed to a specific risk factor in the work environment.

During the period 2012-2022, our research has produced 25 original studies on national surveillance data, identifying specific workplace risk factors that contribute to increased health problems and sick leave among the Norwegian working population. During the first part of this period, we conducted analyses of mechanical[1,3], organisational/psychosocial[1,2,4] and chemical/physical factors[6] in the workplace, examining key health outcomes based on panel data. These studies elucidated workplace factors associated with neck and shoulder pain, back pain, anxiety, depression, leaving work due to health problems, skin problems, headaches, and registry-based sick leave. The insights gleaned from these findings provided valuable guidance on preventive measures aimed at reducing the risk of mental distress and musculoskeletal complaints that are the main contributors to work-related sick leave. In the latter part of the period, we

published articles documenting relationships between workplace conflicts, threats/violent incidents, bullying, unwanted sexual attention, and risk of mental health problems and medically certified sick leave in the Norwegian workplace[5]. These findings underscore the significant potential of prevention to reduce these health problems.

Impact of research: Based on studies conducted between 2012 and 2022, our research has successfully identified specific work factors that increase health risks and contribute to sick leave at Norwegian workplaces. This insight serves as the foundation for actionable interventions. By regularly updating the Factbook on working conditions and health, together with our Web-based surveillance system every three years, we actively disseminate updated data to key stakeholders, improving their understanding of risk factors associated with work-related accidents and illnesses. Through collaboration with the Norwegian Labour Inspection Authority, our research plays a pivotal role in decision-making, influencing the areas that the labour inspectorate prioritises in its inspections. Another notable impact is the "A Great Day at Work" tool, meticulously designed to map industry-specific work environment factors. This tool empowers organisations to make informed, knowledge-based decisions that aim to prevent ill health and reduce absenteeism.

Names of the key researchers

Name	Position	Period
Johannessen, Håkon. PhD.	Research Associate Professor	2012 – 2022
Sterud, Tom. PhD.	Lead Research Professor	2012 – 2022
Tynes, Tore. PhD, MD.	Research Associate Professor	2012 – 2018

3. References to the research

1. **Sterud, T, Tynes, T**. Work-related psychosocial and mechanical risk factors for low back pain: a 3-year follow-up study of the general working population in Norway. Occupational and environmental medicine (2013) 70(5) s. 296-302. Impact factor 4.9 https://doi.org/10.1136/oemed-2012-101116

2. **Johannessen, HA, Tynes, T, Sterud, T**. Effects of occupational role conflict and emotional demands on subsequent psychological distress. Journal of occupational and environmental medicine (2013) 55(6) s.605-613. Impact factor 3.2 https://doi.org/10.1097/JOM.0b013e3182917899

3. **Sterud, T.** Work-related mechanical risk factors for long-term sick leave: a prospective study of the general working population in Norway. The European Journal of Public Health 2014;24(1):111-116. Impact factor 2.6 https://doi.org/10.1093/eurpub/ckt072

4. **Johannessen HA, Sterud T**. Psychosocial factors at work and sleep problems: a longitudinal study of the general working population in Norway. International archives of occupational and environmental health 2017;90:597-608. Impact factor 3.1 https://link.springer.com/article/10.1007/s00420-017-1222-2

5. **Sterud, T, Degerud, E, Skare, Ø, Hanvold, TN, Christensen, JO**. Adverse social behaviour at the workplace and subsequent physician certified sick leave: a three-wave prospective study of the general working population in Norway, Occupational and Environmental Medicine 2021;78(8):576-582. Impact factor 4.9. https://doi.org/10.1136/oemed-2020-106973

6. **Alfonso, JH, Thyssen, JP, Tynes, T, Mehlum, IS, Johannessen, HA**. Self-reported occupational exposure to chemical and physical factors and risk of skin problems: a 3-year follow-up study of the general working population of Norway. Acta Dermato-Venereologica (2015) 95(8) s. 959-962. Impact factor 4.2. https://doi.org/10.2340/00015555-2135

4. Details of the impact

STAMI's national surveillance data and scientific analyses produce updated knowledge of prevalences of occupational exposures in a wide range of occupations and sectors. Furthermore, STAMI's analyses enables the estimation of health problems, illnesses, and injuries attributed to workplace factors. This methodological approach supports informed prioritisation of practical preventive measures, forming the foundation for the identification of critical areas in preventive occupational health initiatives. In essence, by producing knowledge about the impact of the work environment on health, we have contributed to promote activities aimed at fostering a healthier workforce and improving economic efficiency through targeted and informed preventive measures. The impact of the research has unfolded through a systematic and well-coordinated approach, emphasising strategic dissemination to diverse stakeholders. Regular updates to the Fact book on working environments and health 2021[6], which represents STAMI's national overview of the current situation and the latest developments with respect to working environments in Norway, and the accompanying Web-based surveillance system[5], ensures broad accessibility of our findings. This extends the benefits beyond academic circles as it serves scientific knowledge to authorities, the working life partners, businesses, media and the general public.

Impacts on the authorities and stakeholders common understanding of work environment:
STAMI's Occupational Health Surveillance (NOA) plays a key role in organising, systematising, and sharing knowledge and statistics related to the work environment and health with government authorities and stakeholders. STAMI's extensive research and utilization of national data sources establish a comprehensive national knowledge base in the field. This thorough surveillance has served as the basis for the "Factbook on working conditions and health" and the "National Work Environment Surveillance Tool", providing a shared understanding and definition of the work environment. The triannual publication of the Factbook from 2012 to 2022 offers a unified overview of the Norwegian work environment, fostering a common knowledge base that authorities and stakeholders collaboratively use to identify challenges and implement measures. The knowledge base in the Fact Book has been used as a knowledge basis in a previous parliamentary report[1] and in several public investigations in Norway[2,3,4].

Impacts on decision making through cooperation with the Labour Inspection Authority:
The national knowledge base played an important role in decision-making through its collaborative partnership with the Norwegian Labour Inspection Authority. Using this knowledge, the Labour Inspection Authority effectively pinpointed branches and industries characterised by elevated levels of exposure and a higher risk of health problems and injuries related to work[8]. This targeted approach facilitated the identification of areas with the greatest need and impact, by using the national knowledgebase as a key factor for their prioritizing efforts regarding inspection.

STAMI's Occupational Health Surveillance knowledgebase is instrumental in guiding the Labour Inspection Authority's risk-based core activities and prioritising interventions in areas of highest concern. Drawing on the Authority's own experiences and data, this collaborative knowledge-building process establishes a solid foundation for informed decision making. The outcome is a systematic framework that directed the Labour Inspection Authority's risk-based initiatives and

ensured a safer and more compliant working environment through the prioritisation of activities with maximum effectiveness.

Influence on the IA Agreements for preventing sick leave and withdrawal from work life: The inclusive working life agreement (IA agreement) is a tripartite cooperation for a more inclusive working life adopted to help achieve high employment and mobilise the workforce through preventing and reducing sick leave and withdrawal from working life. The IA agreement 2019-2022 aimed to improve collaboration between involved parties (i.e., representatives of the employer and the trade union) in local working environment initiatives, providing enterprises with access to effective knowledge-based support[9].

To support the objectives of the IA agreement, in 2019, a sector programme[10] was established to prioritise and target efforts toward selected industries with significant prevention potential. The national knowledge base served as the basis for this prioritisation. Furthermore, as a component of this agreement STAMI has developed the knowledge-based work environment tool, "A Great Day at Work"[7]. This tool uses NOA's national work environment statistics and scientific research to map important factors in the work environment to mitigate health problems and contribute to reducing sick absence and attrition of the workforce.

The factors addressed by the tool are tailored to the specific needs of different branches and sectors, enhancing recognition and usability at the company level. This tool promotes a knowledge-based approach to preventive efforts in the workplace. By providing companies with the means to address work factors that are likely to have the most significant impact on their health and well-being, the tool facilitates a targeted approach to address the main challenges within each workplace. This transformation supports a more proactive and informed approach to preventive work aligning with the overarching goals of the IA Agreement.

Societal and Economic Impact of Advancing Knowledge about the Working Environment for Health, Welfare, and Productivity: Occupational health and work environment research and statistics play a fundamental role in assessing the state of working conditions in Norway, forming a crucial foundation for knowledge-based preventive efforts at both the societal and business levels. The Work Environment Portal[11] was developed through collaboration between the Labour Inspection Authority, the Norwegian Labour and Welfare Administration (NAV), the Petroleum Safety Authority of Norway (PTIL), and the National Institute of Occupational Health (STAMI). This portal is built upon STAMIs analyses of working conditions in various industries and professions based on the national surveillance system. Tailored for employers and employees at the workplace level these statistics also play a significant role in pinpointing specific work environmental factors that can be addressed to prevent ill health and sickness absence, resulting in substantial cost savings. Understanding the significant impact of workplace factors on health, well-being, and absenteeism is vital for identifying effective measures. Our monitoring efforts provide comprehensive insights into industries and occupations with challenges, thereby facilitating informed decision-making for targeted interventions and improvements.

5. Sources to corroborate the impact (indicative maximum of ten references)

1) Parliamentary report. Meld. St. 29 (2010–2011) A shared responsibility for a good and decent working life.
Meld. St. 29 (2010–2011) - regjeringen.no

2) Parliamentary report. Meld. St. 19 (2014-2015) The Public Health Report — Coping and Opportunities.
Meld. St. 19 (2014-2015) - regjeringen.no

3) Official Norwegian Report (NOU): NOU 2021: 2 Skills, activity and income security- 4 Measures to increase employment: NOU 2021: 2 - regjeringen.no

4) Official Norwegian Report (NOU): Private actors in the welfare state - The Welfare Services Committee's sub-investigation I and II on publicly funded welfare services.
NOU 2020: 13

5) The National occupational health surveillance tool:
STAMI NOA Forside - STAMI NOA

6) The Factbook on occupational health and work environment:
2021: Faktabok-om-arbeidsmiljo-og-helse-2021-2.pdf (stami.no)
2018: Faktabok om arbeidsmiljø og helse 2018. Status og utviklingstrekk (unit.no)
2015: Faktabok om arbeidsmiljø og helse 2015 - status og utviklingstrekk (unit.no)

7) The tool to improve the work environment
A Great Day at Work - STAMI

8) The Labour Inspection Authority's risk-based initiatives:
Risikobilde-2023--sammendrag-.pdf (arbeidstilsynet.no).

9) The Governmental Agreement for an Inclusive workplace 2019-2024:
The IA Agreement 2019–2024 - regjeringen.no

10) The sector programme under the inclusive working life (IA) agreement:
Bransjeprogrammer under IA-avtalen 2019–2022 - regjeringen.no

11) The Occupational Health Portal:
https://www.arbeidsmiljoportalen.no/om

National Institute of Occupational Health, STAMI - Case no. 4

Institution: STAMI
Administrative unit: STAMI
Title of case study: Health effects, mechanisms and regulation of occupational exposure to engineered nanomaterials
Period when the underpinning research was undertaken: 2012-2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2012-2022
Period when the impact occurred: 2012-2022

7. Summary of the impact

Engineered Nanomaterials (ENM) are novel materials made by nanotechnology. There is, however, lack of scientific knowledge on potential health outcomes of ENM. STAMI has created infrastructure, performed research, built national and international capacities, and educated nano-safety experts for safe and sustainable nanotechnology development. The impacts of the case study have i) affected the understanding, awareness and change of the attitudes about ENM hazards among producers and users, ii) influenced policy- and decision-making that led to new or amended nano-safety guidelines to better cope with negative health impacts and promote sustainable ENM production and use, iii) promoted efficient, cost-effective, and animal-free toxicity testing for next generation risk assessment, iv) created national capacity and preparedness and educated nano-safety experts for risk assessment of nanomaterials by the industry and regulatory authorities.

8. Underpinning research

Context of the research: Engineered nanomaterials (ENM), materials of 1-100 nanometres in size, are engineered by nanotechnologies. ENM are used in e.g. electronics, (nano)biomedicines, aeronautics, building and construction, cosmetics, and textiles. ENMs have significant societal and economic benefits. However, there is suspicion that some ENMs such as carbon nanotubes (CNT), titanium dioxide (TiO_2) and silica may cause serious health effects (e.g., cancer) in humans. Thus, research on occupational safety of various types of ENMs is important for safe and sustainable development of nanotechnologies and will have societal, economic, and regulatory impacts. In line with STAMI's strategy, this case study was undertaken to create research infrastructure and perform research, and build national and international capacities, that will contribute to understand the potential health outcomes of various ENMs and educate nano-safety experts, to perform risk assessment of these materials.

In the period 2012-2022 several research projects were conducted to characterize physicochemical properties and to develop exposure assessment methods, pulmonary exposure, and 3D cell-models to determine effect mechanisms. Methods for dispersion and physical-chemical characterization of several types of ENMs e.g., CNTs, TiO_2, cerium oxide, silver, carbon black, silica and nanocellulose were developed. The research results showed that some ENMs e.g., CNTs exhibited asbestos-like cellular responses *in vitro* and, induced inflammation and fibrosis *in vivo* [1,2,3]. Long-term exposure to occupationally relevant doses of CNTs as well as TiO_2 led to cancer-like phenotypes and alterations in several biomarkers of exposure and effect[4]. Focusing on pulmonary health outcomes, e.g., inflammation, fibrosis, and cancer and biomarkers of disease development, we established Air Liquid Interface (ALI) and advanced 3D-ALI lung cell models[5] and tested multiple ENMs[6] . The research was conducted using industrial test cases from national and international ENM producers.

In summary, the results showed that health hazards posed by various ENMs depend on type and form of the ENM and some ENMs, e.g. cerium oxide and nanocellulose may be less hazardous than others. This science-based knowledge benefits producers, users, regulatory authorities, and the general population as it challenges the initial attitude that ENM in general, independent of type, are hazardous.

The developed in vitro exposure and tissue-like 3D cell models of this case-study show good in vivo correlations and contribute to the efforts of the European regulatory authorities towards next generation risk assessment (NGRA) using non-animal new approach methodologies (NAMs) for more efficient, cost effective and animal-free toxicity testing, thus increasing in public and industrial revenue and profits. These models will directly impact on animal well fare by saving animals and, resolving human ethical concerns sacrificing animals for safety testing of chemicals.

The research undertaken has been conducted through multiple national and international collaborations and received funding from Research Council of Norway (4 projects) and the European Union's FP7 and Horizon 2020 programs (4 projects). The scientific and international impact of the research is underpinned by over 20 articles co-authored with national and international nanotoxicology experts published in peer-reviewed scientific journals.

Names of the key researchers

Name	Position	Period
Zienolddiny (Narui), Shan. PhD.	Lead Research Prof./Head, Research Field	2012 – 2022
Skaug, Vidar. MD.	Head Physician	2012 – 2021
Arnoldussen, Yke. PhD.	Postdoc	2012 – 2018
Samulin-Erdem, Johanna. PhD.	Postdoc/Research Associate Prof.	2013 – 2022
Alswady-Hoff (Kasem), Mayes.	PhD fellow	2012 – 2022
Ervik Kringlen, Torunn. PhD.	Research Professor	2017 – 2022
Camassa, Laura. PhD.	Postdoc/ Research Associate Prof.	2020 – 2022
Wallin, Håkan. PhD.	Lead Research Prof/Head, Research Field	2017 – 2022

3. References to the research

1. **Arnoldussen Y.J., Skogstad A., Skaug V., Kasem M., Haugen A.**, Benker N, **Weinbruch S.**, Apte RN, **Zienolddiny S**. Involvement of IL-1 genes in the cellular responses to carbon nanotube exposure. Cytokine (2015) 73(1):128-37. Impact factor 2.94. http://doi.org.10.1016/j.cyto.2015.01.032

2. **Arnoldussen Y.J., Skaug V.**, Aleksandersen M, Ropstad E, **Anmarkrud K.H., Einarsdottir E.**, **Chin-Lin F**., Granum Bjørklund C, **Kasem M**., **Eilertsen E**, Apte RN, **Zienolddiny S**. Inflammation in the pleural cavity following injection of multi-walled carbon nanotubes is dependent on their characteristics and the presence of IL-1 genes. Nanotoxicology. (2018) 12(6) s.522-538. Impact factor 5.95. http://doi.org/10.1080/17435390.2018.1465139

3. **Alswady-Hoff M., Erdem J.S.**, Aleksandersen M, **Anmarkrud K.H., Skare Ø., Lin F.C.**, **Simensen V., Arnoldussen Y.J., Skaug V.**, Ropstad E, **Zienolddiny-Narui S**. Multiwalled Carbon Nanotubes induce Fibrosis and Telomere Length Alterations. Int J Mol Sci. (2022) 23(11):6005. Impact factor 5.92. https://doi.org/10.3390/ijms23116005

4. **Phuyal S., Kasem M.,** Knittelfelder O, Sharma A, Fonseca DM, Vebraite V, Shaposhnikov S, Slupphaug G, **Skaug V., Zienolddiny S.** Characterization of the proteome and lipidome profiles of human lung cells after low dose and chronic exposure to multiwalled carbon nanotubes. Nanotoxicology. (2018) 12(2) s.138-152. Impact factor 5.95. http://doi.org/10.1080/17435390.2018.1425500

5. **Camassa LMA**, Elje E, Mariussen E, Longhin EM, Dusinska M, **Zienolddiny-Narui S**., Rundén-Pran E. Advanced Respiratory Models for Hazard Assessment of Nanomaterials-Performance of Mono-, Co- and Tricultures. Nanomaterials. (2022) 29;12(15):2609. Impact factor 5.30. https://doi.org/10.3390/nano12152609

6. **Samulin Erdem J., Alswady-Hoff M., Ervik TK, Skare Ø, Ellingsen DG, Zienolddiny S.** Cellulose nanocrystals modulate alveolar macrophage phenotype and phagocytic function. Biomaterials. (2019) 203: s. 31-42. Impact factor 10.32. http://doi.org/10.1016/j.biomaterials.2019.02.025

4. Details of the impact

Effects on understanding, awareness, change of attitudes on ENM hazards: Occupational safety of ENMs has societal, scientific, and regulatory impacts as it may affect safe and sustainable development of nanotechnology industry. During 2012-2022 STAMI has acquired significant laboratory infrastructure (nanotoxicology laboratory), realistic pulmonary exposure and cell models to determine health hazards of nanomaterials. Using these capacities, STAMI has performed safety and exposure assessment of nanomaterials from several national and international nanomaterial producers[1]. We have through several projects generated experimental data using industrial test cases, exposure and advanced in vivo-like cell models and nano-safety infrastructure to create scientific knowledge important to increase understanding, awareness and change the attitude that not all ENM in general are hazardous[2]. This knowledge is important to ensure safe and sustainable NMs, increasing national and international competitiveness of the Norwegian nanotechnology.

Influence on policy, decision-making and socioeconomics: The research results contributed to new or amended Norwegian guidelines and to the 2017 World Health Organization (WHO) guidelines for safe handling of the ENMs and protection of employees from hazards of exposure to ENM. These guidelines have helped the nanotechnology industry and, the occupational health and safety professionals, to better cope with ENM exposures that might have a negative health impact and/or cause non-sustainable ENM production. The research results from our in vitro and in vivo models will contribute, in future criteria documents for setting occupational exposure limits for these nanomaterials.

During 2012-2022 STAMI has provided the regulatory authorities in Norway with scientific safety knowledge for practical use in making decisions on the workplace safety of ENMs. Specifically, in 2014-2015 STAMI was a member of the committee that made the first national guidelines for safe handling of nanomaterials at workplaces by the Norwegian Labor Inspection Authority[3]. In 2012-2022 STAMI led the Expert Group for Monitoring of Occupational Related Health Effects of Nanomaterials ("Nanogruppen"). The group reviews state-of-the art available knowledge on health effects of ENM and an updated is anticipated in 2024/2025. STAMI has provided regulatory advice on demand to the occupational health professionals, e.g. to physicians and health and safety (HSE) personnel.

In 2014-2017 STAMI, as a WHO collaborating centre, participated in preparation of WHO's guidelines for protection of workers from the risk of nanomaterials[4]. Furthermore, STAMI scientists participate in several European toxicology committees such as the national EUROTOX committee to certify European Registered Toxicologists, the EUROTOX Faculty to help foster education and training of new generation toxicologists, regulatory toxicologist experts in the Nordic Expert Group[5].

Promotion of next generation risk assessment, animal-free toxicity testing: STAMI has developed in vitro cell models for hazard assessment of several types of ENMs with good correlations to in vivo models[6]. This complies well with animal-welfare considerations (3R principle), societal expectations, regulatory measures and working life's need to bring safe nano-based products to the market without new animal testing. Additionally, our models are in line with the need for New Approach Methodologies (NAMs) for use in the Next Generation Risk Assessment (NGRA) that uses a range of NAMs. The European Union has initiated several research projects for the development, testing, validation and use of NGRA by regulatory authorities. The nanosafety expertise and research performed at STAMI has received international recognition and paved the way for STAMI's participation in several EU projects aiming at use of NGRA for regulatory purposes[7]. These models are also applicable for human health assessment of other substances than nanomaterials for example chemical carcinogens or micro/nano plastics.

Creation of national capacity, preparedness and education of nano-safety experts: STAMI has recruited and trained highly competent researchers in the field of occupational nano-safety from Norway and abroad, providing top-class expertise, and in vitro and in vivo experimental infrastructure for highly relevant occupational health and safety research. The institute has made available its infrastructure and expertise to postgraduate, PhD and postdoctoral fellows in collaboration with several of the Norwegian universities, e.g. University of Oslo, Norwegian University of Science and Technology, Norwegian University of Life Sciences, and research institutions, e.g., Norwegian Institute of Public Health, and Norwegian Institute of Air Research. STAMI is responsible for the occupational toxicology course, which is obligatory for the speciality of occupational medicine, also open to other HSE personnel[8]. During the evaluation period two full time and one guest PhD fellow, six postdoctoral and fourteen postgraduate MSc students in addition to several laboratory personnel have been educated and trained. These collaborations have placed STAMI as a major knowledge provider and, a major player as a research institute in national capacity building within the field of (nano)toxicology and, promoting occupational nanotoxicology in Norway[9].

5. Sources to corroborate the impact

1) Links to collaborating national and international ENM producers: https://www.appliednanoparticles.eu), https://multimedia.3m.com/mws/media/713346O/filtek-z500); https://www.sintef.no/projectweb/ferroforsk/; https://snl.no/Kronos_Titan;

2) Links to key projects and funding sources important for the impact case: i) STAMI funded "NanoCancer" project (https://stami.no/prosjekt/nano-cancer: ii) RCN-funded projects: (https://prosjektbanken.forskningsradet.no/en/project/FORISS/204341; https://nornanoreg.nilu.no/; https://prosjektbanken.forskningsradet.no/en/project/FORISS/288768; https://prosjektbanken.forskningsradet.no/en/project/FORISS/245216); and iii) EU funded projects: https://stami.no/en/project/nanoreg-eu-prosjektet; https://safenmt.com/; https://cusp-research.eu ;https://www.eu-parc.eu.

3) Link to the Norwegian guidelines for safe handling of ENM at workplaces by the Norwegian Labor Inspection Authority: https://www.arbeidstilsynet.no/tema/kjemikalier/nanomaterialer-og-arbeidsmiljo/.

4) Link to the 2017 WHO guidelines for protection of workers from the risk of nanomaterials and related publications: https://www.who.int/publications/i/item/9789241550048); https://www.sciencedirect.com/science/article/pii/S0273230018301004;

5) Links to Eurotox and Nordic Expert Group (NEG): https://www.eurotox.com/faculty/; https://www.av.se/en/the-nordic-expert.group/.

6) Links to publications on in vitro cell models with good in vivo correlations for hazard assessment of nanomaterials: https://pubmed.ncbi.nlm.nih.gov/30654492/: https://pubmed.ncbi.nlm.nih.gov/33846018/; https://pubmed.ncbi.nlm.nih.gov/34301283/

7) Links to EU projects STAMI participates aiming at use of NAMs in NGRA for regulatory purposes: https://nanopass.eu and https://www.eu-parc.eu

8) Link to STAMIs educational activities: Toxicology for occupational physicians Educational Activities - STAMI

9) Link to the Norwegian Society of Pharmacology and Toxicology, as the national arena and platform for toxicology where STAMI has several members in its board: www.nsft.net

Impact case

Sunnaas Rehabilitation Hospital, Department of Research. Case number 1

Institution:	Sunnaas Rehabilitation Hospital
Administrative unit:	Department of Research
Title of case study:	Aphasia telerehabilitation
Period when the underpinning research was undertaken: 2012 – 2022	
Period when staff involved in the underpinning research were employed by the submitting institution: 2012 – 2013, 2015 – 2019, 2021 – ongoing	
Period when the impact occurred: 2021 – ongoing	

1. Summary of the impact

Over the past decade, we have performed several projects – developmental, research and innovation – regarding the delivery of speech and language therapy (SLT) for people with aphasia post stroke via videoconference. Primarily, this has contributed to the implementation of aphasia telerehabilitation in ordinary clinical practice by several service providers. This work has also provided speech and language therapists with resources on how to provide telerehabilitation during the covid-19 pandemic, it has led to the establishment of a national network on aphasia telerehabilitation and contributed to international stroke guidelines.

2. Underpinning research

Intensity of SLT seems to be a key factor to regain language function for persons with post stroke aphasia. Ensuring satisfying intensity however is difficult, especially in rural areas. In addition, several studies have documented a substantial lack of speech and language therapists in Norway. Telerehabilitation also has potential other gains, e.g. regarding the environment and the saving of patient and therapist time.

Based on a long-standing tradition of aphasia services and research at SRH, together with a history of several telerehabilitation activities, our work regarding aphasia telerehabilitation started in 2012 with a developmental project financed by the DAM foundation. In a small study, a model for delivering SLT by videoconference was developed and tested with 4 patients. Head physician of the brain injury department Frank Becker acted as project leader and supervisor, while speech and language therapist Silje Hansen was employed to conduct the project. Head of speech and language therapy Melanie Kirmess was co-supervisor. The feasibility of providing SLT for aphasia via videoconference was proven, resulting in the wish to test the model on a larger scale.

In 2014, Frank Becker acquired funding from the South Eastern Regional Health Trust for a PhD-project in which he acted as project leader and main supervisor. Hege Prag Øra, MD under specialization, was employed as the PhD candidate from 2015 to 2019. Secured by additional funding from the University of Oslo, three speech and language therapists from SRH were employed to provide the SLT in the project. The project collaborated with stroke units in the area and an internationally renowned aphasia researcher. A randomized controlled trial of speech-language telerehabilitation in post stroke aphasia in addition to usual care was performed. Technical features were described, and a high level of feasibility and acceptability was found. The telerehabilitation intervention significantly improved repetition and sentence production four months post randomization. The study is one of the few on synchronous aphasia telerehabilitation, with a relatively high number of participating subjects (n=62) compared to similar trials.

The promising results from the RCT lead to the idea to work with implementation of aphasia telerehabilitation. In 2020, Dr. Sonja Erlenkamp, a linguist with experience in aphasia research employed at SRH's innovation unit, gained funding from the South Eastern Regional Health Trust for an innovation project. In addition to her, speech and language therapist at SRH Iselin Partee, was employed in the project. Even though the RCT-project was clinically oriented, it involved some demanding logistics and one had identified several areas that needed to be further worked with in order to facilitate implementation into everyday clinical practice. In a collaboration with several external clinicians, researchers and user representatives, the project worked on aspects as economy, logistics and collaboration between service levels, and therapeutic issues and suggested a model for clinical implementation.

In another ongoing innovation project, again supported by the South Eastern Regional Health Trust with funds specifically aiming to support implementation of innovation, Erlenkamp now conducts a project together with four service providers to implement the model.

3. References to the research

Hansen SM, Bønes E, **Becker F**, **Kirmess M** (2013): "Språktrening rett hjem", NST-rapport 01-2013, Nasjonalt Senter for samhandling og telemedisin, ISBN 978-82-8242-032-7 NST prosjektrapport Norsk (ehealthresearch.no)

Øra HP, **Kirmess M**, Brady MC, Partee IAC, Hognestad RB, Johannessen BCB, Thommessen B, **Becker F** (2020): "The effect of augmented speech-language therapy delivered by telerehabilitation on post stroke aphasia – a pilot randomized controlled trial" *Clinical Rehabilitation*, 34 (3), 369 – 381 M.Brady_The_effect_of_augmented_telerehabilitation_on_post_stroke_aphasia_HP_021219.pdf (gcu.ac.uk)

Øra HP, **Kirmess M**, Brady MC, **Sørli H**, **Becker F** (2020): "Technical Features, Feasibility, and Acceptability of Augmented Telerehabilitation in Post-stroke Aphasia—Experiences From a Randomized Controlled Trial" *Frontiers in Neurology*, 11:671 Frontiers | Technical Features, Feasibility, and Acceptability of Augmented Telerehabilitation in Post-stroke Aphasia—Experiences From a Randomized Controlled Trial (frontiersin.org)

Erlenkamp S (2021): "Sluttrapport for prosjektet «telelogoped»" https://www.sunnaas.no/49b7f9/siteassets/dokumenter/sluttrapport-for-prosjekt-telelogoped.pdf

4. Details of the impact

The work presented in this case study has contributed to the implementation of aphasia telerehabilitation in ordinary clinical practice by several institutions. These include Sunnaas and three other hospitals in the region together with different SLT providers. In addition, delivering SLT for persons with aphasia by means of telerehabilitation has in general become significantly more widespread in recent years, not the least by therapists working in communities and in private practice. While this most certainly is due also to other factors than our research, our work has contributed to this development as it has shown to the Norwegian community of speech and language therapists that aphasia rehabilitation is feasible, and that there is high satisfaction with the model in patients, but also therapists. Furthermore, we have provided therapists with information and practical advice on how to deliver aphasia telerehabilitation.

Main means to accomplish impact have been the two innovation projects and broad dissemination of results through a number of channels. The work has been presented on a number of conferences, seminars etc.

The ultimate beneficiaries of our work are of course the patients with aphasia. Close cooperation with the National Aphasia Association (now fused with another user organization under the name "LHL hjerneslag og afasi") has been important from the start. Disseminating results to users has also been an important part of our efforts, e.g. through articles in user magazines or contributions to use conferences. Our work has also been presented in a large number of social media contributions and newspaper articles. Furthermore, the RCT was selected as one of the projects presented in the "National research and innovation report 2019". This work has also provided speech and language therapists with resources on how to provide telerehabilitation during the covid-19 pandemic. When the pandemic started, we could elaborate a webpage on short notice with a number of resources on different aspects of aphasia telerehabilitation (technical, legal, therapeutical etc.)

Also during the covid-19 pandemic, when the National Directorate of Health made regulations regarding reimbursement of SLT delivered digitally distance, we contributed with expert advice in the process.

In 2022, a national network on aphasia telerehabilitation was established, as a joint initiative of our group and the aphasia user organization.

As an international contribution, the main article presenting the results of our RCT has contributed to the knowledge base of international stroke guidelines; it is cited in the recently updated NICE guidelines for stroke rehabilitation as well as the Australian and New Zealand guidelines. Our engagement in international aphasia networks (especially the Collaboration of Aphasia Trialists (CATs)) has possibly contributed to this.

5. Sources to corroborate the impact

-"Språktrening på avstand", webpage, last updated 29.11.22 Språktrening på avstand - Sunnaas sykehus HF

- Marianne Brodin, special advisor for aphasia at the user organization LHL hjerneslag og afasi
- Kathrine Kvisgaard, head of Norwegian National Organization of Speech and Language therapists
- Marian Brady, Professor, Research Group Lead for Living with Stroke, Glasgow Caledonian University
- Hege Eiklid, innovationist and entrepreneur, innocom
- Unn Tinbod, speech and language therapist, Logopedsenteret Askim
- Linn Dejgaard, head of the follow-up department for brain injuries at Sunnaas Rehabilitation Hospital

Impact case

Sunnaas Rehabilitation Hospital, Department of Research. Case number 2

Institution:	Sunnaas Rehabilitation Hospital (SRH)
Administrative unit:	Department of Research
Title of case study:	The Child-In-Context-Intervention (CICI): A randomized controlled trial addressing chronic symptoms of Pediatric Acquired Brain Injury
Period when the underpinning research was undertaken: 2019 – ongoing	
Period when staff involved in the underpinning research were employed by the submitting institution: 2019 – ongoing	
Period when the impact occurred: 2021 – ongoing	

1. Summary of the impact

Children with acquired bran injury (pediatric ABI - pABI) often struggle with chronic cognitive, behavioral and emotional impairments, affecting everyday functioning, quality of life and participation. pABI research however lags behind that of the adult population. SRH opened its pediatric unit in 2017 and has needed to establish a research portfolio. The CICI study has contributed to new knowledge about treatment needs and options in chronic pABI, the scientific and clinical qualifications of staff is improved, and collaborative relationships with the regional acute hospital pABI, with the special education system (StatPed), and international research partners have been developed.

2. Underpinning research

Pediatric ABI is the most common cause of pediatric mortality and morbidity, representing a major challenge to the health care system due to the heterogeneity with respect to causation of injury, severity, outcome, and complex, costly long-term treatment needs. However, evidence-based knowledge is limited. Rehabilitation of children needs to be contextualized, i.e. involve families and schools, and interventions need to be individualized. The CICI is a complex and innovative randomized controlled trial that combines an individualized goal-oriented approach with a parenting group-intervention and school sessions, tailoring the intervention to the needs and problem perception of each child and family.

Since 2011, there has been national and regional work on improving pABI rehabilitation, resulting in rehabilitation guidelines in 2018.
(https://metodebok.no/index.php?action=chapter&item=BJLJRAwY).
The CICI adheres with the need noted here for more focus on the chronic phase of pABI. The study thus answers to documented needs at international, national, regional and institutional levels.

As noted, the CICI study was modelled after an adult study using individualized goal-oriented rehabilitation funded by the Norwegian Research Council (NRC): “Traumatic brain injury; needs and treatment options in the chronic phase. A randomized controlled community-based intervention”. Marianne Løvstad, Principal Investigator (PI) of the CICI, was also Co-PI of this adult study, enabling her to develop the pediatric study. In this way, previous collaborations have resulted in funding of new studies. The CICI study was funded with 15.5 million NOK by the NRC from 2019 until 2024, i.e. is still ongoing.
Researchers and clinicians at SRH have been responsible for the development, conduction, dissemination and implementation of the study. Marianne Løvstad is head of Psychology at SRH, and professor at The University of Oslo. She has previously been co-PI on two RCTs in collaboration

with Oslo University Hospital, and the CICI study is her first NRC-funded study as PI and with SRH as owner. The CICI attracted two experienced neuropsychologists from SRH as PhD candidate (Ingvil Laberg Holthe; March 2019 -) and post doc fellow (Nina Rohr Baumgartner; Febr 2019 -), and a second post doc was recruited externally (Edel Jannecke Svendsen; May 2020 -). She is a specialist in pediatric nursing and has after commencement of her post doc been recruited as Head of nursing at SRH. We have also attracted a researcher from the adult study to help with outcome measurements (PhD Ida Borgen – Jan 2022 – December 2023). The CICI staff thus involves hospital staff whom will continue to contribute to pABI rehabilitation. The CICI has involved strong collaborations with special education system Statped, and collaboration is established internationally with e.g. prof. Shari Wade from Cincinnattis Childrens hospital. Although publication of the final RCT results, and a process evaluation is pending, the study has already resulted in several international peer reviewed papers, and to various presentations at institutional, national and international meetings. One PhD thesis has been finalized, with the defence taking place in February 2024. There is ongoing work to secure funding for implementation of study findings into regular clinical services at SRH.

3. References to the research

Rohrer-Baumgartner, N, Holthe, IL,Svendsen, EJ, Røe, C, Egeland, J, Borgen, IMH, Hauger, SL, Forslund, MV, Brunborg, C., Øra, HP, Dahl, HM, Bragstad, LK, Killi, EM, Sandhaug, M, Kleffelgård, I, Strand-Saugnes, AP, Dahl-Hilstad, I, Ponsford, J, Winter, L, Wade, S, **Løvstad, M.** Rehabilitation for children with chronic acquired brain injury in the Child in Context Intervention (CICI) study: study protocol for a randomized controlled trial. Trials (2022) 23:169. https://doi.org/10.1186/s13063-022-06048-8.
Rehabilitation for children with chronic acquired brain injury in the Child in Context Intervention (CICI) study: study protocol for a randomized controlled trial | Trials | Full Text (biomedcentral.com)

Holthe, I.L., Rohrer-Baumgartner, N., Svendsen, E.J., Hauger, S.L., Forslund, M.V., Borgen, I.M.H., Øra, H.P., Kleffelgård, I., Strand-Saugnes, A.P., Egeland, Røe, C., Wade, S., **Løvstad, M.** (2022). Feasibility and Acceptability of a Complex Telerehabilitation Intervention for Pediatric Acquired Brain Injury: The Child in Context Intervention (CICI). *J. Clin. Med., 11*,2564. Doi: https://doi.org/10.3390/ jcm11092564.
Feasibility and Acceptability of a Complex Telerehabilitation Intervention for Pediatric Acquired Brain Injury: The Child in Context Intervention (CICI) - PubMed (nih.gov)

Holthe, IL, Dahl, HM, Rohrer-Baumgartner, N., Eichler, S., Elseth, MF, Holthe, Ø., Berntsen, T., Yeates, K.O., Andelic, N., **Løvstad, M.** (2022). Neuropsychological Impairment, Brain Injury Symptoms, and Health-Related Quality of Life After Pediatric TBI in Oslo, Frontiers in Neurology, doi:10.3389/fneur.2021.719915.
Neuropsychological Impairment, Brain Injury Symptoms, and Health-Related Quality of Life After Pediatric TBI in Oslo - PubMed (nih.gov)

Svendsen, E.J., Killi, E.M., Rohrer-Baumgartner, N., Lagerg-Holthe, I., Sandhaug, M., Borgen, I.M.H., Wade, S., Hauger, S.L., **Løvstad, M**., Kildal Bragstad, L. (2023). Children's, parents', and teachers' experiences of the feasibility of a telerehabilitation intervention for children with acquired brain injury in the chronic phase – a qualitative study of acceptability and participation in the Child In Context Intervention (CICI). *BMC Health Serv Res* **23**, 603. https://doi.org/10.1186/s12913-023-09589-z

Eriksen, H., Linnestad, A.-M., Laberg Holthe, I., Rohrer-Baumgartner, N., **Løvstad, M.** & Tuntland, H. (2022). Oversettelse av spørreskjemaet «The Family Needs Questionnaire - Pediatric» til norsk. *Ergoterapeuten*. The_familiy_needs_questionnaire.pdf

Currently, two additional papers reporting on goal attainment and baseline characteristics of the sample, are under review in international journals. Three additional papers are under preparation. In addition, the study has attracted interest and resulted in talks and presentations at conferences and meeting, and in the mass-media.

4. Details of the impact

The CICI study has contributed to an increased evidence base regarding rehabilitation in the chronic phase of pABI, and has strengthened the clinical milieu at SRH in the task of developing improved paediatric services in the future. Since the field rehabilitation after pABI is not robust at an international level, the study has potential to attract international interest. The CICI study was as noted strongly inspired by the work in the adult goal oriented study at Oslo University hospital where the PI was also heavily involved. In addition, there is an ongoing PhD study at Oslo University hospital, regarding unmet rehabilitation needs after paediatric traumatic injury. Løvstad is co-supervisor on that study and was involved in its funding. The PhD candidate in this study, Hilde Dahl, is also a consulting paediatric neurologist at SRH, and has ben pivotal in contributing to participants in the CICI study. In this way, the CICI represents an early stage development of a more robust research milieu regarding children with ABI in Norway. The collaboration with Cincinnattis Childrens´ hospital and prof. Shari Wade has been very important in ensuring that the study holds high international standards. The collaboration with Statped has made a closer collaboration between the health sector and special education services possible, which is highly needed. In addition to the specific paediatric aspects of the study, the CICI together with its model adult study has provided ample experience in the use of goal-oriented rehabilitation in the community setting. Rehabilitation should be goal-oriented and specific, targeting everyday life. The study researchers e.g. have provided workshops for clinicians at SRH regarding the goal setting process in rehabilitation. Due to the clinical researchers involved in the CICI study all being regular staff at SRH, implementation is highly feasible, and we are currently working on attracting external funding for implementation of study results in regular clinical services. This involves the development of a regular rehabilitation program in the chronic phase in our health region. The collaborating user organisation, Personskadeforbundet LTN have been involved throughout the study period and have expressed great interest in the study.

5. Sources to corroborate the impact

- Lise Kristoffersen, collaboration partner Statped
- Ingeborg Dahl Hilstad, General Secretary Personskadeforbundet LTN
- Cecilie Røe, prof. Head of Dept of physical medicine and rehabilitation, Oslo University Hospital
- Hilde Dahl, pediatric neurologist Oslo University Hospital/SRH, collaborater regarding patient recruitment
- Birgitte Dahl, head of the pediatric unit, SRH
- Shari Wade, prof. Cincinnatti Children´s Hospital, University of Cincinnatti

Impact case

Sunnaas Rehabilitation Hospital, Department of Research. Case number 3

Institution:	Sunnaas Rehabilitation Hospital (SRH)
Administrative unit:	Department of Research
Title of case study:	International Spinal Cord Injury survey (InSCI)
Period when the underpinning research was undertaken: 2017 – ongoing	
Period when staff involved in the underpinning research were employed by the submitting institution: 2015 - ongoing	
Period when the impact occurred: 2019 - ongoing	

1. Summary of the impact

A spinal cord injury (SCI) greatly affects an individual's life. Weaknesses in health and rehabilitation systems can worsen the burden of disability and lead to poorer health outcomes and reduced well-being. Inconsistent data and comparable figures on the functional consequences, health services and social provisions for people with SCI, are however scarce. The International Spinal Cord Injury survey (InSCI) is a structured approach to collect internationally comparable data on the lived experience of persons with SCI, highlighting the impact of SCI on the everyday lives of people. InSCI provides a systematic evaluation and comparative analysis of the societal response to SCI on both a national and a global level and identify issues and gaps in the quality and access to SCI-specific healthcare and rehabilitation systems. The results of the InSCI survey will be used as evidence for implementation of recommendations for improving the societal response to the needs of individuals with SCI at the national level.

2. Underpinning research

InSCI is a multinational cross-sectional community survey and is the first global survey for persons with SCI. The first wave of the survey was conducted in 2017-2019 in 22 countries across 6 regions of the World Health Organization (WHO). InSCI is initiated and coordinated by Swiss Paraplegic Research. The participating countries were recruited through the networks of the International Society of Physical and Rehabilitation Medicine (ISPRM) and the International Spinal Cord Society (ISCoS). The Norwegian part of InSCI (InSCI-Nor) is a national effort among the entire SCI community in our country, established in 2015, including SRH, the SCI units at St. Olav's Hospital, Trondheim and Haukeland University Hospital, Bergen, and the Norwegian Spinal Cord Injury Registry (NorSCIR) and the Norwegian Spinal Cord Injuries Association (LARS). InSCI-Nor is coordinated and managed from SRH, from 2015 to 2019 under the leadership of our former Director of Research, Professor *Johan K. Stanghelle*, later followed by the present Director of Research, Professor *Anne Catrine Martinsen* (2019-2022) and Head of Research, Assoc. Professor *Vegard Strøm* (from 2023). Other key personnel from SUN Research include then Chief Medical Advisor *Grethe Månum*, and physiotherapist/PhD-candidate *Pia Wedege*.

The background for InSCI is to be found in a report from the WHO in 2013 (International Perspectives on Spinal Cord Injury; IPSCI), which highlighted a strong need to obtain a comprehensive overview and description of the life situation of people with SCI across different nations, different economic systems, and different health- and rehabilitation systems. InSCI is grounded in the International Classification of Functioning, Disability and Health (ICF), both in terms of the dimensions of the experience of SCI and in terms of the underlying conceptualization of functioning. InSCI forms the basis for the Learning Health System for SCI (LHS-SCI), which is s a joint effort of ISCoS and ISPRM to implement the recommendations of the IPSCI-report. LHS-SCI is grounded on the principle that health systems "learn" when they can rely on cyclical dynamics to identify issues, create responses, implement changes, observe the consequences, respond to the implementation results, and revise and reshape the responses – thus, learn from success and failure.

The overall objective of InSCI is to identify the factors that explain functioning and well-being of people living with SCI. The InSCI data provides comprehensive and comparable information about the lived experience of disability. The survey consisted of a comprehensive questionnaire relying on the ICF, comprising components of body functions and structures, activities and participation, environmental and personal factors, lesion characteristics, and appraisal of health and well-being. The SCI participants in Norway are people with traumatic or atraumatic SCI, aged 18 or older, admitted for initial sub-acute rehabilitation after 2000. We identified totally 1456 potential participants. Of these, 610 people answered the survey, which makes this study the largest of its kind conducted in Norway on people with SCI. The entire InSCI study includes more than 12500 participants.

3. References to the research

Bychkovska, O., **Strøm, V**., Tederko, P., Engkasan, J. P., Juocevičius, A., Battistella, L. R., ... & Gemperli, A. (2023). Health System's Role in Facilitating Health Service Access among Persons with Spinal Cord Injury across 22 Countries. International Journal of Environmental Research and Public Health, 20(11), 6056. DOI: 10.3390/ijerph20116056.
Health System's Role in Facilitating Health Service Access among Persons with Spinal Cord Injury across 22 Countries - PubMed (nih.gov)

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Pacheco Barzallo D, Gross-Hemmi M, Bickenbach J, Juocevičius A, Popa D, Wahyuni LK; InSCI, **Strøm V**. Quality of Life and the Health System: A 22-Country Comparison of the Situation of People With Spinal Cord Injury. Arch Phys Med Rehabil. 2020 Dec;101(12):2167-2176.
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Strøm V, Månum G, Arora M, Joseph C, Kyriakides A, Le Fort M, Osterthun R, Perrouin-Verbe B, Postma K, Middleton J. Physical Health Conditions in Persons with Spinal Cord Injury Across 21

Countries Worldwide. J Rehabil Med. 2022 Jun 29;54:jrm00302. DOI: 10.2340/jrm.v54.2040. PMID: 35678293; PMCID: PMC9272839.
Physical Health Conditions in Persons with Spinal Cord Injury Across 21 Countries Worldwide | Journal of Rehabilitation Medicine (medicaljournalssweden.se)

There are by now more than 35 international peer-reviewed scientific publications (Link to publications: InSCI - Search Results - PubMed (nih.gov)).

4. Details of the impact

As a community survey of individuals living with SCI, the InSCI survey is one of few surveys that highlights not only basic medical issues, but also the impact of SCI on the everyday lives. SCI is a relatively low-prevalence, high-cost health condition affecting between 250 000 and 500 000 persons worldwide yearly, and 120-130 new cases (ca 70% men) each year in Norway. The InSCI survey was undertaken between 2017 and 2019, and is to be repeated at five-year intervals to develop both longitudinal and updated data. The InSCI wave II is ongoing. The InSCI-Nor findings thus provide a starting point for identifying how our society can respond to the needs of individuals with SCI, and - through the LHS-SCI principle – be implemented to shape and deliver information that informs agenda setting and policy formation. InSCI provides information that can improve the societal response to SCI, and implementation is the next step.

An overall finding is that Norway seems to be at a high international level when it comes to the SCI care, as our participants are scoring high on the functioning and well-being outcomes. Many receive health care and are satisfied with the health service, and they have frequent contact with the health service even after discharge. The three specialized SCI rehabilitation units in Norway are committed to life-long follow-up of persons with SCI. Based on the results from InSCI-Nor, focus have now, in the long-term follow-up programs, been put on treatment and problems related to secondary health conditions. Such problems are for example pain, muscle spasms and sexual dysfunction, problems that may affect quality of life and social participation.

The InSCI-Nor has established a sustainable research collaboration network and interdisciplinary competence sharing within the SCI field in Norway. InSCI-Nor has also enabled the opportunity to embrace the entire Norwegian SCI population in research, increasing the publication productivity- and quality and the impact of the publications, as well as increasing the impact of the Norwegian data both nationally and internationally.

5. Sources to corroborate the impact

Link to the InSCI web-site: InSCI Survey

Link to web-site at Sunnaas Rehabilitation Hospital: The International Spinal Cord Injury Survey – Norway - Sunnaas Rehabilitation Hospital

The International Spinal Cord Injury Survey: The Way Forward (swisci.ch)

The International Society of Physical and Rehabilitation Medicine (ISPRM):
InSCI: International Spinal Cord Injury Survey – ISPRM

Stavanger University Hospital, SUH [1]

Institution: Stavanger University Hospital, SUH
Administrative unit: Stavanger University Hospital, SUH
Title of case study: The Norwegian PARKWEST study
Period when the underpinning research was undertaken: 2004 - to date
Period when staff involved in the underpinning research were employed by the submitting institution: 2004 – to date
Period when the impact occurred: 2012-2022

1. Summary of the impact (indicative maximum 100 words)

Since 2004, the Norwegian ParkWest study has been a cornerstone in advancing our understanding of the clinical course and neurobiology of Parkinson's disease. Between 2012 and 2022, the study had widespread and profound impact, heightening awareness of key symptoms, innovating diagnostic and prognostic methods, and catalysing clinical trials for more effective treatment. The study has made a pivotal contribution to establishing national initiatives to optimize patient care across Norway, such as ParkinsonNet Norway and the Norwegian Parkinson Registry and Biobank. Its impactful contribution has not only elevated knowledge but also catalysed changes in patient awareness and care, and stimulated innovation across various sectors.

2. Underpinning research (indicative maximum 500 words)

Parkinson disease (PD) is an important cause of disability and death worldwide. Major challenges include a high misdiagnosis rate, substantial heterogeneity in disease course, high risk of disabling non-motor symptoms (NMS), and a lack of interventions to stop disease progression.

The Norwegian ParkWest study was initiated in 2004 to study the incidence, neurobiology, and prognosis of PD. Distinguished as one of the pioneering projects in its field, the study has meticulously tracked the natural course of PD for nearly two decades, offering unparalleled insights into the lived experiences of patients and the far-reaching consequences of the disease on individuals, their families, and the healthcare system.

Primary research output:

The study was the first to determine the incidence of PD in Norway, at the same time demonstrating a high misdiagnosis rate among referring doctors (2009). The study has provided crucial insights into the extensive spectrum of motor and non-motor symptoms, notably in areas such as cognitive and behavioural changes. Using these data, our group was among the first to introduce the concept of mild cognitive impairment (MCI) to the field of PD, and to demonstrate that PD-MCI is an important risk factor for early development of dementia (2009-2013). We subsequently dissected the underlying neurobiology of cognitive impairment in PD, demonstrating the potential of cerebrospinal fluid amyloid beta (2013) and *GBA1*/GCase (2018-2022) as valuable early prognostic biomarkers of evolving MCI and future dementia. In 2008/9, recognizing the crucial role of non-motor symptoms in PD, the study expanded its focus. This included more detailed monitoring of impulse control disorders (ICDs), revealing their high prevalence in the Norwegian PD population and not least a strongly increased risk in dopamine agonist users (2017). The study's profound impact extends across a diverse spectrum of researchers, yielding over 100 articles on diverse topics, with >35% published in high impact (level 2) journals, accompanied by >10 editorials, and supporting >15 doctoral theses.

Resulting new research at the unit:

ParkWest uncovered pivotal insights into the early stages of PD, emphasizing that already at diagnosis patients experience a substantial NMS burden. This spurred the inception of **(1) The**

prodromal Lewy Body Disease (Pro-LBD) study – a multidisciplinary, clinical-biological exploration of 'at-risk' individuals and healthy controls to investigate prodromal disease mechanisms of PD and dementia with Lewy bodies (DLB). Additionally, ParkWest underscored the profound impact of NMS on patients' quality of life, catalyzing the **(2) ePARK study**. This decentralized, remote, randomized, delayed-start trial assesses the efficacy of online, video-assisted cognitive-behavioural therapy (eCBT) for depressive symptoms. Our deepened understanding of PD's neurobiology prompted the development of new biomarker methods, fostering collaborations like the industry-linked **(3) MOlecular Diagnosis of ALpha-synucleinopathies (MoDAl) project**, and unveiling novel clinical trial targets. To bridge knowledge gaps in related diseases, we initiated the **(4) GCase-Responders Across Neurodegenerative Diseases (GRAND) project**, designed to identify similarities and differences in disease courses and biomarkers for PD and DLB. Further we were founding members of **(5) The Parkinson Incidence Cohorts Collaboration (PICC)** – an international collaboration of six population-based PD incidence cohorts to investigate the progression of PD across Northern Europe's general PD population.

***Key researchers of the group*:**

Prof. Jan Petter Larsen (neurologist, 2004-2016), Prof. Guido Alves (neurologist, 2004 – to date), Ass. prof. Jodi Maple Grødem (molecular biologist, 2014 – to date), Ass. prof. Johannes Lange (chemist, 2011 – to date), Kenn Freddy Pedersen (neurologist, 2007 – to date), Ass. prof. Aleksander Hagen Erga (clinical psychologist, 2015 – to date)

3. References to the research (indicative maximum of six references)

1. Incidence of Parkinson's disease in Norway: the Norwegian ParkWest study. Alves G, Müller B, Herlofson K, HogenEsch I, Telstad W, Aarsland D, Tysnes OB, Larsen JP. J Neurol Neurosurg Psychiatry. 2009 Aug;80(8):851-7. doi: 10.1136/jnnp.2008.168211. Epub 2009 Feb 25. PMID: 19246476

Incidence of Parkinson's disease in Norway: the Norwegian ParkWest study (bmj.com)

2. Prognosis of mild cognitive impairment in early Parkinson disease: the Norwegian ParkWest study. Pedersen KF, Larsen JP, Tysnes OB, Alves G. JAMA Neurol. 2013 May;70(5):580-6. doi: 10.1001/jamaneurol.2013.2110. PMID: 23529397

Prognosis of Mild Cognitive Impairment in Early Parkinson Disease (Jamanetwork.com)

Editorial: Can Mild Cognitive Impairment in Parkinson Disease Predict the Development of Dementia? (Jamanetwork.com)

3. CSF Aβ42 predicts early-onset dementia in Parkinson disease. Alves G, Lange J, Blennow K, Zetterberg H, Andreasson U, Førland MG, Tysnes OB, Larsen JP, Pedersen KF. Neurology. 2014 May 20;82(20):1784-90. doi: 10.1212/WNL.0000000000000425. Epub 2014 Apr 18. PMID: 24748671

CSF Aβ42 predicts early-onset dementia in Parkinson disease (neurology.org)

4. GBA and APOE Impact Cognitive Decline in Parkinson's Disease: A 10-Year Population-Based Study. Szwedo AA, Dalen I, Pedersen KF, Camacho M, Bäckström D, Forsgren L, Tzoulis C, Winder-Rhodes S, Hudson G, Liu G, Scherzer CR, Lawson RA, Yarnall AJ, Williams-Gray CH, Macleod AD, Counsell CE, Tysnes OB, Alves G, Maple-Grødem J; Parkinson's Incidence Cohorts Collaboration. Mov Disord. 2022 May;37(5):1016-1027. doi: 10.1002/mds.28932. Epub 2022 Feb 2. PMID: 35106798

GBA and APOE Impact Cognitive Decline in Parkinson's Disease: A 10-Year Population-Based Study (Movementdisorders.onlinelibrary.wiley.com)

5. Association of CSF Glucocerebrosidase Activity With the Risk of Incident Dementia in Patients With Parkinson Disease. Oftedal L, Maple-Grødem J, Dalen I, Tysnes OB, Pedersen KF, Alves G, Lange J. Neurology. 2023 Jan 24;100(4):e388-e395. doi: 10.1212/WNL.0000000000201418. Epub 2022 Oct 17. PMID: 36253102

Association of CSF Glucocerebrosidase Activity With the Risk of Incident Dementia in Patients With Parkinson Disease (neurology.org)

Editorial: Low Glucocerebrosidase Activity Predicts Dementia in Parkinson Disease (neurology.org)

6. Impulsive and Compulsive Behaviors in Parkinson's Disease: The Norwegian ParkWest Study.

Erga AH, Alves G, Larsen JP, Tysnes OB, Pedersen KF. J Parkinsons Dis. 2017;7(1):183-191. doi: 10.3233/JPD-160977. PMID: 27911342

Impulsive and Compulsive Behaviors in Parkinson's Disease: The Norwegian ParkWest Study (content.iospress.com)

4. Details of the impact (indicative maximum 750 words)

The ParkWest study was initiated as a collaboration between five health trusts in southwestern Norway, has co-principal investigators at two sites (Stavanger University Hospital and Haukeland University Hospital), and is coordinated by our research group at the Norwegian Centre for Movement Disorders. Beyond academic realms, our group's comprehensive understanding of the lived experience of PD has led to elevated awareness of crucial PD symptoms among health professionals, patients, and the public, and impacted our contribution to innovation across diverse sectors.

Impact on health

The impact of ParkWest on health is exemplified by our work on ICDs. Our group was the first to show that 30% of Norwegian patients with PD were impacted by ICDs and this was strongly linked to dopamine agonist (DA) use (odds ratio: 7.4). This knowledge, disseminated through articles, seminars, and campaigns, prompted several impactful actions between 2017 and 2022. We collaborated with the National Parkinson Foundation (NPF) on coordinated informational campaigns, using NPF's and our groups webpages, patient leaflets, and hosting both face-to-face and online seminars and presentations for patients. Additionally, to enhance diagnosis and screening, we translated and distributed the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease Rating Scale (QUIP) to neurology departments nationwide, available on our webpages. We also incorporated the assessment of ICDs into the Norwegian Parkinson Registry (expanded on below), which has enhanced comprehensive monitoring at the national level. Notably, our research has steered a recent shift in treatment recommendations, with dopamine agonists no longer considered the first-choice treatment.

Impact on innovation

In the first ParkWest publication, we revealed a significant early misdiagnosis rate of PD, emphasising a critical need for biomarkers to support the clinical diagnosis of PD. Utilising samples collected in ParkWest, we developed an innovative molecular diagnostic method. This breakthrough prompted the establishment of an industrial collaboration (2022) to develop this method into an accessible kit, with the first patent filed the same year.

The recognition of the challenge of early accurate diagnosis also led our group to establish a brain donation program within ParkWest, with nearly half of the patients consenting to autopsy for research. This invaluable resource has contributed to advancements in PD neurobiology, exemplified by the work from our collaborators in Bergen, laying the groundwork for their national clinical trials into nicotinamide adenine dinucleotide replenishment therapy (2020 to date; PI Charalampos Tzoulis, Helse Bergen; NCT03568968).

Our foundational research on dementia in PD spurred the development of both genetic and protein dementia biomarkers from Alzheimer's pathology (*ApoE*/Amyloid beta) and lysosomal function (*GBA1*/GCase; Section 3, references 4 and 5). These biomarkers were integrated into a national clinical trial for Ambroxol in new and early Dementia with Lewy Bodies (2021-to date; PI Arvid Rongve, Helse Fonna; NCT04588285). Their inclusion serves to improve patient stratification, response assessment, and overall trial efficacy, signalling a significant step towards refining treatment interventions and advancing the field of PD research.

Impact on society

The global recognition of the ParkWest study has contributed to the group's standing in the field and role in designing and conducting new national initiatives to optimize patient care across Norway. For example, the group has applied their experience in ParkinsonNet Norway (pilot 2017-2019; national implementation 2020 - to date), a nationwide healthcare network prioritizing optimal treatment and enhancing the quality of life for individuals with PD and parkinsonism. ParkWest clearly showed that patients' prognosis and quality of life was impacted by both motor and NMS at all disease stages and highlighted the need for a multidisciplinary approach to care. ParkinsonNet Norway was designed to conduct specialist and interdisciplinary practice-based training for healthcare professionals from both the specialist health service, the municipal health service, and the private sector.

Insight from the ParkWest study, for example regarding impulsivity, side effects of medication, and assessment of motor functioning, also influenced the design of The Norwegian Parkinson Registry and Biobank. The Registry was commissioned in 2016 to register all patients with neurodegenerative parkinsonian disorders, encompassing PD and atypical parkinsonism, with the aim to ensure uniform diagnosis, treatment, and follow-up for these patients. The registry has now close to 6,000 registered participants, representing about 60% of all patients in Norway, and numbers are increasing rapidly.

5. Sources to corroborate the impact (indicative maximum of ten references)

Impact on health

Podcast on impulse control disorders

An episode of the National Parkinson Foundation's podcast that invites leading researchers to discuss different aspects of the disease; in Norwegian.

Hvem kan utvikle impulskontrollforstyrrelser og hvordan oppdages det - Norges Parkinsonforbund

An article on "Who can develop impulse control disorders and how is it detected" to provide information on ICDs for the Norwegian Parkinson Association webpages; in Norwegian.

Impulskontroll-interaktivt-quip-skjema.pdf (helse-stavanger.no)

The Norwegian translation of QUIP; in Norwegian.

Treatment of motor symptoms in Parkinson's disease | Tidsskrift for Den norske legeforening (tidsskriftet.no)

Information on the treatment of Parkinson Disease in the Journal of the Norwegian Medical Association.

Impact on innovation

Study Details | A Randomized Controlled Trial of Nicotinamide Riboside Supplementation in Early Parkinson's Disease | ClinicalTrials.gov

Study Details | Ambroxol in New and Early DLB, A Phase IIa Multicentre Randomized Controlled Double Blind Clinical Trial | ClinicalTrials.gov

Impact on society

ParkinsonNet - Helse Stavanger HF (helse-stavanger.no)

The ParkinsonNet Norway homepage.

Healthcare finder

The catalogue of healthcare professionals linked to ParkinsonNet; in Norwegian.

Dagens medisin

An article on ParkinsonNet Norway in Dagens Medisin, a newspaper for healthcare professionals: "ParkinsonNet: – Samhandling er en gordisk knute som denne modellen har løst", " ParkinsonNet: – Solving the Gordian knot of interaction"; In Norwegian.

Registry and Biobank - Helse Stavanger HF (helse-stavanger.no)

Dagens medisin

An article on The Norwegian Parkinson Registry and Biobank in Dagens Medisin, a newspaper for healthcare professionals: "Parkinsonregisteret først ute med ny løsning som skal sørge for mer pasientdata", "The Parkinson register is the first out with a new solution that will provide more patient data"; in Norwegian.

Stavanger University Hospital, SUH [2]

Institution: Stavanger University Hospital (SUH)
Administrative unit: Stavanger University Hospital (SUH)
Title of case study: Safer Births Bundle of Care (SBBC)
Period when the underpinning research was undertaken: 2009 -ongoing
Period when staff involved in the underpinning research were employed by the submitting institution: 2009 - ongoing
Period when the impact occurred: 2009 - ongoing

1. Summary of the impact (indicative maximum 100 words)

SBBC builds upon the Safer Births collaboration with 12 years of research and >130 publications. SBBC consists of innovative training and clinical tools for improved labor care and newborn resuscitation. It integrates with new strategies for continuous quality improvement (CQI) and incorporates into national systems to be sustainable. SBBC has demonstrated increased maternal and newborn survival when implemented in 30 hospitals in Tanzania. Due to promising preliminary results, the World Bank Global Financing Facility (GFF) have awarded additional funding to scale SBBC in 150 hospitals in Tanzania. If implemented globally, SBBC has potential to save 250,000 lives worldwide, annually.

2. Underpinning research (indicative maximum 500 words)

Safer Births related studies started in 2009 with pilot testing of the Helping Babies Breathe (HBB) simulation-based education program in Tanzania, followed by Helping Mothers Survive (HMS) research at Haydom Lutheran Hospital (HLH) in rural Tanzania. The first Safer Births projects started at HLH in 2013, with **Hege Ersdal** and **Esto Mduma,** and later **Paschal Mdoe** leading the project. In 2017-2020, the landmark immediate Kangaroo Mother Care (iKMC) randomised controlled trial (coordinated by WHO) was conducted with Safer Births colleagues (**Robert Moshiro** and **Siren Rettedal**) in key positions. In the same time period, the project conducted an advanced immediate Kangaroo Mother Care (iKMC) study at SUH (IPISTOS). Figure 1. illustrates the scientific logic of the program, following the mother and child from fetal monitoring to 7-day endpoints.

The research insights and findings of the program can be summarized as follows:

New basic medical knowledge about:

- Fetal to newborn cardio-respiratory transition: normal and abnormal (the asphyxia process)
- The theory – practice gap in newborn resuscitation
- Newborn resuscitation

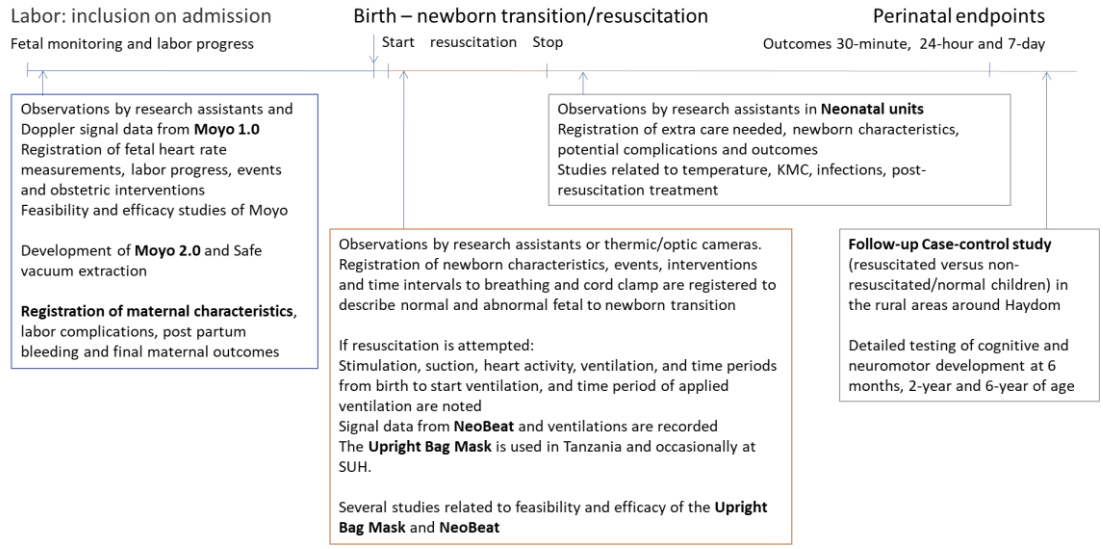

Figure 1. Research logic of the Safer Births program.

New knowledge of effective training methods:

- Development and testing of low-dose high-frequency in situ simulation training for both newborn and maternal emergencies
- Strategies for implementation of sustainable continuous QI processes
- Use of AI in data analysis

The major research outputs are:

- Influence on international guidelines for newborn resuscitation (International Liaison Committee On Resuscitation (ILCOR), European Resuscitation Council (ERC), Norwegian Resuscitation Council (NRR).
- Influence on WHO recommendations for training strategies
- Development of clinical devices (Laerdal Global Health, LGH)
- Development of training devices (LGH)
- Development of training strategies (SimBegin) (SAFER-Laerdal-SUS)
- Increased maternal and neonatal survival (Tanzania)
- Improved household coping mechanisms

The key researchers (PI's) in the project are:
Hege Ersdal (overall project leader)
Internal PIs Tanzania: Benjamin Kamala, Paschal Mdoe, Esto Mduma, Robert Moshiro,
Co-PI Tanzania: Jørgen Linde
Internal PIs SUH: Siren Rettedal and UiS: Kjersti Engan
A complete list of Safer Births researchers can be found PhD candidates and researchers – Safer Births

A full overview of the evolution of the project components, research activity and main research findings is shown in figure 2. The academic and innovative achievements of Safer Births have received extensive international recognition by international organisations (such as the WHO, ILCOR, simulation societies (SSH, SESAM), American Academy of Pediatrics (AAP), USAID, UNICEF,

Norwegian Agency for Development Cooperation (NORAD) and clinical and academic personnel on a global scale.

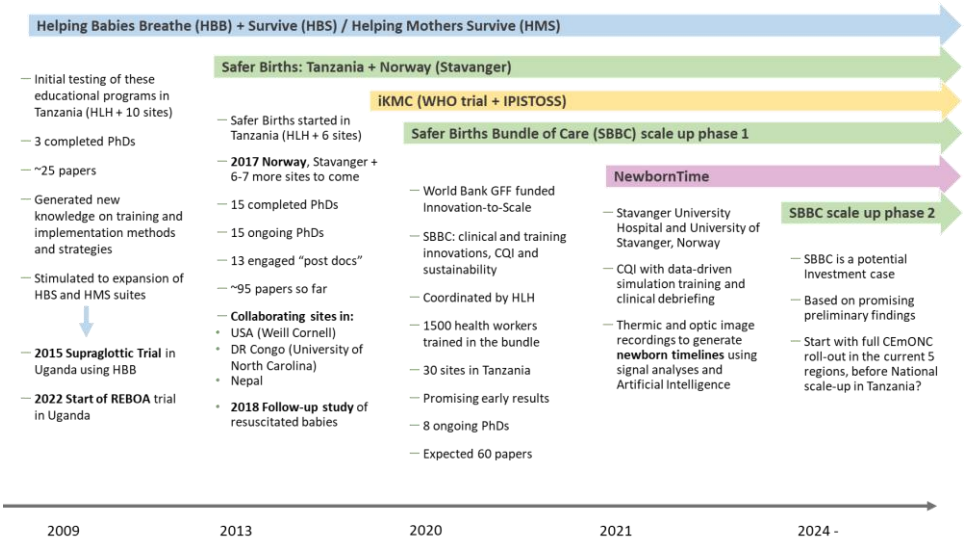

Figure 2. Evolution of Safer Births program components.

3. References to the research (indicative maximum of six references)

1. Linde J, Perlman J, Øymar K, Schultz J, Eilevstjønn J, Thallinger M, Kusulla S, Kidanto H, Ersdal H. Predictors of 24-hour outcome in newborns needing positive pressure ventilation at birth in a low-resource setting. 2018 Resuscitation (Level 2). DOI: 10.1016/j.resuscitation.2018.05.026

2. Holte K, Ersdal HL, Eilevstjønn J, Gomo Ø, Klingenberg C, Thallinger M, Linde JE, Stigum H, Yeconia A, Kidanto H, Størdal K. Positive End-Expiratory Pressure in Newborn Resuscitation Around Term: A Randomized Controlled Trial. 2020 Pediatrics (Level 2). DOI: 10.1542/peds.2020-0494

3. Perlman JM, Velaphi S, Massawe A, Clarke R, Merali H, Ersdal H. Achieving Country-wide Scale for Helping Babies Breathe and Helping Babies Survive. 2020 Pediatrics (Level 2). DOI: 10.1542/peds.2020-016915K

4. Ersdal HL, Eilevstjonn J, Perlman J, Gomo Ø, Moshiro R, Mdoe P, Kidanto H, Hooper S, Linde JE. Establishment of functional residual capacity at birth; observational study of 821 neonatal resuscitations. 2020 Resuscitation (Level 2) URL:https://doi.org/10.1016/j.resuscitation.2020.05.033

5. Eilevstjønn J, Linde JE, Blacy L, Kidanto H, Ersdal HL. Distribution of heart rate and responses to resuscitation related to outcome among 1237 apnoeic term newborns at birth. 2020 Resuscitation (Level 2) DOI: 10.1016/j.resuscitation.2020.04.037

6. May Sissel Vadla, Robert Moshiro, Paschal Mdoe, Joar Eilevstjønn, Jan Terje Kvaløy, Barikiel Hhando Hhoki, Hege Ersdal. Newborn resuscitation simulation-based skill-training and changes in clinical performance and perinatal outcomes: clinical observational study of 10 481 births. 2022 Advances in Simulation (Level 1). URL: https://doi.org/10.1186/s41077-022-00234-z

4. Details of the impact (indicative maximum 750 words)

Building on the Safer Births research and development collaboration with 12 years of research in Tanzania and Norway, the SBBC was developed. The bundle consists of proven innovative training and clinical tools for improved labor care and newborn resuscitation. It also integrates with new strategies for CQI and incorporates into national systems to be sustainable (figure 3.)

In 2020 SBBC was rated with the highest score among 320 proposals submitted in response to the World Bank Global Financing Facility (GFF) Innovation-to-Scale call. As a result, the program became one of five recipients of a grant of 5 million USD, enabling the scale up to 30 district hospitals in five regions with the highest perinatal mortality in Tanzania.

The goals of the SBBC scale-up to 30 hospitals in Tanzania, based on the results from the Safer Births program, were to achieve 10% reduction in maternal deaths, 25% reduction in fresh stillbirths, and 50% reduction in early neonatal deaths.

The components of the bundle are implemented together to systematically improve the quality of care provided to mothers and newborns. For sustained change, country ownership, regular mentorship, and supportive supervision are key.

Figure 3. Safer Births Bundle of Care: training innovations, clinical innovations, continuous quality improvement and sustainability.

SBBC's training innovations are designed to integrate with simulation scenarios, focusing on key maternal and newborn lifesaving skills. This bridges the gap between clinical theory and care. The local facility champions regular simulation training on labor management, postpartum bleeding, newborn resuscitation, and essential newborn care. The training sessions are guided by the Helping Mothers and Babies Survive programs. The local facility champions receive weekly feedback on their own facility's clinical data (key performance indicators and perinatal outcomes) and adjust ongoing trainings to address identified gaps. The clinical innovations are designed to ease the job of the health workers in fetal heart rate monitoring and newborn resuscitation. CQI is integrated through regular on-the-job, low-dose, high-frequency simulation-based training. Targeted training is done by utilizing local data and feedback loops, to visualize gaps in clinical care and guide areas for improvement. Adequate training of local facility champions who can facilitate CQI simulation training is considered

essential for these processes to stimulate a gradual and sustainable culture change. To implement SBBC in a sustainable way, it is also important that the program is incorporated into national systems.

The project has made a substantial impact on maternal and neonatal mortality and morbidity, with preliminary unadjusted analysis in 2023 indicating 70% reduction in maternal mortality and 45% reduction in early neonatal mortality. In addition to improving every individual's health, the result of the project therefore has a larger effect on the empowerment of women and financial sustainability of households in the society. This impact has influenced international guidelines for the resuscitation of newborns and contributed to the development of innovative clinical and training tools that can be scaled up globally. Due to the promising preliminary results, the GFF awarded an additional 8.5 million USD funding to implement SBBC in 150 hospitals in Tanzania. If these early results are maintained, this could pave the road for a full national scale-up with the potential of saving more than 20,000 extra lives in Tanzania – every year.

For the SBBC implementation to 30 hospitals in Tanzania, the estimated cost is 78 USD per life year gained. Scaling up to over 100 hospitals in five regions, that cost could come down to 32 USD and further down to 19 USD with national scale-up. If results in the best regions so far could be reproduced on a national scale, the cost could be as low as 6 USD per life saved. Compared with 100 USD considered by WHO to be the threshold of cost-effective interventions, the program has demonstrated both an initial, and potentially improved use of scarce resources.

In summary, the Safer Births program targets the UN SDG's 1 (No Poverty), 3 (Good Health and Well-being), 5 (Gender Equality), 9 (Industry, Innovation and Infrastructure) and 10 (Reduced Inequalities). To meet the UN SDG 3 targets for maternal and neonatal mortality, countries need to make reductions at a significantly faster pace. Evidence-based solutions which have been tested at scale are key. We therefore believe SBBC will play a significant role on a global scale in the years to come. If scaled-up globally and implemented well, the SBBC program has the potential to save 250,000 lives worldwide, every year.

5. Sources to corroborate the impact (indicative maximum of ten references)

References that have agreed to be contacted for impact verification of SBBC:

- *Technical expert World Bank Global Financing Facility Allison Morgan amorgan3@worldbank.org*
- *Founder Laerdal Tore Lærdal tore.laerdal@laerdal.com*

Links to external resources acknowleding impact of SBBC:

- GFF announcement of innovation to scale winners (globalfinancingfacility.org)
- GFF announcing additional SBBC funding (globalfinancingfacility.org)
- Dr. Juan Pablo Uribe, Global Director of Health in the World Bank GFF talking about SBBC in Tanzania
- H.E Health Minister Ummy Mwalimu talking about SBBC in Tanzania
- TV Tanzania reports on the impact of SBBC in the Manyara region
- Program Information Document, The World Bank GFF
- Alison Morgan from GFF and Dr. Godwin Mollel Deputy Minister of Health in Tanzania talking about SBBC in Tanzania
- Article including SBBC in Business Fights Poverty

Stavanger University Hospital, SUH [3]

Institution: Stavanger University Hospital, SUH
Administrative unit: Stavanger University Hospital, SUH
Title of case study: Implementation of artificial intelligence (AI) as support tools for pathology
Period when the underpinning research was undertaken: 2011 - to date
Period when staff involved in the underpinning research were employed by the submitting institution: 2011 - to date
Period when the impact occurred: 2020- to date

1. Summary of the impact

Facilitating and implementation of the possibility of using computer-aided diagnostic (CAD) systems in order to make pathology diagnostics more objective and faster while, more importantly, patients benefit from the best tissue diagnostics that form the basis for personalized treatment.

2. Underpinning research

Few pathology departments and even fewer regions in the world have currently realized a complete digitization of their pathology workflow and hardly anyone has implemented CAD tools. The department of pathology at SUH started in 2001 with improving diagnostic routine pathology using digital image analysis of tissue. The department has performed extensive research on quantitation of biomarkers for diagnostics, treatment response prediction and prognostication for cancer patients. Furthermore, SUH was a driving force in implementing digital pathology in the Western Norway Regional Health Authority, which currently is the first region in Norway to be fully digitized. The regional network has formed PiV - Pathology services in the Western Norway Health Region, which is a joint project of Helse Bergen and Helse Stavanger with participation of the universities of Stavanger and Bergen as well as the Western University of Applied Sciences. This has again provided the unique basis for research projects related to the developmen, validation and implementation of CAD tools.

Resulting in new research

Based on this implementation and Stavanger's many years of work in the application of image analysis tools, this has led to many new research projects such as:

- Improved diagnostics of prostate cancer by means of artificial intelligence (AI)
- Developing and implementing digital pathology for clinical practiceCLoud ARtificial Intelligence For pathologY an Eu -project for innovation training network (EU-ITN, number 860627) which consists of a training programming for 12 PhD-students that will work interdisciplinary with computational pathology

Key researchers: ***Emiel A.M. Janssen*** *(PhD),* (co)-PI and Professor; Head of Research at the Department of Pathology at SUH and Professor of Biomedicine at the University of Stavanger, Norway. Adjunct professor at Menzies school of medicine, Griffith University, Australia.

3. References to the research

- Emma Rewcastle, Einar Gudlaugsson, Melinda Lillesand, Ivar Skaland, Jan P.A. Baak, Emiel A.M. Janssen Automated prognostic assessment of endometrial hyperplasia for progression risk evaluation using artificial intelligence. Modern Pathology, Volume 36, Issue 5, May 2023, 100116.
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- Fernandez-Martín, C., Kiraz, U., Silva-Rodríguez, J., Morales, S., Janssen, E.A.M., Naranjo, V. (2022). Challenging Mitosis Detection Algorithms: Global Labels Allow Centroid Localization. In: Yin, H., Camacho, D., Tino, P. (eds) Intelligent Data Engineering and Automated Learning – IDEAL 2022. IDEAL 2022. Lecture Notes in Computer Science, vol 13756. Springer, Cham.
- Neel Kanwal, Roger Amundsen, Helga Hardardottir, Luca Tomasetti, Erling Sandoy Undersrud, Emiel A.M. Janssen, Kjersti Engan. Detection and Localization of Melanoma Skin Cancer in Histopathological Whole Slide Images. 2023 31st European Signal Processing Conference (EUSIPCO), Helsinki, Finland, 2023, pp. 975-979, doi: 10.23919/EUSIPCO58844.2023.10290087
- Mosquera-Zamudio A, Launet L, Tabatabaei Z, Parra-Medina R, Colomer A, Oliver Moll J, Monteagudo C, Janssen E, Naranjo V. Deep Learning for Skin Melanocytic Tumors in Whole-Slide Images: A Systematic Review. Cancers. 2023; 15(1):42.
- Timothy B. Fisher, Geetanjali Saini, T. S. Rekha, Jayashree Krishnamurthy, Shristi Bhattarai, Grace Callagy, Mark Webber, Emiel A. M. Janssen, Jun Kong, Ritu Aneja. Digital image analysis and machine learning-assisted prediction of neoadjuvant chemotherapy response in triple-negative breast cancer. Breast Cancer Res 26, 12 (2024).

4. Details of the impact

The impact from the ongoing research projects is clearly shown in the Pathology in West project, where we are shaping the future of pathology services (PiV; Pathology services in the Western Norway Health Region – a centre for applied digitization). Led by Prof. Emiel Janssen together with Prof. Leh from Bergen, PiV focuses on developing, validating and implementing CAD tools into the four pathology departments of our region in western Norway.

In this project we have developed algorithms for distinguishing benign from malign skin lesions and consecutively assessing the risk for progression for the malignant lesions, and we have investigated how to recognize and delete folds and other artifacts from whole slide images. Furthermore, we have compared existing commercial algorithms for quantitation of Ki67 in breast cancer with the current manual method, the guidelines from the international workgroup for Ki67, and an in-house developed algorithm. This study showed that although the algorithms used are CE-IVD marked, self-validate is essential to understand the implications of implementing such an algorithm on patient selection and treatment. For the Ki67-algorithms, the prognostic information was similar for all, but patient selection for PAM50 testing gave varying numbers and, as such, different numbers to test and economic consequences. For prostate cancer we have been working closely with the Karolinska institute to validate an algorithm for the detection of cancerous tissue and Gleason grading. Here we have worked on adding a prediction score and included an uncertain group, making the algorithm more robust for clinical practice. Furthermore, we are also assessing the possible financial impact of implementing this algorithm by calculating the potential cost savings in terms of the number of immunohistochemical stains one could spare (= real money saved). Preliminary data show that 30-50% of IHC can be spared, depending on the required sensitivity and specificity for detecting cancer.

Although many laboratories have been using WSI-scanners for several years, nobody has investigated how stable the image quality of these scanners are and whether the image quality changes over time as the instrument's, lamp gets older. To investigate this, we have scanned the same test set of prostate cancer samples over and over again, so as to assess whether the scanners are able to produce the same results over time, with the same results from a certain algorithm. Preliminary data indicate that frequent use of a calibration slide might be necessary as the scanner's data are not reproducible enough and will lead to changes in algorithm performance over time.

These diverse projects have led to a more uniform idea among pathologists, IT departments, AI-experts (from both the University of Stavanger and the University of Bergen) and clinicians on how

to develop/validate/implement CAD-tools in our region and we are currently looking into prospectively evaluating 1) an algorithm for prostate cancer detection and Gleason grading, and 2) prospective evaluating an algorithm for Ki67 detection in breast cancer in our whole region. Together with 2 university hospitals and 2 regional hospitals, we will choose which algorithm to use for these tasks and together purchase and evaluate them.

We plan to develop this project into a regional center of expertise and eventually offer our expertise to other regions in Norway as well, providing them with advice on how to develop/validate and implement CAD-tools.

5. Sources to corroborate the impact

As the results are still quite new, the only sources to corroborate the impact might be the fact that the group has been asked to contribute to several other studies like COMMITMENT in the Netherlands and the GLORIA study in Colombia.
COMMITMENT (COMputational pathology for IMproved Treatment decision Making for brEast caNcer paTients) is a large international collaboration aiming to derive and validate computational biomarkers, based on known tissue features assessed using AI from digitized tissue sections, and study relationship with clinical and molecular data and existing prediction models.
Prof. Emiel Janssen has been involved in the planning and currently acts as an external advisor for the GLORIA (Globalization of a Telepathology Network with Artificial Intelligence Applications) project, that aims to implement digital pathology into Colombia.
Furthermore, he will also contribute to a computational/digital pathology workshop organized by the Australasian Immunohistochemistry Society.
Also, in 2022, a grant application for Helse Vest Innovation funds was approved; this application has the goal to validate and implement an algorithm for Ki67 quantitation in breast cancer and an algorithm for detection and grading of prostate cancer in all 4 pathology departments of Helse Vest. A total sum of 1.1 million NOK has been dedicated to this project.
The idea of establishing a regional/national centre of competence for computational pathology has been included as a work package in the recent NOR-X-CHANGE application for Infrastructure funds form the Norwegian research council.

The impact is highlighted in these review articles.

- Image analysis and machine learning in digital pathology: Challenges and opportunities. Madabhushi A, Lee G. Med Image Anal. 2016 Oct;33:170-175. doi: 10.1016/j.media.2016.06.037. Epub 2016 Jul 4.PMID: 27423409, Citations 848 https://pubmed.ncbi.nlm.nih.gov/27423409/
- Deep learning for digital pathology image analysis: A comprehensive tutorial with selected use cases A Janowczyk, A Madabhushi - Journal of pathology informatics, 2016 Citations 1204, Deep learning for digital pathology image analysis: A comprehensive tutorial with selected use cases - ScienceDirect
- Artificial intelligence in digital pathology - new tools for diagnosis and precision oncology. Bera K, Schalper KA, Rimm DL, Velcheti V, Madabhushi A. Nat Rev Clin Oncol. 2019 Nov;16(11):703-715. doi: 10.1038/s41571-019-0252-y. Epub 2019 Aug 9. PMID: 31399699, Citations: 933 Artificial intelligence in digital pathology — new tools for diagnosis and precision oncology - PMC (nih.gov)

Stavanger University Hospital, SUH [4]

Institution: Stavanger University Hospital, SUH
Administrative unit: Stavanger University Hospital, SUH
Title of case study: The early detection and Intervention in Psychosis Study (TIPS): Long-term outcomes
Period when the underpinning research was undertaken: 2012-2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2012-2022
Period when the impact occurred: 2012-2022

1. Summary of the impact (indicative maximum 100 words)

Since the mid 1990´s the TIPS study has had a major impact on international psychiatry research, specifically on psychosis; on knowledge and awareness of psychosis in health care and the public; on the duration of untreated psychosis (DUP) and on course and outcome in psychosis. The TIPS long-term research has driven a continuing paradigm shift from interventions in chronic and late-stage psychosis, to early intervention and significantly better prognoses through the prevention of poor symptom and function outcomes. The primary long-term results were disseminated between 2012 and 2022.

2. Underpinning research: One of the few malleable prognostic factors in psychosis and schizophrenia is the duration of untreated psychosis (DUP), associated with poorer outcomes. The early Treatment and Intervention in Psychosis Study (TIPS) engineered an early detection (ED) intervention to reduce DUP through early detection teams and extensive information campaigns. A quasi-experimental design compared an early (ED area) (Rogaland County) to a usual detection (NoED) (Ullevål sector, Oslo, Roskilde sector, Denmark) area. In the ED area, DUP was reduced from 26 to 4 weeks (median value). **Primary** r**esearch output**: The ED area had significantly superior symptom and function outcomes compared to the NoED area ten years after diagnosis. These results were published in April 2012, featuring on the front page of the American Journal of Psychiatry, and introduced by an editorial. They were presented on the national TV-news (NRK Dagsrevyen, January 2013). This article won the prize for best article in psychiatry from the National Research Council for 2012. Further, a long DUP was associated with an increased risk of death (published in World Psychiatry in June 2017). The twenty-year follow- up study, the first of its kind, is currently being undertaken, investigating twenty-year ED-NoED differences in symptom, function and somatic outcomes. TIPS have published >150 papers, supervised seven PhD-studies 2012-2022, and per 2022 five PhD-studies are being completed as well as two postdoc-projects. TIPS are regularly invited to national and international conferences and symposia. Today DUP is a standard term in global psychiatry.

Resulting new research at TIPS:

1) Most patients experience a Clinical High Risk (CHR) phase before psychosis onset. The Prevention of Psychosis study (POP) started in 2012 and built on the ED experience in the TIPS-study, information campaigns now tailored towards high-risk symptoms. Findings indicate challenges detecting CHR early, and negative symptoms emerging as significant predictors.

2) In spite of better prognosis due to earlier treatment, psychosis still has high unemployment rates and benefits dependence. The project called Job- and School Prescription arose from TIPS and is best described as a local adaptation to Individual Placement and Support for persons with psychosis. A matched control prospective design investigated results, and the intervention has

become an integral part of mental health care at Stavanger University Hospital and is co-funded by the Norwegian Employment and Welfare Services (NAV).
3) The TOPUS (part of OPUS early intervention in schizophrenia and TOP-projects in Denmark, as well as MINDMAP at Yale Medical School, USA are current replications of TIPS. of TIPS.
4) Covid-19: In collaboration with TIPS South-East at Oslo University Hospital, TIPS investigated the impact Covid-19 had on mental health in persons with severe mental illness and on their families and carers.
5) NORSMI (Norwegian Research in Severe Mental Illness) is a national collaboration between health regions. It has initiated several multi-site studies on factors pertaining to mental illness, including cause- and mechanism studies using genetic and imaging data. TIPS have had active, and in several projects, leading roles.
Key researchers: Profs. Jan Olav Johannessen and Tor Ketil Larsen, psychiatrists, ass.prof Wenche ten Velden Hegelstad (clinical consultant psychologist); ass. prof Inge Joa (psychiatric nurse); profs Johannes Langeveld (clinical consultant psychologist) and Jone Bjørnestad (psychologist), ass. prof Melissa Weibell, (psychiatrist).

3. References to the research

1. Hegelstad WtV, Larsen TK, Auestad B, Evensen J, Haahr U, Joa I, Johannesen JO, Langeveld J, Melle I, Opjordsmoen S, Rossberg JI, Rund BR, Simonsen E, Sundet K, Vaglum P, Friis S, McGlashan T (2012): Long-term follow-up of the TIPS early detection in psychosis study: effects on 10-year outcome. Am J Psychiatry 169: p. 374-380.
2. Hegelstad WtV, Larsen TK, Auestad B, Evensen J, Haahr U, Joa I, Johannesen JO, LangeveldJ, Melle I, Opjordsmoen S, Rossberg JI, Rund BR, Simonsen E, Sundet K, Vaglum P, Friis S, McGlashan T (2013): Early detection, early symptom progression and symptomatic remission status after ten years in a first episode of psychosis study. Schiz Res 143, p. 337-343.
3. Langeveld, J., Bjorkly, S., Auestad, B., Barder, H., Evensen, J., Ten Velden Hegelstad, W., Joa, I., Johannessen, J. O., Larsen, T. K., Melle, I., Opjordsmoen, S., Rossberg, J. I., Rund, B. R., Simonsen, E., Vaglum, P., McGlashan, T., & Friis, S. (2014). Treatment and violent behavior in persons with first episode psychosis during a 10-year prospective follow-up study. Schizophr Res, 156(2-3), 272-276.
4. Weibell MA, Hegelstad WT, Auestad B, Bramness J, Evensen J, Haahr U, Joa I, Johannessen JO, Larsen TK, Melle I, Opjordsmoen s, Rund BR, Simonsen E, Vaglum P, McGlashan T, McGorry P, Friis S (2017). The Effect of Substance Use on 10-Year Outcome in First-Episode Psychosis. Schizophrenia Bulletin; doi: 10.1093/schbul/sbw179.
5. Melle, I; Johannessen, JO; Haahr, U; Hegelstad, W ten Velden; Joa, I; Langeveld, J; Larsen, TK; Opjordsmoen SI; Qin P; Rossberg JI; Rund BR; Simonsen E; Vaglum P; McGlashan T; Friis, S. (2017). Causes and predictors of premature death in first-episode schizpphrenia spectrum disorders. World Psychiatry, 16(2).
6. Inge Joa, Jone Bjørnestad, Jan Olav Johannessen, Johannes Langeveld, Helen Stain, Melissa Weibell and Wenche ten Velden Hegelstad (2021). Early detection of ultra-high risk for psychosis in a Norwegian catchment area: The two-year follow-up of the Prevention of Psychosis study. Frontiers in Psychiatry https://doi.org/10.3389/fpsyt.2021.573905.

4. Details of the impact

TIPS was the first study to investigate if and to what degree DUP could be reduced, using a quasi-experimental design comparing sociodemographically similar health care regions with and without

extensive early detection efforts. This was done in close collaboration with Yale medical school in USA, Oslo (Norway) and Roskilde (Denmark). An experimental early detection site (TIPS Rogaland County) used multi-level multi-focus awareness campaigns aimed at the public, general practitioners (GPs), schools, police, welfare services and others using; radio, cinema and newspaper adverts; large bus bumper stickers; brochures/leaflets and marked merchandise (pens, post-its et cetera) to inform about early signs of psychosis. This was combined with a low-threshold detection team situated at Stavanger University Hospital and accessible by telephone all workdays, receiving about 600 calls per year. Information campaigns aimed at the public and selected target groups and the low threshold early detection team was- and still is- a specialized team providing screenings for and assessments of psychosis within one to two workdays of the call, prompting start of adequate treatment. The annual six hundred calls result in 200 assessments and 50 new cases of psychosis or psychosis risk. DUP at the experimental early detection site (Rogaland county) has been reduced by half. Symptoms and level of suicidality have been significantly reduced, and chances of full recovery after ten years were doubled compared to the usual-detection (Oslo, Roskilde) sites. This accomplishment was featured on the front page of the American Journal of Psychiatry and an editorial was devoted to it.

As the world's first study on reducing DUP, TIPS has been at the front of a paradigm shift in psychiatry internationally. Today DUP is a standard term in global psychiatry. Since the start of TIPS, PubMed lists 1104 publications with DUP in the title, compared to five in total the preceding 30 years. Early detection has become mainstream and several projects in the world today replicate the TIPS model, such as TOPUS and TOP in Denmark and STEP/Mindmap at Yale, and La CLAve, Los Angeles, USA. In addition, early detection efforts are being conducted in Canada, Singapore, Ireland, the Netherlands, and the UK.

TIPS has had a profound impact on health care organisation for severe mental illness in Norway, with a shift from long waiting lists and bureaucratic referral procedures to immediate access to specialist care. It has gained a prominent place in local Norwegian communities, as many health care regions have now adopted the term and the method. TIPS promotes mental health and mental health care for young people also by having twice-yearly visits to local high schools, meeting both staff and students informing about early signs of psychosis and about mental health care. Anti-stigma work is an important part of these activities. Many people are reluctant to seek mental health care because of fear of "sections and injections"; that is, fear of involuntary hospital admissions, involuntary restraint and involuntary medication treatment. The TIPS information campaigns focus -aside from sign and symptoms- also on what modern psychiatric treatment entails: Psychotherapy, family group interventions, internet-based support for families, music and creative therapies, in most cases *voluntary* use of medication, physical activity, and help gaining or keeping employment or education.

In 2013, the Norwegian Health Directorate appointed a working group to establish Norwegian guidelines for the assessment and treatment of psychosis. One of the main founders of TIPS led the group, and early detection ad modus TIPS as well as DUP are central foci. Finally, TIPS has been the driving force behind the annual Schizophrenia Days, the largest Nordic conference in psychiatry. Today TIPS is conducting one of very few 20-year follow-up studies in first-episode psychosis.

5. Sources to corroborate the impact

- Editorial in the American Journal of Psychiatry, April 2012: https://ajp.psychiatryonline.org/doi/10.1176/appi.ajp.2012.12010094

- Presentation of the Mindmap project at Yale school of medicine, February 2022
- Doctorate (PhD)-study at Maastricht University 2021: Early intervention in Psychosis
- Early Intervention in psychosis: obstacles and opportunities.
- TIPS-replication in Los Angeles, USA, (2014-2018) (Johannessen and Joa, external consultants)
- TIPS-replication in Louisiana, USA
- Paper on Duration of Untreated Psychosis and early detection from OPUS; Denmark:
- Meta-analysis of studies to reduce the duration of untreated psychosis
- Meta-analysis in duration of untreated psychosis
- The importance of a global focus on mental services to young persons. Comment.
- Global initiatives addressing early interventions in psychiatry and young person's mental health:
    - https://iepa.org.au/early-intervention-in-mental-health/
    - https://www.iaymh.org/about-iaymh/

Stavanger University Hospital, SUH [5]

Institution: Stavanger University Hospital, SUH
Administrative unit: Stavanger University Hospital, SUH
Title of case study: DemVest study
Period when the underpinning research was undertaken: 2005 – to date
Period when staff involved in the underpinning research were employed by the submitting institution: 2005 – to date
Period when the impact occurred: 2016 – to date

1. Summary of the impact (indicative maximum 100 words)

The DemVest study - Dementia Study in Western Norway, commenced in 2005 with the primary aim of characterizing the diagnostic, clinical and biomarker features of people with newly diagnosed dementia and describing the course and clinical impact on patients, families and society during the entire disease course until death, followed by a neuropathological examination. The study has had impact in terms of increased awareness of key symptoms among clinicians, patients, and caregivers, characterized the societal impact, and catalysing clinical trials for effective treatment.

2. Underpinning research (indicative maximum 500 words)

New insights based on DemVest: Dementia is characterized by the progressive loss of cognitive and daily functioning, caused by a many different diseases, of which Alzheimer's disease (AD) is the most common. Due to demographic changes, dementia is already one of the major health challenges, and this will increase during the next three decades. The DemVest study was the first comprehensive study in Norway aiming to study the clinical characteristics of dementia and its longitudinal course, associated biomarker features, postmortem brain changes, and impact on patients, caregivers and society in a representative cohort of people with all types of dementia from diagnosis to death.

Between 2005 to 2013, a total of 266 persons with mild dementia and a caregiver were included. After a comprehensive clinical and biomarker assessment at baseline, they were followed annually with clinical assessments until death, including after nursing home admission, with very low withdrawal rate. A particular focus was on dementia with Lewy bodies (DLB), which was under-diagnosed, under-treated and under-researched. The study found that 16% of newly diagnosed dementia cases in secondary care had DLB, and that this group had a worse outcome compared to AD on key milestones such as time to nursing home admission, mortality, health-related costs, and caregiver-burden. The findings have led to increased awareness and improved care of this group of patients. Importantly, the high accuracy of clinic-pathologic diagnosis of DLB and AD underlines the quality of the research and the validity of the findings. DemVest has a major focus on neuropsychiatric symptoms and is one of the first studies to describe the longitudinal disease course in detail. This includes a detailed examination of both the high and persistent frequency of symptoms, the clinical impact for caregivers, prognosis, and the pathological corelates based on both in-vivo biomarkers and post-mortem neuropathology.

Due to the wealth and quality of data collected, the study still serves as a valuable source for research publications. The study has also underlined the importance of nutrition as an outcome, with the surprising finding that 25% of people with newly diagnosed dementia have malnutrition, with negative functional consequences. The study has also underlined the importance of the loss of muscle strength and volume (sarcopenia) and frailty as negative prognostic factors.

Additionally, the study explores the challenges faced by caregivers of dementia patients, linking sleep disturbances in patients to increased stress in caregivers. Caregivers of individuals with DLB are found to have a higher risk of developing mental health issues compared to those caring for individuals with AD.

Resulting new research at the unit:

The study has had a widespread and profound impact, with an international, multidisciplinary involvement, yielding over 100 articles on topics such as magnetic resonance imaging, cerebrospinal fluid analysis, genetic examinations, and post-mortem brain examinations, to correlate symptoms and challenges with underlying brain pathology. Publications using DemVest data exceeds 100, with 25% published in high impact (level 2) journals and supporting >15 doctoral theses and several post-doc researchers. This was the first study of DLB in Norway and has led to Norway being one of the most active countries in the world for DLB research. For example, the European DLB Consortium, the world's largest DLB network and database, is lead and coordinated by SESAM. SESAM researchers were instrumental in establishing the ISTAART DLB Professional Interest Area, including the Global Working group, with the aim of disseminating awareness of DLB globally. The DemVest study team is highly collaborative both regionally, nationally and internationally, and has contributed with genetic data to the large and successful Norwegian DemGene study, one of the largest genetic consortia worldwide, as well as to international DLB genetic networks.

In addition, based on the work undertaken in the DemVest study, the recently funded ANeED-study has started to include patients to a phase IIa multicentre randomized controlled double blind clinical trial to demonstrate clinical efficacy on cognitive, neuropsychiatric and functional outcomes of Ambroxol in New and Early patients with prodromal and mild Dementia with Lewy bodies.

Key researchers:

Prof. Dag Aarsland (geriatric psychiatry, 2005-to date)

Hogne Sønnesyn (geriatrics, 2009-to date)

Ass. Prof. Audun O. Vik-Mo (geriatric psychiatry, 2005-to date)

Ass. Prof. Ketil Oppedal (neuroimaging 2012-to date)

Ass. Prof. Ragnhild Djønne Østerhus (pharmacist, 2013-to date)

Post-doc Miguel Borda

3. References to the research (indicative maximum of six references)

1. Alzheimer's disease cerebrospinal fluid biomarkers predict cognitive decline in lewy body dementia. Abdelnour C, van Steenoven I, Londos E, Blanc F, Auestad B, Kramberger MG, Zetterberg H, Mollenhauer B, Boada M, Aarsland D; European DLB Consortium. Movement Disorder, 31(8), 1203-1208. https://doi.org/10.1002/mds.26668

2. Accuracy of Clinical Diagnosis of Dementia with Lewy Bodies versus Neuropathology. Skogseth R, Hortobágyi T, Soennesyn H, Chwiszczuk L, Ffytche D, Rongve A, Ballard C, Aarsland D.J Alzheimers Dis. 2017;59(4):1139-1152. doi: 10.3233/JAD-170274.PMID: 28731443

3. Neurocognitive Deficits Distinguishing Mild Dementia with Lewy Bodies from Mild Alzheimer's Disease are Associated with Parkinsonism. Brønnick K, Breitve MH, Rongve A, Aarsland D. Journal of Alzheimer's disease, 53(4), 1277-1285. DOI: 10.3233/JAD-160294

4. Cognitive decline in dementia with Lewy bodies: a 5-year prospective cohort study. Rongve A, Soennesyn H, Skogseth R, Oesterhus R, Hortobagyi T, Ballard C, Auestad BH, Aarsland D. BMJ open, 6(2), e010357. DOI: 10.1136/bmjopen-2015-010357

5. The course of depressive symptoms in Lewy body dementia and Alzheimer's disease. Römer B, Dalen I, Ballard C, Aarsland D. J Affect Disord. 2023 Jul 15;333:459-467. doi: 10.1016/j.jad.2023.04.076. Epub 2023 Apr 25.

6. The individual course of neuropsychiatric symptoms in people with Alzheimer's and Lewy body dementia: 12-year longitudinal cohort study. Vik-Mo AO, Giil LM, Borda MG, Ballard C, Aarsland D. Br J Psychiatry. 2020 Jan;216(1):43-48. doi: 10.1192/bjp.2019.195.PMID: 3150611

4. Details of the impact (indicative maximum 750 words)

Impact on health

The DemVest study is a collaboration between the local health trusts in the counties of Rogaland and Hordaland in Western Norway. Patients were referred from geriatric medicine, old age psychiatry and neurology outpatient clinics in these counties. This work initially included research environments in the western region of Norway and expanded throughout all of Norway and beyond to Europe. Nationally, this has led to the development of several major collaborative projects in dementia research, active partnerships with the Norwegian Health Association, Norwegian National Advisory Unit on Ageing and Health, the dementia research community at Akershus University Hospital, and the Norwegian Center for Research on Mental Disorders, University of Oslo.

This applies in particular to the projects Dementia Disease Initiation (DDI) and DemGene, and the support of >15 doctoral theses, including internationally at Karolinska Institute (eg Ellen J. Svendsbø, 2018). Many doctoral students have continued and developed successful research careers with post-doc and senior academic positions across the region (Rongve, Vik-Mo, Borda, Svendsbø, Skogseth). For example, professor Arvid Rongve, who completed his PhD on DLB based on the DemVest study, has successfully continued his DLB research, and initiated one of very few randomized clinical drug trials, the ANEED study.

DemVest has led to guidelines for diagnosis and management of the disease. DemVest and the focus on DLB has also had international impact. In 2015, based on a small grant from the EU Joint Program for Neurodegenerative Diseases, we convened an expert group and published guidelines for multicentre cohort studies in DLB (see below). This led to the development of the European DLB Consortium (E-DLB), the world's largest DLB network which includes more than 30 established DLB clinical research centres across Europe, coordinated from SESAM. The impact has spread globally, via the Alzheimer's Association ISTAART DLB PIA established in 2019, which includes the Global DLB Work group, producing a paper on global DLB research. DemVest was also among the first studies in Norway focusing on the importance of neuropsychiatric symptoms in people with dementia and has inspired subsequent research in this area with important Norwegian studies and guidelines.

Based on the widespread dissemination of results from DemVest, the PI has been invited to contribute to the development of the international consensus criteria for DLB (in 2005 and 2017), prodromal DLB (2020), and dementia (2007) and mild cognitive impairment (2012) in Parkinson's disease, published in highly cited papers with tremendous impact on research and clinical practice.

Impact on innovation

The biomarker focus, including one of the first CSF-based papers focusing on neuropsychiatric symptoms in people with dementia, has contributed to the mechanistic understanding of psychiatric features in people with DLB and other dementias. This work has fuelled subsequent

work to develop fluid biomarkers and drug therapies for neuropsychiatric symptoms. A recent innovation has been the development and validation of a new method to diagnose sarcopenia in people with dementia by capitalizing on the routine MRI brain scan for dementia assessment, with a novel software to measure muscle volume. This work is being developed for IP application (PMID:35134612)

Impact on society

Research in Norway has demonstrated that 50% of people with dementia are not diagnosed. DemVest has led to an increased focus on DLB, which is underdiagnosed, in Western Norway, and thus increased the likelihood of correct and timely diagnosis of this group.

The focus on key societal outcomes such as risk of nursing home admission, health-related costs, and increased burden and stress for caregivers, has led to increased focus on the challenges faced by caregivers and user involvement in research. The WiseAge platform for user involvement and engagement with society, was established in 2015 following the need to involve all stakeholders in research on prevention and treatment of dementia, and on living well with dementia.The finding that DLB patients have a high risk of nursing home placement has led to increased awareness among home care staff of the importance of symptoms of DLB and new strategies for improved management, with the likely reduced use of harmful medication, reduced need for institutionalization, and lower risk of unnecessary and unhelpful hospitalization.

5. Sources to corroborate the impact (indicative maximum of ten references)

1 https://www.e-dlb.com/ (Link to The European DLB consortium)

2 https://www.helse-fonna.no/behandlinger/demens-med-lewylegemer-dlb (Norwegian)(Link to hospital page (Helse Fonna) about DLB)

3 https://www.aldringoghelse.no/demens/fakta-om-demens/demens-med-lewylegemer-dll/ (Norwegian)(Link to The Norwegian National Centre for Ageing and Health pages about DLL)

4 Multi-Centre Cohort-Studies in Lewy-Body Dementia: Challenges in Harmonizing Different Clinical and Biomarker Protocols Report of a JPND Working Group on Longitudinal Cohorts

5 https://istaart.alz.org/groups/home/56 (Link to the Alzheimer's Association and their International Society to Advance Alzheimer's Research and Treatment (ISTAART)'s page about LBD)

6 Dementia with Lewy bodies research consortia: A global perspective from the ISTAART Lewy Body Dementias Professional Interest Area working group. D'Antonio F, Kane JPM, Ibañez A, Lewis SJG, Camicioli R, Wang H, Yu Y, Zhang J, Ji Y, Borda MG, Kandadai RM, Babiloni C, Bonanni L, Ikeda M, Boeve BF, Leverenz JB, Aarsland D; ISTAART Lewy body dementias Consortia Working Group.Alzheimers Dement (Amst). 2021 Sep 14;13(1):e12235. doi: 10.1002/dad2.12235. eCollection 2021.

7 Colombian consortium for the study of Lewy body dementia COL-DLB Miguel Germán Borda, Francisco Lopera, Omar Buritica, Catalina Cerquera-Cleves, Maria Camila Gonzalez, Elkin Garcia-Cifuentes 5, Alberto Jaramillo-Jimenez, David Aguillon, Yamile Bocanegra, Beatriz Elena Munoz-Ospina 4, Carlos Alberto Cano-Gutierrez, Daniela Patiño-Hernandez, Carlos Tobón 2, Hernando Santamaría-García 7, José Manuel Santacruz, Diego Andrés Chavarro-Carvajal 7, Gabriel Pinilla 4, Elly Morros-González 7, Camila Pantoja, Valentina Quintana-Peña 4, Jaime Valderrama 9, Ketil Oppedal 10, Dag Aarsland 11, Jorge Orozco. J Neurol Sci . 2020 May 15:412:116807. doi: 10.1016/j.jns.2020.116807. Epub 2020 Mar 27.

8 https://www.helse-fonna.no/avdelinger/forsking-og-innovasjon/aneed-studien (Norwegian)

9 Research criteria for the diagnosis of prodromal dementia with Lewy bodies. McKeith IG, Ferman TJ, Thomas AJ, Blanc F, Boeve BF, Fujishiro H, Kantarci K, Muscio C, O'Brien JT, Postuma RB, Aarsland D, Ballard C, Bonanni L, Donaghy P, Emre M, Galvin JE, Galasko D, Goldman JG, Gomperts SN, Honig LS, Ikeda M, Leverenz JB, Lewis SJG, Marder KS, Masellis M, Salmon DP, Taylor JP, Tsuang DW, Walker Z, Tiraboschi P; prodromal DLB Diagnostic Study Group.Neurology. 2020 Apr 28;94(17):743-755. doi: 10.1212/WNL.0000000000009323. Epub 2020 Apr 2.

10 Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. McKeith IG, Boeve BF, Dickson DW, Halliday G, Taylor JP, Weintraub D, Aarsland D, Galvin J, Attems J, Ballard CG, Bayston A, Beach TG, Blanc F, Bohnen N, Bonanni L, Bras J, Brundin P, Burn D, Chen-Plotkin A, Duda JE, El-Agnaf O, Feldman H, Ferman TJ, Ffytche D, Fujishiro H, Galasko D, Goldman JG, Gomperts SN, Graff-Radford NR, Honig LS, Iranzo A, Kantarci K, Kaufer D, Kukull W, Lee VMY, Leverenz JB, Lewis S, Lippa C, Lunde A, Masellis M, Masliah E, McLean P, Mollenhauer B, Montine TJ, Moreno E, Mori E, Murray M, O'Brien JT, Orimo S, Postuma RB, Ramaswamy S, Ross OA, Salmon DP, Singleton A, Taylor A, Thomas A, Tiraboschi P, Toledo JB, Trojanowski JQ, Tsuang D, Walker Z, Yamada M, Kosaka K.Neurology. 2017 Jul 4;89(1):88-100. doi: 10.1212/WNL.0000000000004058. Epub 2017 Jun 7.

University of Agder, FacHealthSportSci, 1

Institution: University of Agder
Administrative unit: Faculty of Health and Sport Sciences
Title of case study: The establishment of telemedicine treatment in the Agder region
Period when the underpinning research was undertaken: 2011 - 2019
Period when staff involved in the underpinning research were employed by the submitting institution: 2011 - 2019
Period when the impact occurred: 2015 - 2022

1. Summary of the impact

1. Establishment of a new joint service domain within remote patient monitoring and care management in Agder region.
2. Establishment of a regional coordination group for e-health and welfare technology (RCG) and the adoption of a Quadruple Helix model for collaboration in e-health.
3. Establishment of transferable best practices at the national and international levels.
4. Establishment of international research networks which forms basis for Centre for e-health's collaboration in new projects, applications and publications.
5. Knowledge about establishment of new services across administrative levels.
6. Knowledge of how health services are delivered, legislated and organised, and financial incentives at various levels of administration.
7. Knowledge of barriers to scaling (are raised at a national level).

2. Underpinning research

Research insight is derived from extensive interdisciplinary research activity over 10 years.
Knowledge has been developed about:

1. **Technical prerequisites for sharing of medical information during medical follow-up and interaction, 2010 – 2015 (Fensli, Trinugroho)**: Development and testing of an integration architecture based on Service-Oriented Architecture (SOA). Special attention was given to a service broker component, the Information Integration Platform (IIP), developed to bridge communications between everyday objects and Internet-based services. The feasibility of the IIP solution was evaluated both through prototyping and by testing the platform's representative healthcare services, e.g., remote health monitoring and emergency alarms. Experiments revealed how performance aspects are affected by needs for security, privacy, high availability, and scalability.

2. **Design and user-oriented usability evaluations, 2015 - 2018 (Smaradottir, Gerdes, Martinez):** Design, development and evaluation of a reference solution for integrated eHealth services and applications targeting remote monitoring and decision support in telehealth and telecare. Involvement of end-users in workshops in an early design phase and in usability evaluations during iterative development. This research has led to an understanding on how to involve users in design and development of health information technology and knowledge on how to run usability evaluations in high fidelity laboratory settings, health care environment and patients' homes. Recommendations for a technical infrastructure to optimize the outcome of usability evaluations was provided. A field trial with more than 100 patients in South-Norway revealed insights about the technical solution and the support for specialized nurses taking care remotely of patients.

3. **Patients' and nurses' experiences with telemedicine and identification of patient groups benefiting most from remote monitoring, 2016 - 2017 (Barken, Thygesen):** Research on patients' and nurses' use of telemedicine showed that use of telemedicine gives patients and nurses a strong personal relationship through dialogue. The relationship translates into care and follow-up of the patient. It also turns out that the poorest patients benefit most from the use of telemedicine follow up.

4. **Ways to improve Benefit Management (BM) in complex e-health efforts, 2017-2020 (Askedal, Aanestad, Moe, Thygesen):** Inter-organisational e-health collaboration is complex and there has been a lack of models and methods to handle such complexity. This research shed light on which gains have been realized in complex e-health collaboration and why it is challenging to realize gains. Lack of mechanisms for management and organizational learning are the main challenges. The existing model for profit realization was further developed to suit both organizational and inter-organisational e-health initiatives. In addition, learning and management were included in the model. For practice, a six-point checklist was proposed to stimulate organizational learning.

5. **Deep Artificial Neural Networks for approach prediction of COPD exacerbations (Nunavath, Goodwin, Moe):** Feed-Forward Neural Networks (FFNN) and Long Short-Term Memory (LSTM) models were trained on data collected from remote monitoring of 94 patients through a real monitoring session and therefore represented realistic home monitoring situations. Most deep learning models require large datasets to predict with a high degree of accuracy. These experiments show that with only 94 patients, the FFNN model was able to reproduce health condition provided by a medical doctor with an accuracy of 92.86% and the LSTM model able to predict COPD patients' health conditions one-day ahead with an accuracy of 84.12%.

These insights have contributed during the process of designing the current remote follow-up service in the Agder region.

Key researchers:

Researchers	**Positions at the time of research (2011-2019)**
Rune Fensli	Academic lead (2010-2017), Professor (2014-2020)
Elin Thygesen	Associate Professor (2010-2019), Professor 2019 -
Dafferianto Trinugroho	PhD fellow (2011-2014)
Berglind Smaradottir	PhD fellow (2011-2016), Postdoc (2017-2021)
Martin Wulf Gerdes	PhD fellow (2012-2019), Assistant Professor (2017-2019), Associate Professor 2019 -
Tina Lien Barken	PhD fellow (2014-2017) Assistant prof. (2018-2019), Associate Professor 2019 -
Elisabeth Holen-Rabbersvik	PhD fellow (2011-2015), Assistant Professor 2015-2020, Associate Professor 2020 -
Kirsti Askedal	PhD fellow (2017-2020)
Santiago Gil Martinez	Postdoc. (2014-2016), Associate Professor (2016 -), joined in 2014

Carl Erik Moe	Associate Professor (2001-2016), Professor 2016 -
Anne Wenche Emblem	Associate Professor, joined in 2015
Margunn Aanestad	Professor, joined in feb. 2019
Torunn Kitty Vatnøy	Assistant Professor (2010-2014), Associate Professor 2014 -
Vimala Nunavath	PhD (2013-2017), Postdoc (2018-2020)

Key contextual information about this area of research

In the early stages of these initiatives around 2010-2011, sharing health information between municipalities or sectors was not yet feasible. However, as the projects progressed, technological solutions were implemented to facilitate the exchange of electronic messages.

At the same time, remote patient follow-up was not widely practiced in Norway, except for certain efforts in Northern Norway led by the Norwegian Centre for Telemedicine, which later was transformed into the Norwegian Centre for E-health Research. Through collaborative efforts, the Agder region emerged as one of the pioneers in Norway to introduce services for remote patient follow-up.

6. References to the research *(indicative maximum of six references)*

Trinugroho, Yohanes Baptista Dafferianto (2014). Service-Oriented Architecture for Patient-Centric eHealth Solutions: (Thesis: Supervisor Rune Fensli)

Smaradottir, Berglind (2016). User-centred Design and Evaluation of Health Information Technology: (Thesis: Supervisor Rune Fensli)

Gerdes, M. (2019). Holistic System Design for Distributed National eHealth Services: (Thesis: Supervisor: Rune Fensli)

Barken, Tina Lien (2019). "The humanistic perspective of telemedicine care. COPD patients' and nurses' experiences of receiving/providing telemedicine care" (Thesis: Supervisor Elin Thygesen)

Askedal, Kirsti (2020). Enhancing the Benefits Management Model for Complex eHealth Efforts: (Contribution in paper IV: Margunn Aanestad)

Nunavath, V., Goodwin, M., Fidje, J. T., & **Moe, C. E.** (2018). Deep neural networks for prediction of exacerbations of patients with chronic obstructive pulmonary disease. In *Engineering Applications of Neural Networks: 19th International Conference, EANN 2018, Bristol, UK, September 3-5, 2018, Proceedings 19* (pp. 217-228). Springer International Publishing.

7. Details of the impact

The implementation of telemedicine patient follow-up in the Agder region is outcome of extensive, long-term collaboration and co-creation in several projects between Centre for e-health, municipalities, and the hospital in Agder, user organizations, and businesses (and the National Center for E-health Research in United4Health) since 2011. The Centre for e-health played a pivotal role by contributing to idea development, application writing, service development and research from 2011 to 2019.

An important contribution from Centre for e-health at the start was Professor Rune Fensli' s efforts from 2011 to investigate the necessity of information sharing across different levels and sectors within the healthcare system. This research was conducted under the project 'eHealth-extended Care

Coordination,' spanning from 2011 to 2015. The project focused on examining characteristics of and barriers to inter-municipal communication and information sharing in the health care services. Findings from this research laid the groundwork for a requirements specification in 2012-2014, guiding the development of an ICT tool at the centre designed for the exchange of medical information during healthcare follow-ups and interactions.

This tool proved instrumental in the first introduction of telemedicine follow-up for patients with COPD in the Agder region, as part of the 'United4Health' project (2013-2015) and the 'Collaborative Point-of-Care Services Agder' project (2013-2016). During these initial projects, researchers at the Centre for e-health contributed by delving into integration architecture for medical information sharing during follow-ups, employing user-driven design principles, and conducting evaluations and usability testing.

Later, as part of the following 'TELMA' project, spanning from 2015 to 2019, researchers, together with employees from the municipalities and the hospital, have actively engaged in the collaborative development of patient pathways and algorithms for remote follow up for various health conditions, including COPD, diabetes, heart failure, mild to moderate anxiety and depression, and multimorbidity. This involvement extends to the creation of a self-treatment plan specifically tailored for COPD. Furthermore, the researchers' contributions have encompassed the mapping of both patients' and healthcare personnel's experiences with telemedicine follow-up during 2015-2016. This mapping gives insights in how telemedicine enabled close yet distant encounters, where nurses and patients learned from each other through dialogue and contributed to the COPD patients' well-being and more-being and increased the clinical and personal knowledge of the TM nurses.

Within the 'TELMA' project, researchers have delved into the phenomenon of Benefit Management (BM) in the realm of complex e-health initiatives. This research has provided valuable insights into understanding who stands to benefit from telemedicine (TM) and the underlying reasons.

The research on Benefit Management has yielded a comprehensive Benefits Management Model (BMM) extension. It has put forth propositions addressing learning and governance within the Benefit Management context of complex e-health efforts. These propositions have been translated into a practical checklist designed to stimulate learning from the Benefit Management process itself, providing a framework for continuous improvement in complex e-health endeavours.

In addition to their extensive work in various health conditions, researchers conducted a test to explore the potential of machine learning (2018). The results of this test indicated significant promise in leveraging machine learning to detect the deterioration of COPD.

5. Sources to corroborate the impact *(indicative maximum of ten references)*

1. In a report published by the Nordic Welfare Centre, the cooperation model established based on the extensive cooperation in the region is highlighted

2. The region has achieved the recognition as a reference region as part of the EIP-AHA network (4-star rating)

3. Based on previous experiences in telemedicine follow up, Kristiansand municipality was selected to be part of the National Welfare Technology program, 2018-2021 (in Norwegian), on behalf of the Agder region.

4. Based on reports from the National Welfare technology Program, the Directorate of Health has drawn up national guidelines on digital home monitoring and a guide to regulations on management and quality improvement in the healthcare services. The reports that form part of the basic material also deal with the experiences from the Agder region, and are available on the Directorate's website (in Norwegian)

5. Descriptions of patient pathways and algorithms for several chronic conditions are described in an evaluation report from 2022 (in Norwegian) of the digital home follow-ups in the region. In its presentation, the report emphasizes the work that has been done in the region since 2012.

6. Based on previous experiences and networks, involvement in the project 'Patients and professionals in partnership', led by the Norwegian Centre for e-health research (2015-2020).

7. Based on previous experiences and networks, funding for a new project: 'Digital Infrastructure for Robust and Scalable Patient Monitoring in Pandemic Response Situations' (DIPAR).

8. Based on collaboration (started primarily within the United4Health project), extension of the Centre for health's National and international networks, such as the Norwegian Centre for e-health Research, EIP-AHA and the Digital Health and Care Innovation Centre and the University of Strathclyde (DHI).

9. Based on previous experiences and networks, partner in Digital Health Europe's Digital Telecare Twinning project (2020-2022).

University of Agder, FacHealthSportSci, Case number 2

Institution: University of Agder
Administrative unit: Faculty of health and Sport Sciences
Title of case study: *Scaling up evidence-based early-life nutrition interventions for community resilience and lifecourse health (Nutrition Now)*
Period when the underpinning research was undertaken: 2012- now
Period when staff involved in the underpinning research were employed by the submitting institution: 2008-now
Period when the impact occurred: 2016-now

1. Summary of the impact (indicative maximum 100 words)

The *Nutrition Now project* implements digital, evidence-based early life interventions at community and county level to enhance community resilience and lifecourse health, underpinned by four original studies.

Key impacts include:

1) improved pregnancy diet, child diet and dietary care, and meal practices in Early Childhood Education and Care (ECEC)
2) enhanced municipal public health work demonstrated by i) improved food and meal practices in ECEC settings, ii) strengthened nutritional/dietary guidance in primary health care, and iii) support for municipal efforts with nutrition-sensitive and nutrition-specific challenges
3) changes in Agder County Council's approach to early life nutrition, both in their thematic focus and workforce
4) integration into the educational programs of ECEC teachers and primary health care nurses at the University of Agder (UiA)
5) a research-based curriculum (academic textbook) for ECEC students and ECEC personnel
6) elevated awareness among leaders in the specific county about the fundamental importance of focus on the first 1000 days and early life diet
7) presence in mass media, national and international forums

2. Underpinning research (indicative maximum 500 words)

The nature of the research insights or findings which relate to the impact claimed in the case study. *Numbers in parentheses refer to the references in box 3.*

Aiming to improve nutrition and quality of life in the first 1000 days of life, we have combined four efficacious dietary interventions (1-4) into a single comprehensive and tailored digital resource, *Nutrition Now*, for implementation in Norwegian community settings. The resource targets dietary care from pregnancy to child aged 2 years through municipal services such as Early Childhood Education and Care (ECEC), Maternal and Child Health care (MCH), and local municipal authorities.

Key findings from the four original efficacy trials are as follows: i) dietary advice combined with physical activity during pregnancy optimized gestational weight gain (1), ii) an e-health intervention targeting parents of 6 months olds to improve child diet and parental feeding practices, improved child vegetable intake and meal practices (2), iii) an e-health intervention targeting 12-24 months old children showed effect on vegetable intake postintervention (3) and iv) a hot meal and pedagogical intervention in ECEC led to better meal practices in ECEC and higher vegetable intake among children exposed to the intervention (4, 5). The *Nutrition Now resource* and project were developed in co-creation with stakeholders in various settings within a specific municipality (6).

An outline of what the underpinning research produced by the submitted unit was (this may relate to one or more research outputs, projects or programmes).

The submitting unit is host for the *Nutrition Now project*, and for three of the four original studies (*1: Fit for Delivery; 2: Early Food for Future Health; 3: Food4Toddlers; 4: Child Food Courage*). While the Fit for Delivery trial was hosted by Sørlandet hospital, the majority of the research team (7 out of 9 active researchers) belonged to the submitting unit. The four original interventions, all tested in efficacy trials in the form of randomized controlled trials, were included in one comprehensive digital resource for use in municipal services and by pregnant couples and parents of infants and toddlers directly. The *Nutrition Now project* is funded by the Norwegian Research Council (ref.nr: 320521, 2021-2025.

Dates of when it was carried out. 2012- today

Names of the key researchers and what positions they held at the administrative unit at the time of the research (where researchers joined or left the administrative unit during this time, these dates must also be stated).

Nina C. Øverby, Prof. and PI for the four efficacy trials and *Nutrition Now*, has been with the unit since 2008. **Elisabet R. Hillesund**, initially a PhD student (2012-2015, Fit for Delivery), then PhD supervisor on three of the efficacy trials and co-PI for *Nutrition Now*, has been affiliated since 2012, Professor from 2020. **Frøydis N. Vik**, starting as Assoc. Prof. in Food4Toddlers and later co-PI for *Nutrition Now*, has been part of the unit since 1999, Professor since 2020. **Sissel H. Helland** joined as a PhD student in 2013 and became Assoc. Prof. in 2018, involved in Child Food Courage and *Nutrition Now*, with her affiliation to the unit beginning in 2013. **Anine C. Medin**, Assoc. Prof. in Food4Toddlers and *Nutrition Now*, has been with the unit since Feb 2019. **Christine Helle**, a PhD student (2015-2019) and now a Postdoc, has been affiliated since 2015. **Margrethe Røed**, Asst. Prof. since 2010 and later a PhD student (2016-2020) and Assoc. Prof., has been with the unit since 2010. **Eli Anne Myrvoll,** completing her PhD (2017-2021) and becoming Assoc. Prof. in 2023, has been affiliated since 2017.

Any relevant key contextual information about this area of research.
The first 1000 days of life, from conception until a child's second birthday, is a window of opportunity for promoting long-term health and well-being. Disappointingly, few efficacious health interventions are successfully scaled up and implemented in real world settings. This represents an evidence-to-practice gap with loss of opportunity to improve practice. This also holds for nutrition-related interventions targeting the first 1000 days of life, which underpinned and inspired the work of *Nutrition Now*.

3. References to the research (indicative maximum of six references)

1) Hillesund ER, Bere E, Sagedal LR, Vistad I, Øverby NC. Effect of a diet intervention during pregnancy on dietary behavior in the randomized controlled Norwegian Fit for Delivery study. J Dev Orig Health Dis. 2016 Oct;7(5):538-547. doi: 10.1017/S2040174416000258.

2) Helle C, Hillesund ER, Wills AK, Øverby NC. Evaluation of an eHealth intervention aiming to promote healthy food habits from infancy -the Norwegian randomized controlled trial Early Food for Future Health. Int J Behav Nutr Phys Act. 2019 Jan 3;16(1):1. doi: 10.1186/s12966-018-0763-4.

3) Røed M, Medin AC, Vik FN, Hillesund ER, Van Lippevelde W, Campbell K, Øverby NC. Effect of a Parent-Focused eHealth Intervention on Children's Fruit, Vegetable, and Discretionary Food Intake

(Food4toddlers): Randomized Controlled Trial. J Med Internet Res. 2021 Feb 16;23(2):e18311. doi: 10.2196/18311.

4) Blomkvist EAM, Wills AK, Helland SH, Hillesund ER, Øverby NC. Effectiveness of a kindergarten-based intervention to increase vegetable intake and reduce food neophobia amongst 1-year-old children: a cluster randomised controlled trial. Food Nutr Res. 2021 Oct 8;65. doi: 10.29219/fnr.v65.7679. eCollection 2021.

5) Helland SH, Øverby NC, Myrvoll Blomkvist EA, Hillesund ER, Strömmer S, Barker M, Bjørkkjær T. Wow! They really like celeriac! Kindergarten teachers' experiences of an intervention to increase 1-year-olds' acceptance of vegetables. Appetite. 2021 Nov 1;166:105581. doi: 10.1016/j.appet.2021.105581. Epub 2021 Jun 30.PMID: 34214639

6) Øverby NC, Hillesund ER, Helland SH, Helle C, Wills AK, Lamu AN, Osorio NG, Lian H, Ersfjord TI, Van Daele W, Bjørkkjær T, Valen EN, Gebremariam MK, Grasaas E, Kiland C, Schwarz UVT, Abel MH, Love P, Campbell K, Rutter H, Barker ME, Vik FN, Medin AC. Evaluating the effectiveness and implementation of evidence-based early-life nutrition interventions in a community setting a hybrid type 1 non-randomized trial - the Nutrition Now project protocol.
Front Endocrinol (Lausanne). 2023 Jan 10;13:1071489. doi: 10.3389/fendo.2022.1071489. eCollection 2022.

4. Details of the impact (indicative maximum 750 words)
How the research underpinned (made a distinct and material contribution to) the impact and the administrative unit's part in this:

The digital dietary tool, the *Nutrition Now resource*, targets pregnant women, parents of 0–2-year-olds, ECEC settings, MCH settings, and the municipal setting. Its underpinnings have been developed over years (from 2012- ongoing). The original work from four efficacy trials (RCTs) showed effect on improved dietary and meal practice outcomes. To bridge the gap between research and practice, the *Nutrition Now resource* was co-created with the target groups from 2020 and implemented and provided free to use in one municipality in 2022, and scaled-up and offered in 50 municipalities in two counties in 2023 (ongoing work). It has been and still is implemented through the services, and directly to parents through social media, municipality websites and the local newspaper. Broad anchoring of the project and the coalition built with stakeholders from 2020 have had impact on the implementation.

The nature and extent of the impact including beneficiaries (in blue**)**

1) Improved diet and dietary care. Parents acknowledge the *Nutrition Now resource* as a relevant and valuable tool, reporting positive effect on their children's diet and their family meals. The ECEC meal practices have also improved, as demonstrated in the original studies underpinning *Nutrition Now* (see references 1-6 in box 3).

2) Improved public health work through the services. Since the *Nutrition Now* resource is developed in co-creation with ECEC staff, health care nurses and midwives, it is tailored to their needs (ref 1, box 5). In Arendal (ref 2, box 5), the first municipality adopting *Nutrition Now*, its usage by 50% of all ECECs in Arendal stands as a demonstration of its relevance. Interviews from ECEC leaders (2022-23) have confirmed that the resource has been easy to implement into their daily routines. Further, its positive reception by children, especially in pedagogical sessions and meals, and its impact of *Nutrition Now* on ECECs meal practices, have been reported. The health care services also acknowledge its potential to strengthen nutritional/dietary guidance in primary health care (ref 3, box 5).

The concurrent use of *Nutrition Now* by ECEC services, MHC services and parents is emphasized as crucial by ECEC and MCH (ref 3, box 5). Regular monthly meetings (in 2022) with the public health coordinator in municipality of Arendal during the implementation process have revealed that the municipality is considering innovative approaches to improve dietary care in their public health work, such as collaborating with local grocery shops and working to incorporate topics related to early life nutrition in their action plans.

An essential 'mapping-session' was conducted in an early phase (May 4th 2022, ref 4, box 5), involving diverse municipal stakeholders to create a 'system map' of factors affecting childhood nutrition in the municipality, and the relations between these factors. This two-hour town hall meeting brought together representatives from ECEC, MCH, municipal officers, media, NGOs, and local politicians. The resulting map, described as eye-opening by the ECEC municipal leader, underlined the central role of ECECs in child nutrition, being responsible for providing over 4000 meals during a child's ECEC life attendance. This 'system map' exercise not only illustrated the various factors influencing childhood nutrition but also the important interconnections between these in the municipality context.

3) **Collaboration with Agder County Council.** Our collaboration with Agder County Council in *Nutrition Now* has led to hiring a dedicated person, engaged full-time (call out 26.03.23), responsible for implementing the resource. This role involves carrying out and managing the implementation strategies on a daily basis and serving as the primary contact point. This contributes to the enhancement of the Agder County Council's public health strategies, particularly in improving early life diet, by ensuring sustained access to and dissemination of the *Nutrition Now resource,* thereby supporting the Council's ongoing efforts in early life nutrition.

4) **Integration in university education.** The University of Agder has incorporated the research and results from the original studies underpinning *Nutrition Now* into the education program of ECEC students, as well as in the education of health care nurses.

5) **Curriculum development.** A new curriculum textbook based on the theory and practice from the original *Nutrition Now resource* has been published and implemented as curriculum at UiA for use by the ECEC students and ECEC personnel (ref 5, box 5).

6) **Increased awareness in municipal leadership.** We have conducted 21 meetings with leaders of health and education in the specific county, all of which have heightened stakeholder awareness of the fundamental importance of focus on the first 1000 days and early life diet (ref 6, box 5).

7) **Mass media and presentations.** Media coverage and presentations at national and international meetings have broadened *Nutrition Now's* reach and impact on the general population (ref 4, 6-10, box 5).

The submitted administrative unit's contribution to the impact
This work originated from the administrative unit. Three out of four of the original studies were led by PRC Lifecourse Nutrition, while they were collaborators with the Sørlandet Hospital on the study addressing pregnancy. *Nutrition Now* is funded through the Norwegian Research Council and anchored at the faculty of Health and Sport Sciences with leaders from the PRC Lifecourse Nutrition. In total 16 employees from UiA participate in this study, in addition to national and international collaborators including Deakin University, Mälardalen University, University of Oslo, the Norwegian Public Health Institute.

Dates of when these impacts occurred: 2019-ongoing (some specific dates are provided above)

5. Sources to corroborate the impact (indicative maximum of ten references)

1. **Paper:** Øverby NC, Hillesund ER, Helland SH, Helle C, Wills AK, Lamu AN, Osorio NG, Lian H, Ersfjord TI, Van Daele W, Bjørkkjær T, Valen EN, Gebremariam MK, Grasaas E, Kiland C, Schwarz UVT, Abel MH, Love P, Campbell K, Rutter H, Barker ME, Vik FN, Medin AC. Evaluating the effectiveness and implementation of evidence-based early-life nutrition interventions in a community setting a hybrid type 1 non-randomized trial - the Nutrition Now project protocol. *Front Endocrinol (Lausanne).* 2023 Jan 10;13:1071489. doi: 10.3389/fendo.2022.1071489. PMID: 36704042; PMCID: PMC9871808.

2. ***Nutrition Now* resource and project description**: Available at Arendal municipality website (the intervention municipality) (2022): https://www.arendal.kommune.no/politikk-og-organisasjon/prosjekter-og-utvikling/matnyttig/

3. **Paper:** Helle C, Hillesund ER, Øverby NC. A qualitative study of public health nurses' perspectives and experiences on nutritional guidance for parents of infants and toddlers. Matern Child Nutr. 2024 Jan;20 Suppl 2(Suppl 2):e13546. doi: 10.1111/mcn.13546. Epub 2023 Jul 13.

4. **Mapping session:** Rutter, H; Medin, AC; Vik, FN; Hillesund, ER; Osorio N, Lian H, Øverby, NC. What influences diet the first thousand days of life? Mapping Session in Arendal 2022; 2022-05-04

5. **Book**: Helland S, Øverby N.Children, food courage and meals. Cappelen Dam. https://cappelendamm.no/_barn-matmot-og-maltider-sissel-heidi-helland-nina-c-overby-9788202709778

6. **Reference to all meetings with leaders in the municipality Arendal and Agder county** (2020-2023): https://prosjektbanken.forskningsradet.no/project/FORISS/320521

7. **Local media coverage of the *Nutrition Now* project in *Agderposten*** *(29.10.2022)*: New offer for parents and daycare centres, aim: to improve child diet. https://www.agderposten.no/nyheter/i/4o75MR/nytt-tilbud-til-foreldre-og-barnehager-maal-bedre-kosthold-til-barna

8. **Presentation at Arendalsuka** (17.08.2021): Øverby NC, Helland SH, Helle C, Vik FN. Diet and nutrition the first 1000 days of life- can you make a wiser investment?, https://program.arendalsuka.no/event/user-view/15702?redir=

9. **Debate in *Fædrelandsvennen*, regional newspaper** (26.11.2022)**:** Øverby NC, Helle C, Medin AC, Hillesund ER, Vik FN. Early intervention that works. https://www.fvn.no/mening/debattinnlegg/i/pWVroV/tidlig-innsats-som-virker

10. **Oral presentation:** Vik, Frøydis Nordgård; Medin, Anine Christine; Hillesund, Elisabet Rudjord; Øverby, Nina Cecilie. Implementing Nutrition Now – a digital dietary resource the first thousand days of life. Public Health Conference 2023; 2023-09-20

University of Agder, FacHealthSportSci, Case number 3

Institution: University of Agder
Administrative unit: Faculty of health and Sport Sciences
Title of case study: The Norwegian Fit for Delivery trial
Period when the underpinning research was undertaken: 2009- 2018
Period when staff involved in the underpinning research were employed by the submitting institution: 2009-2018
Period when the impact occurred: 2016-2022

1. Summary of the impact (indicative maximum 100 words)

The Norwegian Fit for Delivery (NFFD) trial's impact relates to:

1) Providing evidence that a diet and physical activity intervention in pregnancy is not only feasible but also effective in improving diet, increasing physical activity and optimizing gestational weight gain.
2) The NFFD findings contribute to impactful meta-analyses and reviews, that has informed the work of lifestyle guidance to pregnant women.
3) By using NFFD data combined with data from three other studies, novel methods have been developed for screening and diagnosis of gestational diabetes.
4) Widespread dissemination of results: Elements of the dietary intervention are currently being implemented in pregnancy primary health care for pregnant women in two counties in Norway.
5) Insights from NFFD are being included in education programs at University of Agder (UiA).

2. Underpinning research (indicative maximum 500 words)

The nature of the research insights or findings which relate to the impact claimed in the case study.

The research insights were gained from the randomized controlled *NFFD* trial that explored the effectiveness of nutritional counseling coupled with exercise classes compared with standard prenatal care on various health outcomes. More than 600 pregnant women were randomized to either the control or intervention group. The intervention was effective in improving maternal diet and physical activity, and reduced gestational weight gain relative to the control group. Women compliant with the intervention also demonstrated lower weight retention one year postpartum compared to the control group.

An outline of what the underpinning research produced by the submitted unit was (this may relate to one or more research outputs, projects or programmes).

The project was led by the Sørlandet Hospital, with Vistad serving as the PI and Sagedal as daily manager and PhD candidate. They were responsible for the study design, recruitment, testing and data collection in the first phases of the study. UiA contributed substantially to the project, with Øverby, Bere and Lohne-Seiler being instrumental in designing and developing the dietary and physical activity interventions in 2008-2009. Furthermore, Øverby, Lohne-Seiler, Torstveit, Hillesund, and Sanda contributed to the data collection and analyses (2013-2018) and were responsible for data collection regarding child diet and activity (2012-2017). Hillesund, Skreden, Sanda, as PhDs and post docs in the project, also made contributions to data collection and analyses. To date, UiA researchers have significantly contributed to 16 published papers from this research and have contributed to continued work with the collected data on gestational diabetes (2019-2024). UiA has carried forward insights from NFFD in another project (Nutrition Now) and is implementing dietary guidance in pregnancy care and for pregnant women through the Nutrition Now project (2021- ongoing).

Dates when it was carried out: 2009-2018.

Names of the key researchers and what positions they held at the administrative unit at the time of the research (where researchers joined or left the administrative unit during this time, these dates must also be stated).
Hilde Lohne- Seiler (Assoc. Prof since 2015), Nina C. Øverby (Assoc. Prof 2008- 2012, Prof since 2012), Elling Bere (Assoc. Prof 2008-2011, Prof since 2011), Elisabet R. Hillesund (PhD student 2012-2015, Assoc. Prof 2015-2020, Prof since mid-2020), Monica K. Torstveit (Assoc Prof 2010-2018, Prof since 2018), Birgitte Sanda (PhD), Marianne Skreden (Post doc). Hillesund joined in 2012, Sanda joined in 2013 and left the unit in 2018, Skreden joined in 2014 and left the unit in 2019. The others have been at the unit from the start of the project until now.

Any relevant key contextual information about this area of research.
The global obesity epidemic has led to increased attention on pregnancy as a critical window, given that many women gain excessive weight and experience post-partum weight retention. Excessive gestational weight gain is associated with numerous complications for both mother and child. At the time the Norwegian Fit for Delivery trial was initiated, few studies had examined the effect of a lifestyle intervention in pregnancy designed to limit maternal weight gain.

3. References to the research (indicative maximum of six references)

1.Sagedal LR, **Øverby NC, Bere E, Torstveit MK, Lohne-Seiler H,** Småstuen M, **Hillesund ER,** Henriksen T, Vistad I. Lifestyle intervention to limit gestational weight gain: the Norwegian Fit for Delivery randomised controlled trial. BJOG. 2017 Jan;124(1):97-109. doi: 10.1111/1471-0528.13862. Epub 2016 Jan 14.PMID: 26768233

2. Sagedal LR, **Sanda B, Øverby NC, Bere E, Torstveit MK, Lohne-Seiler H, Hillesund ER**, Pripp AH, Henriksen T, Vistad I The effect of prenatal lifestyle intervention on weight retention 12 months postpartum: results of the Norwegian Fit for Delivery randomised controlled trial. BJOG. 2017 Jan;124(1):111-121. doi: 10.1111/1471-0528.13863. Epub 2016 Jan 20.PMID: 26786294

3. **Hillesund ER, Bere E**, Sagedal LR, Vistad I, **Øverby NC**.Effect of a diet intervention during pregnancy on dietary behavior in the randomized controlled Norwegian Fit for Delivery study. J Dev Orig Health Dis. 2016 Oct;7(5):538-547. doi: 10.1017/S2040174416000258. Epub 2016 Jun 16.PMID: 27307037

4. **Hillesund ER, Bere E,** Sagedal LR, Vistad I**, Seiler HL, Torstveit MK, Øverby NC**.Pre-pregnancy and early pregnancy dietary behavior in relation to maternal and newborn health in the Norwegian Fit for Delivery study - a post hoc observational analysis. Food Nutr Res. 2018 Aug 8;62. doi: 10.29219/fnr.v62.1273. eCollection 2018.PMID: 30108471

5. **Sanda B,** Vistad I, Sagedal LR, Haakstad LAH, **Lohne-Seiler H, Torstveit MK**.Effect of a prenatal lifestyle intervention on **physical activity** level in late pregnancy and the first year postpartum. PLoS One. 2017 Nov 27;12(11):e0188102. doi: 10.1371/journal.pone.0188102. eCollection 2017.

6. Haakstad, LA**, Sanda B**, Vistad I, Sagedal LR, **Seiler HL, & Torstveit MK**. Evaluation of implementing a communitybased exercise intervention during pregnancy. Midwifery 2017: 46, 45–51. https://doi.org/10.1016/j.midw.2017.01.010

4. Details of the impact (indicative maximum 750 words)
This section should provide a narrative, with supporting evidence, to explain:

How the research underpinned (made a distinct and material contribution to) the impact
The Fit for Delivery trial was among the first to show that a low-intensity intervention targeting diet and physical activity during pregnancy was effective in improving diet and activity and its primary outcome, gestational weight gain. These results and the data collected are important for the project impact. The results provided insights into the feasibility of lifestyle changes relevant for pregnant women and are being used in guidelines and in education of the public health workforce. The data collected are unique and are being used in other studies/collaborations to explore other aspects of pregnancy care both nationally, (especially gestational diabetes), and internationally.

The nature and extent of the impact and its beneficiaries.
The results from The Norwegian Fit for Delivery trial have been disseminated in scientific papers as well as through the media. It has been presented at several national and international conferences. The impact relates to the following including notions of beneficiaries:

1) **Enhanced participant health:** The participants involved in the intervention group experienced improvement of their diet and activity level. Knowledge from this study is being used at the hospital and in local pregnancy care.
2) **Influence on global guidelines**: The data from the study are included in the work of the International Weight Management in Pregnancy (i-WIP) Collaborative Group, that has published several papers based on a large international dataset, that improves pregnancy care (*ref 1&4 in part 5*). This work has informed several guidelines. This includes the Healthy Start recommendations in Germany and a consensus on physical activity in pregnancy in Asia/Pacific countries (*ref 2&3 in part 5*). This impacts the individual mothers and children directly as well as the society and services that rely on evidence-based guidelines. (Dates of impact: Sep 2018-onwards, May 2021). The results of the NFFD trial have also informed the Guidelines of the Norwegian Society for Obstetrics and Gynecology, specifically for care of pregnancy complicated by obesity (*ref 10, part 5*).
3) **Improved gestational diabetes screening**: In Norway, data from the Norwegian Fit for Delivery trial is included in the The Norwegian Hyperglycemia in Pregnancy consortium (NHIP) with three other pregnancy cohorts/interventions. This work suggests new ways to identify gestational diabetes (GDM) searching for minimal risk of related complications. Results suggest that a two-step approach to GDM diagnostics, with an initial universal FPG screening for exclusion of low-risk women from further testing, could potentially limit the use of OGTT (oral glucose tolerance tests) to less than 30% of all pregnancies. This means reduced burden on pregnant women and the health care workforce (ref 5 in part 5). This work is followed closely by the Norwegian Directorate of Health and will inform GDM guidelines in the future for the Norwegian population of pregnant women. (Dates of impact: Ongoing)
4) **Widespread dissemination**: The dietary intervention applied in the Fit for Delivery trial has inspired a digital version targeting diet in pregnancy (the Nutrition Now- trial). This digital version is now used in pregnancy care in one municipality and 20 others are planning to use it (ref 6, part 5). The midwives use the resource in their work in primary pregnancy care in these municipalities. The digital version is also offered to pregnant women directly through social media. (Dates of impact: October 2022 and onwards)
5) **Integration into education**: The results and insights from NFFD is being included in our educations in public health and nutrition as well as in Teacher's education at the University of Agder (refs 7-9, part 5). The students are presented with the intervention and its results as knowledge-based examples of ways of improving diet and activity in pregnancy and as part of a bigger picture highlighting the importance of societal investments the first thousand days of life for early development and lifelong health. (Dates of impact: from autumn 2016)

The submitted administrative unit's contribution to the impact

For the impacts numbered 1, 2 and 4 above, the contribution is in line with what is described in *2. Underpinning research*. However, for the impact referring to guidelines, only the two leaders of the projects, Sagedal and Vistad were included in the i-WIP-consortium as representatives of the whole Fit for Delivery group. Regarding impact number 3 there are several other institutions providing data for this work. These are The STORK Groruddalen, University of Oslo (Jenum and Sletner), The STORK Rikshospitalet (Voldner), Rikshospitalet University hospital, TRIP, St. Olavs Hospital, Trondheim University Hospital, and Stavanger University Hospital, and the presented impact case, Fit for Delivery, Sørlandet Hospital and University of Agder. Anam Shakil Rai, Sørlandet Hospital and University of Agder has been the PhD-candidate on this work, and the project group include Linda Sagedal (Sørlandet Hospital), Anne Karen Jenum (University of Oslo), Line Sletner (Directorate of Health) and Nina Øverby (University of Agder). The University of Agder personnel are the contributors to impact number 5.

5. Sources to corroborate the impact (indicative maximum of ten references)

1. International Weight Management in Pregnancy (i-WIP) Collaborative Group.BMJ. Effect of diet and physical activity based interventions in pregnancy on gestational weight gain and pregnancy outcomes: meta-analysis of individual participant data from randomised trials. 2017 Jul 19;358:j3119. doi: 10.1136/bmj.j3119.
2. Koletzko B, Cremer M, Flothkötter M, et al. Diet and Lifestyle Before and During Pregnancy - Practical Recommendations of the Germany-wide Healthy Start - Young Family Network. Geburtshilfe Frauenheilkd. 2018 Dec;78(12):1262-1282. doi: 10.1055/a-0713-1058. Epub 2018 Sep 25.
3. Lee R, Thain S, Tan LK, Teo T, Tan KH; IPRAMHO Exercise in Pregnancy Committee. Asia-Pacific consensus on physical activity and exercise in pregnancy and the postpartum period. BMJ Open Sport Exerc Med. 2021 May 17;7(2):e000967. doi: 10.1136/bmjsem-2020-000967.
4. Rogozińska E, Marlin N, Jackson L, …, Thangaratinam S. Effects of antenatal diet and physical activity on maternal and fetal outcomes: individual patient data meta-analysis and health economic evaluation. Health Technol Assess. 2017 Aug;21(41):1-158. doi: 10.3310/hta21410.
5. Rai AS, Sletner L, Jenum AK, Øverby NC, Stafne SN, Qvigstad E, Pripp AH, Sagedal LR. Employing fasting plasma glucose to safely limit the use of oral glucose tolerance tests in pregnancy: a pooled analysis of four Norwegian studies. Front Endocrinol (Lausanne). 2023 Nov 30;14:1278523. doi: 10.3389/fendo.2023.1278523. eCollection 2023.
6. Øverby NC, Hillesund ER, Helland SH, .., Medin AC. Evaluating the effectiveness and implementation of evidence-based early-life nutrition interventions in a community setting a hybrid type 1 non-randomized trial - the Nutrition Now project protocol. Front Endocrinol (Lausanne). 2023 Jan 10;13:1071489. doi: 10.3389/fendo.2022.1071489.
7. Bachelor's program in public health nutrition, University of Agder: https://www.uia.no/studier/samfunnsrettet-ernaeringsarbeid (In Norwegian)
8. Bachelor's program in public health, University of Agder: https://www.uia.no/studier/folkehelsearbeid (In Norwegian)
9. Master's program in public health science, University of Agder: https://www.uia.no/studier/folkehelsevitenskap (In Norwegian)
10. Magnussen E, et al. Obesity in pregnancy and at delivery. Norwegian Society for Obstetrics and Gynecology Obstetrical Guidelines (December 2022) ePub ISBN 978-82-692382-0-4 Adipositas i svangerskap og fødsel ((in Norwegian)

University of Agder, FacHealthSportSci, Case number 4

Institution: University of Agder
Administrative unit: Faculty of health and Sport Sciences
Title of case study: Starting Right ™
Period when the underpinning research was undertaken: 2018- 2023
Period when staff involved in the underpinning research were employed by the submitting institution: 2018-2023
Period when the impact occurred: 2019-2023

1. Summary of the impact (indicative maximum 100 words)

Starting Right™ impacts relates to:

1. Innovation in the public health sector
2. Up to date structured and evidence-based knowledge and overview of children's health and development, to increase early identification of children's needs
3. Insights in how the digital solution affect work processes and assessments in child and school health services
4. Insights and knowledge of implementation of a digital solution in child health services/school health service
5. Insights in how the digital solution contributes to early evidence-based intervention and interaction.
6. Establishment of research collaboration
7. Including insights from the study in the education at University of Agder, UiA
8. Increased health literacy in parents and children

2. Underpinning research (indicative maximum 500 words)

Research insight is a result from extensive interdisciplinary research activity from the project start (2018), and includes researchers within health, technology and social sciences. Through the collaboration, knowledge has been developed

1. **Innovation in the public health sector** Starting Right is an innovation project, and the innovation in this project lies in establishing a *digital solution* for collecting data on children and adolescents' health and quality of life, using validated survey methodologies. These methodologies are designed to 1) serve as a guidance tool in direct interactions between service providers and parents/children/adolescents; 2) enable municipalities to gain a comprehensive understanding of the health status and influencing factors for the child and adolescent population, in line with the objectives of the Public Health Act; 3) facilitate data export for use in health research and health registries. The digital solution developed by Egde integrating electronic patient records with online questionnaire administration delivered by CheckWare Ltd. is now implemented and in use in 7 municipalities in Agder.

2. **Up to date structured and evidence-based knowledge and overview of children's health and development, to increase early identification of children's needs.** A PhD project (2021-2024) with PhD candidate Eva G Befus explore parent reported HRQoL and mental health in 6-year-old children participating in Starting Right ™. In another study we have investigated the Use of the SDQ (Strengths and Difficulties Questionnaire) in child and school health services among children aged 4 and 6 years. We found that parents report poorer mental health in boys than girls from age 4, and public health nurses should be aware of mental health problems at a lower cut-off than provided by UK norms (Mølland et al. 2023).

3. **Insights in how the digital solution affect work processes and assessments in child and school health services.** A PhD project (2021-2025) with the candidate Trine Holm will explore how the integration of electronic patient-reported outcome measures influences the work processes of public health nurses, including the study of parents' experiences. A master´s project on children´s experiences is also conducted. Data collection is finished and papers for publication are under construction.

4. **Insights and knowledge of implementation of a digital solution in child health services/school health service.** The implementation paper by Westergren et al (2021) show that core implementation components were adjusted throughout the pilot implementation and informs further implementation of the 'Starting Right ™ health service innovation. The overall adoption rate was satisfactory and higher in child health centers where administrative support was provided. Parental acceptability, measured as the response rate, was high with a tendency for higher rates when both parents received the questionnaires, as well as for 6-year-old appointments compared with appointments for 4- and 2-year-old children. (Westergren et al.2021), By gaining in-depth understanding of critical factors for a successful implementation, we will be ready to scale up. The *Starting Right ™* project has the potential to be extended to all municipalities in Norway in the long term.

5. **Insights in how the digital solution contributes to early evidence based -based intervention and interaction.** Our paper on how public health nurses experience the Starting Right model and how this model contributes to early intervention and evidence-based practice was published in 2022, showing that Starting Right provides good overview of children´s health and development, however interpretation can be challenging, and implementation is time-consuming (Robstad et al.2022).

6. **Establishment of research collaboration.** The collaborative partnership in Agder, encompassing the university, 7 municipalities, county councils, hospitals, and the private sector (Egde, CheckWare), has gained national attention, with the Norwegian Institute of Public Health, (NIPH), becoming a partner in the project.

7. **Insights from the study is included in the education at UiA.** Knowledge developed in the project **i**s used in teaching in master programme in public health nursing, and masterprogram in pediatric nursing. Articles published in the project are being used as curriculum material in master's programs at UiA, and other Norwegian Universities.

8. **Parents and children may increase their health literacy. The** Starting Right™ project aims to empower parents with the knowledge, skills, to make informed decisions about their children's health, thereby improving their health literacy. Preliminary findings from qualitative studies with parents and children reflect improved health literacy.

Names of the key researchers and what positions they held at the administrative unit at the time of the research

Kristin Haraldstad (Project leader, professor since 2019, *Thomas Westergren*, Ass. Prof, professor since 2022, **Department** of health and nursing sciences, UiA, (perm. From 1.10.2023), *Eirin Mølland*, Ass.professor at the Department of Economics at the School of Business and Law, UiA*, Liv Fegran,* Professor, **Department** of health and nursing sciences, UiA, *Eirik Abildsnes.* Ass.professor, Head of research and innovation, Kristiansand municipality, *Unni Mette Köpp,* Ass.professor specialist in pediatrics, research counselor and chief physician at Sorlandet Hospital, department of child and

adolescents, *Åshild T Håland*, Ass.professor, Professor since 2022, Psychologist, Head of Research, Sorlandet Hospital department of child and adolescent's mental health, *Elling Bere*, Professor, Norwegian institute of public health, NIPH, dep of evaluation of public health interventions, health, and inequality, *Sølvi Helseth* Professor, Vice Dean, OsloMet, and professor II, at UiA, *Sandra Nolte* Ass. Professor, University of Melbourne from 2022, (Charité Universitätsmedizin Berlin 2018-2022), *Eva-Grethe Befus*, PhD fellow, UiA, *Trine Holm* PhD fellow, UiA

Any relevant key contextual information about this area of research.
Health resources and problems during childhood may have a substantial impact on the quality of life (QOL), development, school functioning, and social relationships with family and friends; and may further impose sustainability as well as burdens not only on individuals and their immediate environment, but also on the society. Key institutions in supporting families in relation to health issues in Norway are the *child and school health services run by municipalities*. To offer an effective health service, and health promoting activities and policy which is knowledge-based and optimally adapted to the individual child/family, as well as the population, the public health nurses (PHNs) and health administrators/politicians need to be informed by rich sets of relevant data. Today, such data sets are made available through the first step of the *Starting Right* ™ project, gradually implemented in 7 municipalities in the county of Agder since 2018.

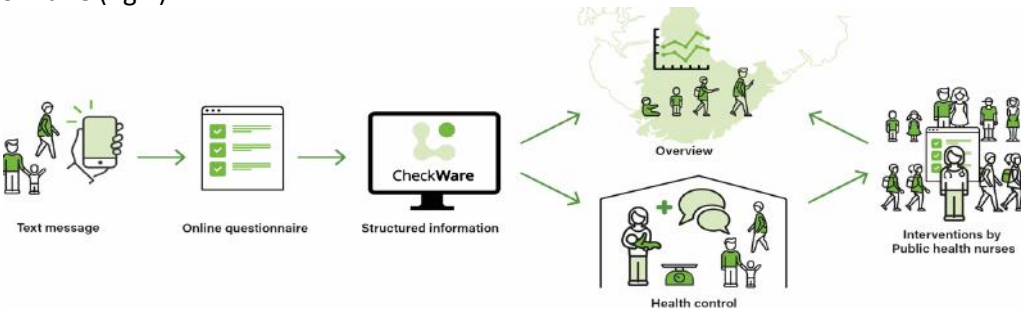
3. References to the research (indicative maximum of six references)

1. Westergren T, Mølland E, Haraldstad K, Tellefsen Håland Å, Stamnes Köpp UM, Fegran L, Abildsnes E. (2021) Implementation of the Norwegian 'Starting right' child health service innovation: implementation adjustments, adoption, and acceptability. *BMC Health Serv Res*. 23;21(1):86. doi: 10.1186/s12913-021-06096 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7824922/
2. Robstad N, Westergren T, Mølland E, Abildsnes E, Haraldstad K, Stamnes Köpp UM, Håland ÅT, Fegran L.(2022). Experiences of Norwegian child and school health nurses with the "Starting Right™" child health assessment innovation: a qualitative interview study. *BMC Health Serv Res* 1;22(1):728. https://pubmed.ncbi.nlm.nih.gov/35650581/
3. Befus EG, Helseth S, Mølland E, Westergren T, Fegran L, Haraldstad K. (2023) Use of KIDSCREEN health-related quality of life instruments in the general population of children and adolescents: a scoping review. *Health Qual Life Outcomes.* 2023 Jan 20;21(1):6.doi: 10.1186/s12955-023-02088-z. PMID: 36670428; PMCID: PMC9857919.https://pubmed.ncbi.nlm.nih.gov/36670428/
4. Mølland E, Haraldstad K, Abildsnes E, Håland ÅT, Köpp UMS, Fegran L, Westergren T. (2023) Use of the Strengths and Difficulties Questionnaire in child and school health services among children aged 4 and 6 years in Southern Norway: clinical considerations. *BMC Pediatr*.;23(1):30. doi: 10.1186/s12887-023-03837-1. PMID: https://bmcpediatr.biomedcentral.com/articles/10.1186/s12887-023-03837-1
5. Befus EG, Mølland E, Helseth S, Hagen M, Stea TH, Nolte S, Haraldstad K .(2024) The use of youth healthcare services and its association with health-related quality of life, physical and mental health and over-the-counter analgesics use in 13-19-year-old adolescents: a cross-sectional study. *BMC Public Health*. 5;24(1):104. :https://pubmed.ncbi.nlm.nih.gov/36670428/
6. Holden Berg, I FHI, Westergren T, Haraldstad K, Bere E, Abildsnes E, Nissen Bjørnsen H & Mølland E,
   Public health nurses´ reports of follow-up needs in children aged 2−6 and the associations with child gender, maternal education, and health parameters assessed in the Norwegian child and school health services – a cross sectional analysis from the Starting Right™ cohort (in progress)

4. Details of the impact (indicative maximum 750 words)

How the research underpinned (made a distinct and material contribution to) the impact;

The development and implementation of Starting Right ™ in the municipalities in Agder is an outcome of long-term collaboration. Since 2018, we have worked together with the municipalities in Agder to innovate child and school health services including the development and initial implementation of validated instruments into an online solution to measure development, mental health and HRQoL in children aged 6 months to 16 years. Before attending their regular appointments, parents and children receive an SMS text message asking them to answer an online questionnaire (fig 1)



The use of digital solution can;

1) serve as a guidance tool in *direct interactions* between public health nurses and parents/children/adolescents,
2) enable municipalities to gain a comprehensive *understanding of the health status* and influencing factors for the child and adolescent population, in line with the objectives of the Public Health Act and make informed decisions/interventions
3) facilitate data export for use *in health research and health registries*.

The `Starting Right ™´ health care innovation complies with national guidelines for child and school health services and hence have the potential to be transferred and applied nationally beyond the study context. The innovative use of structured information also has the potential to provide municipal and county health authorities beyond Agder with an overview about the health and well-being of their child population.

The project's screenings and the structured dialogue help identify concerns about children who might otherwise go unnoticed and unsupported. The project was piloted in Kristiansand municipality, with a high response rate from different age groups. Public health nurses reported the tools as useful and well-received by parents, indicating positive impacts from the project's implementation.

The collaborative partnership in Agder, encompassing the university, municipalities, county councils, hospitals, and the business sector, has gained national attention, with the Norwegian Institute of Public Health becoming a partner in the project as well as the national competence center for child and school health services. The long-term objective is thus not solely to develop the Agder region but to contribute solutions and knowledge that benefit the entire nation and internationally. This initiative positions us at the forefront in the implementation of the BarnUnge21 strategy. The project Starting Right ™ provides an important source of population data in both short- and long term to address questions about onset, prevalence and trajectories of health and QoL in children and adolescents. Such data are not available in the Norwegian registry today; thus, the potential for knowledge development and dissemination is extensive.

One major challenge in implementing Starting Right ™ was the lack of technical integration between service journal systems and CheckWare, however. In the project we have developed and implemented a sustainable technical solution together with Egde and CheckWare, to support evidence -based public health work in the municipalities. The project's sustainable technical

solution has significant reuse value for similar solutions and will drive necessary standards and descriptions, opening up new markets for handling citizen-generated health data.

5.Sources to corroborate the impact (indicative maximum of ten references)

The results from **The Starting Right** ™ have been disseminated in scientific papers as well as through the media. It has been presented at national and international conferences.

1. In collaboration with Agder county and KS Agder, the project is in the process of transferring innovation infrastructure from the project administration into the municipalities' administration.
2. The project has been presented at: EHiN (*E-Health in Norway*) on 10-11 November 2020; "The Starting Right project – early intervention in child health services"
3. Chronicle in the local newspaper Fædrelandsvennen 2020
4. Article at University of Agder (2020)
5. Article in the local newspaper Fædrelandsvennen (2020)
6. Presentation at Arendalsuka (2021)
7. Presentation on *The Health Technology Conference*, organized by Tekna, on 12 October 2022; Starting Right™ "Staring Right for and about children's subjective health in child and school health services"
8. Presentation on the *Nordic Public Health Conference* 28-30 June 2022, Reykjavik, Iceland. "Implementation Components in the Starting Right Service Innovation Providing Evidence-Based Decision Support in Child Health Centers"
9. Presentation at *Nye Mønstre Conference* i Kristiansand municipality, (2022),

Department of Clinical Dentistry, University of Bergen - Case number 1

Institution: University of Bergen (UiB)
Administrative unit: Department of Clinical Dentistry (IKO)
Title of case study: Antibiotic stewardship in dentistry
Period when the underpinning research was undertaken: 2012-2023
Period when staff involved in the underpinning research were employed by the submitting institution: 2017-2021
Period when the impact occurred: 2012-2023

1. Summary of the impact

The research and associated educational efforts has had a major impact on rational antibiotic usage in dentistry. It has formed basis for the national guidelines and knowledge-based antibiotic utilization in dentistry. The understanding of dentists' contribution to the total antibiotic burden has increased. Furthermore, the impact of infection control as an important pilar in the prevention of dissemination of antibiotic resistance has been compiled in national guidelines. An evident effect is that, opposed to many parts of the world, dentists in Norway managed to maintain antibiotic stewardship during the corona pandemic despite lock downs, limiting accessibility to physical dental visits.

2. Underpinning research

Antimicrobial stewardship can be defined as the optimal usage of antibiotics. The components required to attain antibiotic stewardship are guidelines and educational efforts based on solid evidence of clinical efficacy, patient safety aspects on restrictive policy as well as prescribers' attitudes, knowledge, and utilization (2017a, 2020a). The research described here addresses these aspects within odontology.

Bacteria's resistance to antibiotics is an increasing global problem seriously threatening health care, which is dependent on effective antibiotics (2016a, 2018a). Important rational for combating this is preventive measures to minimize antibiotics prescription and stringent hygienic measures to prevent dissemination of resistant bacteria. On a global scale dentistry account for 10% of all prescribed antibiotics. Our research has helped to identify areas in need of more prudent use (2022a, 2023a, 2023b).

Although a reduction has been seen after the publication and implementation of national guidelines (2012a, 2014, 2016b, 2021a) our data has shown indications of over-prescription in dentistry such as geographical and gender differences (2020a, 2022b). There is also a substantial difference in prescription between dentists working in private practices compared to the public sector (manuscript in progress). Besides indicating a potential for improvement, this also suggests that antibiotic treatment is being used unequally. To counteract this iniquitous circumstance detailed knowledge regarding prescribers' attitudes and utilization pattern has been investigated (2015a, 2022a, 2022c, 2022b, 2023b, two further manuscripts in progress).

The efficacy of antibiotics used on indications based on tradition rather than scientific evidence, needs to be scrutinized. One such area is antibiotic prophylaxis, either on the indication of a vulnerable patient, or because of a procedure with high risk for infection (2012b, 2012c, 2016c, 2018b). This field in odontology is a confirmed knowledge-gap (2017b). Our research group was the first to demonstrate that even a single dose of amoxicillin can cause significant disturbance in the oral microbiota and select for resistant bacteria (2016c). Besides reducing the protective effect of the resident microbiota, the efficacy of antibiotic prophylaxis is thereby threatened and could theoretically increase the risk of a severe resistant infection rather than protect against it (2015b).

Data from our research group has also shown that in dentistry it is common to confuse prophylaxis with treatment meaning that the patient is erroneously given a full course of antibiotics instead of a single dose (2015a, 2016c, 2023b). One such area is dental implant surgery and augmentation of jawbone. In Norway approximately 30 000 dental implants are inserted annually. Thus, this may increase the antibiotic load tremendously. Within this area systematic reviews may be an important tool for compiling evidence to form solid recommendations (2015c, 2015d, 2018c, 2020b, 2021b).

When applying restrictive antibiotic policies, it is of outmost importance to assure maintained patient safety. One such area is the use of antibiotic prophylaxis in dentistry to prevent infectious endocarditis (IE), which is a debated issue. However, it seems that cessation of antibiotic prophylaxis to patients with high risk for developing IE does not increase the IE cases caused by invasive dental treatment (2020c, 2022d, 2022e, 2023c).

- Bodil Lund (female), professor since 2017 (University of Bergen 2017-2021, Karolinska Institutet 2021 - present)
- Dagmar Fosså Bunæs (female), associate professor, 2019-2021
- Knut Leknes (male), professor, 2019-2021
- Farnoush Tousi (female), DDS, resident, 2019-2023
- Stein Atle Lie (male), professor, 2019 - present
- Cecile Gjerde (female), associate professor, 2021- present
- Therese Thoresen (female), DDS, resident, 2018-2022
- 4 master students

The related research and collaborations are components in the knowledge-based increase in awareness of drivers of AMR and has formed basis for continuing improvements in code of conduct in terms of recommendations, educational efforts, and routines in the everyday clinical dental practice. Ongoing today is a reach out between Norway and Sweden to work for harmonised recommendations in terms of doses and duration of treatment. If this could be achieved, we are one step closer to reduce the vulnerability in availability of antibiotic compounds on the Swedish and Norwegian market.

3. References to the research (indicative maximum of six references)

1. D Khalil, M Hultin, MU Rashid, B Lund. Oral microflora and selection of resistance after a single dose of amoxicillin. *Clinical Microbiology and Infection*, 22(11):949.e1-949.e4, 2016. PMID: 27569711, DOI:10.1016/j.cmi.2016.08.008
2. A Klinge, D Khalil, B Klinge, B Lund, A Naimi-Akbar, S Tranaeus, M Hultin. Prophylactic antibiotics for staged bone augmentation in implant dentistry. *Acta Odontologica Scandinavica,* 78(1):64-73, 2020. PMID: 31483177, DOI: 10.1080/00016357.2019.1656819.
3. B Lund, A Cederlund, M Hultin, F Lundgren. Effect of governmental strategies on antibiotic prescription in dentistry. *Acta Odontologica Scandinavica*, 78(7):529-534, 2020. PMID: 32293215, DOI: 10.1080/00016357.2020.1751273
4. N Vähäsarja, B Lund, A Ternhag, B Götrick, L Olaison, M Hultin, C Kruger Weiner, A Naimi-Akbar. Incidence of infective endocarditis caused by viridans group streptococci in Sweden – effect of cessation of antibiotic prophylaxis in dentistry for risk individuals. *Journal of Oral Microbiology*, 23;12(1):1768342, 2020. PMID: 33014311, doi: 10.1080/20002297.2020.1768342.
5. Øen M, Leknes KN, Lund B, Bunæs DF. The efficacy of systemic antibiotics as an adjunct to surgical treatment of peri-implantitis A systematic review. *BMC Oral Health*, 2021 Dec 27;21(1):666. doi: 10.1186/s12903-021-02020-1.PMID: 34961495

6. F Tousi, M Al Haroni, S A Lie, B Lund. Antibiotic prescriptions among dentists across Norway and the impact of COVID-19 pandemic. *BMC Oral Health*, 2023. doi:10.1186/s12903-023-03380-6.

4. Details of the impact

The impact case Antibiotic Stewardship in Odontology described above can be exemplified by, but is not limited to, the below.

Commission of trust as result of research (Bodil Lund)

Norway:

- Advisor and co-author of the national guidelines for infection control in dentistry, **The Norwegian Institute of Public Health** (2018).
- Advisor for national guidelines regarding antibiotic use in dentistry in Norway. Revision of national guidelines. Antibiotic Center in Primary Health Care at **Norwegian Directorate of Health** (2017-2021).
- Member of the **Norwegian Dental Associations** expert group working against antimicrobial resistance (AMR), (2019-2020)

Sweden:

- Board-member 2010-2017 of the Swedish Strategic Program Against AMR in dentistry (StramaDent), **Public Health Agency of Sweden**. From 2020-ongoing **chair of StramaDent**. StramaDent acts for increasing awareness of antibiotic stewardship through educational efforts, and advisory for authorities and national recommendations.
- Advisor for reporting of antibiotic use in dentistry by **National Board of Health and Welfare**, Sweden (2018-2019).
- Member of expert group assembled by the **Swedish Medical Products Agency** and **Institute of Infection Control** on the assignment of the Department of Health and the government to improve patient safety regarding antibiotic prophylaxis (2012) and antibiotic treatment in dentistry (2013). This resulted in national recommendations published in 2012 and 2014.
- Member of reference group evaluating existing antibiotics. **Governmental assignment** (2015-ongoing).
- Advisory for the **Swedish Medical Products Agency** to examine and discuss the recommendation on endocarditis prophylaxis (2015). The resulting statement was published in 2016.
- Chair of the National working group on aerosol generating procedures in dentistry on the assignment of **National Program Area in Dentistry**. Commission completed 2020.

Nordic countries:

- Ad hoc editor for the Nordic antibiotic theme of the journals of the Nordic dental societies (2018-2019). The project involved comparison of national recommendations and consensus discussions improving knowledge regarding antibiotic stewardship in odontology among the representatives from the differnet countries.

Europe:

- Invited speaker at European Association of Osseointegration (EAO) Consensus Conference, Pfäffikon, Switzerland (2015). The presentations and workshops resulted in recommendations from EAO for antibiotic use in conjunction with dental implant placement.

Impact on infection control in dentistry and best practice during the covid-19 pandemic: During 2017-2021 BL acted advisor and co-author of the national guidelines for hygienic measure in dentistry published by **The Norwegian Institute of Public Health** in 2018. This was an important cornerstone in the strategic work to counteract AMR because prudent infection control reduces the number of infections and consequently reduces the need for using antibiotics. Furthermore,

infection control prevents already resistant bacteria from disseminating between patients and dental staff. The implementation of the guidelines involved particpating in courses and lecturing. During the initial phase of the covid-19 pandemic she acted advisor for Norwegian authorities regarding actions in dentistry to counteract the spread of covid-19. BL also chaired the Swedish National Working Group on aerosol generating procedures (AGP) in dentistry, appointed by the **Swedish National Program in Dentistry** hosted by Sweden's municipalities and regions. After review of the scientific literature the group published national guidelines for AGP. The results were also disseminated in Norway. Dentists clinical active during the pandemic were later shown to be one of the occupations with the lowest level of covid-19 infection.

Impact on knowledge dissemination 2012-2022

- Educational efforts in undergraduate, postgraduate and research level of dental education
- Hosting a 5-day course on the topic of AMR, research school for dentists funded by the Swedish Research Council (2016)
- 4 book chapters
- 42 publications (original research and reviews)
- 7 guidelines/recommendations
- 82 invited lecturers at courses and meetings
- 10 keynote speaker, international congresses
- Norwegian television (NRK). Interview for radio and TV regarding AMR (2019).
- Podcast interview (2018).
- Interviews (one in 2017 and four in 2019) by the Swedish Dental Society journal.
- Interview by the Norwegian Dental Society journal, Tidende (2021).

Impact on antibiotic prescription: Since the founding of StramaDent a 40% reduction of antibiotic prescription has occurred in Swedish dentistry (Lund et al 2020). This renders antibiotic use in Swedish dentistry the lowest in the world. A reduction is also seen in Norway. Furthermore, despite lock-down and reduced availability to dental care, the antibiotic prescription in Norwegian dentistry during the covid-19 pandemic managed to remain low in contrast to many parts of the world.

Impact on UN sustainability goals: AMR is claimed by WHO to be the second largest threat to humanity by having a negative impact on 11 of the United Nation's 17 sustainability goals. Thus, fighting AMR will have consequences long beyond health with implications for clean environment and water, reducing poverty due to the strong socioeconomic impact of AMR (www.who.int).

5. Sources to corroborate the impact (indicative maximum of ten references)

1. B Lund, G Skoog, B Götrick, J Blomgren, U Snygg-Martin. Systemisk antibiotikabehandling. *Information från Läkemedelsverket*, 25(1):49-53, 2014.
2. B Lund, M Hultin, S Tranæus, A Naimi-Akbar, B Klinge. Complex systematic review - Perioperative antibiotics in conjunction with dental implant placement. *Clinical Oral Implant Research*, 26 (Suppl. 11), 1-14, 2015. https://doi.org/10.1111/clr.12637
3. H Harnesk Nygren, L Blomstrand, Garming Legert K, M Magnusson, M Sjöström, B Lund. Rekommendation för antibiotika till patienter som strålbehandlats mot munhålan. *Tandläkartidningen*, 5:58-59, 2016.
4. B Lund. Book chapter: Antibiotika. Aktuell Nordisk Odontologi, 2017. Universitetsförlaget. ISSN: 1902-3545. DOI:10.1826/issn.2058-7538.
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6. B Lund, M Hultin, T Larsen. Antibiotikaprofylax – forskrivning som kräver kunskap och eftertanke. *Nor Tannlegeforen Tid*, 128:916-22, 2018. DOI:10.56373/2018-11-8
7. H Bentele, M Enersen, H-M Eriksen, A Hensten, B K Lund, I Slinde, B Olin Teigmo, M B Vevelstad. Faglige anbefalinger for smittevern i klinisk odontologisk praksis. 2018. https://www.tannlegeforeningen.no/profesjon-og-fag/Nye-anbefalinger-for-smittevern-i-klinisk-odontologisk-praksis.aspx
8. Ø Olsvik**,** B Lund. Tannmedisinsk turisme – konsekvenser for folkehelsen? *Nor Tannlegeforen Tid*, 128, 2018; 118: 900-5. DOI:10.56373/2018-11-6.
9. Larsen T, Kjerulf A, Lund B. Infektionshygiejnens rolle i forebyggelse af antibiotikaresistens. *Nor Tannlegeforen Tid.* 130, 2019. DOI:10.56373/2019-3-6
10. N Vähäsarja, B Lund, A Ternhag, B Götrick, L Olaison, M Hultin, A Warnqvist, C Krüger Weiner, A Naimi-Akbar. Infective endocarditis among high-risk individuals - before and after the cessation of antibiotic prophylaxis in dentistry: a national cohort study. *Clin Infect Dis*. 2022 Feb 4:ciac095. doi: 10.1093/cid/ciac095. Online ahead of print. PMID: 35134867
11. D Khalil, G Baranto, B Lund, M Hultin. Antibiotic utilization in emergency dental care, a cross sectional study. *Acta Odontologica Scandinavia*, 2022. https://doi.org/10.1080/00016357.2022.2049864

Department of Clinical Dentistry, University of Bergen - Case number 2

Institution: University of Bergen (UiB)
Administrative unit: Department of Clinical Dentistry (IKO)
Title of case study: Mesenchymal stem cell-based regenerative applications
Period when the underpinning research was undertaken:
Period when staff involved in the underpinning research were employed by the submitting institution: 2012 – till present
Period when the impact occurred: 2012 – till present

1. Summary of the impact (indicative maximum 100 words)

Mesenchymal stem-cells (MSC) represent an invaluable therapeutic tool for treatment of many of the currently non-treatable or challenging defects, diseases, and disorders. Providing such treatments has a direct impact on the health and quality of life of the patients and their families and a remarkable economic impact by reducing of the burden and costs on the health systems related to long-term care provided for the patients. We optimized and established protocols for ex vivo culture of MSC and transportation between the GMP cell production facility and hospitals and used these protocols for clinical bone regeneration and other clinical applications.

2. Underpinning research (indicative maximum 500 words)

In the last ten years (2012 – 2022), the **Tissue Engineering Group** and TOR at IKO has evaluated various sources of MSC including bone marrow, adipose tissue, dental tissues, and umbilical cord to select the most suitable source of MSC to be used for bone regenerative applications. Since MSC from bone marrow and adipose tissue are frequently used for regenerative applications, we have conducted a comprehensive in vitro and in vivo donor-matched comparison of these two sources of MSC. We have found that MSC from bone marrow are the most suitable for bone regenerative applications since they provide faster and greater bone regeneration. We have also optimized and validated culture conditions free of any animal products based on Platelet Lysate for manufacturing of MSC for clinical applications. In addition, we have optimized and validated the transportation conditions of MSC from the GMP cell production facility to the hospitals where these MSC are administered to patients. Using these established protocols, we used MSC from bone marrow to treat patients with maxillofacial and long bone defects in phase I/II clinical trials. We found that our MSC therapy was safe and effective in regenerating bone and achieving healing in all treated patients. Now we are conducting a phase III randomized controlled clinical trial comparing our MSC therapy to bone grafting, which is the gold standard for bone regeneration clinically.

We performed the first clinical trial in Norway of this approach in 11 patients for reconstruction of alveolar bone with excellent results at the 12-month examination, and 5-year follow up is in progress. However, only a few early-stage clinical studies with a limited number of patients have proven the safety of this novel regenerative treatment. According to the clinical database (www.clinicaltrials.gov) and Medline, our research is at the forefront of regenerative medicine because we have successfully performed an early-stage clinical trial using **cell therapy** in bone regeneration (Gjerde et al. 2018).

Furthermore, our established protocols have been adopted and used for other clinical therapeutic applications including clinical trials for treatment of multiple sclerosis and extensive skin burn and cornea injuries in collaboration with several research groups and clinicians at The Faculty of Medicine and Haukeland University Hospital. The data generated from the projects placed a significant impact in the community and used to establish the Ex Vivo GMP Laboratory at the hospital in Bergen.

Moreover, we have characterized and evaluated the secreted factors and vesicles from MSC collectively known as MSC secretome, which play a key role in the bone regeneration process.

We have found that a cell-free approach based on MSC secretome can regenerate bone in critical-sized bone defects in small animals. Based on these findings, now we are investigating the effect of this cell-free approach in regenerating bone defects in large animals. This can open the door for cell-free off-the-shelf products ready for allogenic regenerative clinical applications in the future.

The projects have been supported by four EU projects (VASCUBONE, REBORNE, MAXIBONE, BONEFIX) and several programs funded by Research Council of Norway (RCN, 4 projects), Helse Vest, Trond Mohn Foundation (3 projects), Olav Thon Foundation and Meltzer Foundation.

- *Kamal Mustafa (male), professor since 2010.*
- *Cecilie Gjerde, associate professor (female), joined the project in 2012.*
- *Samih Mohammed Ahmed, Researcher (male), joined the project in 2012.*
- *Salwa Suliman, Researcher, female (Awarded Starting Grant), joined the project in 2012.*
- *Niyaz Al Sharabi, Researcher, male, joined the project in 2012.*
- *Inge Fristad, professor, male, joined the project since 2010.*
- *Ahmed Rashad, Researcher, male, joined the project in 2013.*
- *Siddharth Vivek Shanbhag, Researcher, male, joined the project in 2016.*
- *Mohamed Yassin, associate professor, male, joint the project in 2012.*
- *Dagmar Fosså Bunæs, female, joined the project in 2013.*
- *Torbjørn Pedersen, male, joined the project in 2012.*
- *Shuntaro Yamada, male, joined the project in 2018.*
- *Anne Isine Bolstad, female, joined the project since 2010.*
- *More than 20 PhD students and theses were generated from the group during the last 10 years.*

To our knowledge, this case and achievement is unique in Europe as we have been able to translate a laboratory idea into clinical practice. The data and knowledge generated from the project will be utilized to develop translational approaches for regenerative therapies of several types of bone defects.

3. References to the research (indicative maximum of six references)

1. Gjerde C, Mustafa K, Hellem S, Rojewski M, Gjengedal H, Yassin MA, Feng X, Skaale S, Berge T, Rosen A, Shi XQ, Ahmed AB, Gjertsen BT, Schrezenmeier H, Layrolle P. Cell therapy induced regeneration of severely atrophied mandibular bone - Part II: Clinical outcome. **Stem Cell Res Ther**. 9;9(1):213. doi: 10.1186/s13287-018-0951-9 (2018). **Impact Factor: 8.1.**
2. Hassan MN, Yassin MA, Eltawila AM, Aladawi AE, Mohamed-Ahmed S, Suliman S, Kandil S, Mustafa K. Contact osteogenesis by biodegradable 3D-printed poly(lactide-co-trimethylene carbonate). **Biomaterial Res**. 10;26(1):55. doi: 10.1186/s40824-022-00299-x (2022). **Impact Factor: 15.46.**
3. Yamada S, Yassin M.A, Torelli F, Hansmann J, Green J.B.A, Schwarz T, Mustafa K. Unique Osteogenic Profile of Bone Marrow Stem Cells Stimulated in Perfusion Bioreactor is Rho-ROCK-mediated Contractility-Dependent. **Bioengineering & Translational Medicine** (2023). https://doi.org/10.1002/btm2.10509. **Impact Factor: 10.7.**
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5. Hassan MN, Yassin MA, Suliman S, Lie SA, Gjengedal H, Mustafa K. The Bone Regeneration Capacity of 3D-Printed Templates in Calvarial Defect Models: A Systematic Review and Meta-Analysis. **Acta Biomaterialia** 91:1-23. doi: 10.1016/j. (2019). **Impact Factor: 10.6.**
6. Ojansivu M, Rashad A, Ahlinder AE, Massera J, Mishra A, Syverud K, Finne-Wistrand A, Miettinen S, Mustafa K. Wood-based nanocellulose and bioactive glass modified gelatin-alginate bioinks for 3D bioprinting of bone cells. **Biofabrication**. doi: 10.1088/1758-5090/ab0692 (2019). **Impact factor 11.06.**

4. Details of the impact (indicative maximum 750 words)

The increasing number of bone problems and incurable diseases due to the increasing ageing and life expectancy of the population in Europe and Norway, together with the constant demand for improved, reliable and low-cost products, creates the obvious need for innovative treatments. Our goal is that the results of the projects will affect directly and positively the daily life of our patients, leading to treatment of incurable diseases and injuries and to develop new strategies for therapeutic intervention. Thus, we are concerned with a single goal, to produce safe, reliable, patent-protected tissue engineered products that we can bring to market and introduce it as a routine regenerative therapy.

The main objective of the projects is the successful validation of novel, clearly defined clinical applications which answers the demands of the identified questions based on the research, pre-clinical and clinical outcomes of our projects. Furthermore, the ongoing projects pave the way for clinical studies by conducting proof-of-principle clinical studies using stem cell therapy.

The results generated from our first clinical trial which was conducted between 2012 – 2015 and reported in peer reviewed journals (Gjerde et al. 2018; Rojewski et al. 2019), have a positive impact on Nordic and European capability in treating bone defects according to the concept of regenerative medicine. The findings were also disseminated in several national and international conferences, in social media, in local newspapers and at the Norwegian TV. This wealth of knowledge enriches the PhD students and young post-doctoral researchers who have been contributing to the projects. Young researchers and students were involved in short student exchanges, regular online journal clubs and seminars on tissue engineering, stem cell biology, clinical challenges in regenerative medicine and dentistry, etc.

More generally, the proposed different tissue engineered construct materials and designs mitigate multiple unmet clinical bottlenecks by providing personalised tissue-engineering constructs with integrated patterns of bioactive multifunctional biomaterials containing cells and delivering biomolecules and growth factors. Our expected impacts are relevant for this key **target groups**:

i) **patients with tissue defects and incurable injuries**,
ii) **clinicians**, who will apply the regenerative and tissue engineering concept in daily use,
iii) **health policy makers and healthcare payers and providers**
iv) **Our industrial partners/SMEs:**
- **producers of biomaterials/polymers** and **contrast agents**,
- **manufacturers of the bioreactor technology**,
- **producers of 3-D printing facilities**.

The end-users of the products generated from our projects are clinicians and their patients.

Therefore, the expected impacts must be considered from different time points in the value chain. Some side-products will be marketable early, but the personalized 3D-printed implants, however, will take longer due to regulatory requirements of clinical testing as medical devices (without cells) or Advanced Therapy Medicinal Products (with cells).

The group has proven the capacity to manage large multidisciplinary projects and research activities in 4 large collaborative EU projects (VascuBone, Reborne, Maxibone, BoneFix) and several other large projects which are currently ongoing and financed by the Trond Mohn Foundation, Research Council of Norway, Olav Thon Foundation, Meltzer Foundation and Helse Bergen. A substantial effort has been placed by the group to establish, design, approve and initiate Advanced Therapy Medicinal Products (ATMP)-based clinical trials aimed for treating defects in the maxillofacial area and in long bones as well for treating neurological disorders such as multiple sclerosis (SMART-MS project). These clinical trials are among few ATMP-based trials in Europe, indicating that our research is at the front. The experience and knowledge of the group members in tissue engineering, stem cell biology and clinical applications of MSC, translated in more than 200 publications on tissue engineering and stem cell characterization. The group leader is a member of the Board of Bergen Stem Cell Consortium and Mohn Research Center for Regenerative Medicine which aimed to set up

a Good Manufacturing Practice Facility (GMP) in Bergen (Ex Vivo Lab). A standardized protocol for using mesenchymal stem cells has been established and published by the group in collaboration with the University of Ulm in Germany. This protocol is currently used by several other research groups at the Faculty of Medicine and Haukeland Hospital for treatment of multiple sclerosis (MS), long bone non-healed defects, cornea repairs and to promote skin regeneration after burns.

5. Sources to corroborate the impact (indicative maximum of ten references)

1. Gjerde C, Mustafa K, Hellem S, Rojewski M, Gjengedal H, Yassin MA, Feng X, Skaale S, Berge T, Rosen A, Shi XQ, Ahmed AB, Gjertsen BT, Schrezenmeier H, Layrolle P. Cell therapy induced regeneration of severely atrophied mandibular bone - Part II: Clinical outcome. Stem Cell Res Ther. 9;9(1):213. doi: 10.1186/s13287-018-0951-9 (2018).
2. Rojewski MT, Lotfi R, Gjerde C, Mustafa K, Veronesi E, Ahmed AB, Wiesneth M, Körper S, Sensebé L, Layrolle P, Hellem S, Schrezenmeier H. Translation of a standardized manufacturing protocol for mesenchymal stromal cells: A systematic comparison of validation and manufacturing data. Cytotherapy 21: 468-482 (2019).
3. Kvistad CE, Kråkenes T, Gjerde C, Mustafa K, Rekand T, Bø L. Safety and Clinical Efficacy of Mesenchymal Stem Cell Treatment in Traumatic Spinal Cord Injury, Multiple Sclerosis and Ischemic Stroke - A Systematic Review and Meta-Analysis. Front Neurol. 30;13:891514. doi: 10.3389/fneur.2022.891514. (2022).
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5. Kråkenes T, Wergeland S, Al-Sharabi N, Mohamed-Ahmed S, Fromreide S, Costea DE, Mustafa K, Bø L, Kvistad CE. The neuroprotective potential of mesenchymal stem cells from bone marrow and human exfoliated deciduous teeth in a murine model of demyelination. PLoS One. 2023 Nov 9;18(11):e0293908. doi: 10.1371/journal.pone.0293908. eCollection 2023.PMID: 37943848.
6. Hassan MN, Yassin MA, Eltawila AM, Aladawi AE, Mohamed-Ahmed S, Suliman S, Kandil S, Mustafa K. Contact osteogenesis by biodegradable 3D-printed poly(lactide-co-trimethylene carbonate). Biomaterial Res. 10;26(1):55. doi: 10.1186/s40824-022-00299-x (2022).
7. Shanbhag S, Kampleitner C, Mohammed Ahmed S, Yassin MA, Dongre H, Costea DE, Tangl S, Stavropoulos A, Bolstad AI, Suliman S, Mustafa K. Ectopic bone tissue engineering in mice using human gingiva or bone marrow-derived stromal/progenitor cells in scaffold-hydrogel.
8. Rana N, Suliman S, Al-sharabi N, Mohamed-Ahmed S, Mustafa K. Extracellular vesicles derived from primed mesenchymal stromal cells loaded on biphasic calcium phosphate biomaterial exhibit enhanced macrophage polarization. Cells. 29;11(3):470. doi: 10.3390/cells11030470. (2022).
9. Saleem R, Mohamed-Ahmed S, Elnour R, Berggreen E, Mustafa K, Al-Sharabi N. Conditioned Medium from Bone Marrow Mesenchymal Stem Cells Restored Oxidative Stress-Related Impaired Osteogenic Differentiation. Int J Mol Sci 15:13458. doi: 10.3390/ijms222413458 (2022).
10. Shanbhag S, Suliman S, Mohamed Ahmed S, Campleitner C, Hasan MN, Heimel P, Tangl S, Bolstad AI, Mustafa K. Bone regeneration in rat calvarial defects using dissociated or spheroid mesenchymal stromal cells. Stem Cell Res Ther. 14:575 https://doi.org/10.1186/s13287-021-02642-w (2021).

Department of Clinical Dentistry, University of Bergen - Case number 3

Institution: University of Bergen (UiB)
Administrative unit: Department of Clinical Dentistry (IKO)
Title of case study: Increased quality of life in orofacial pain with an interdisciplinary approach
Period when the underpinning research was undertaken: 2013-present
Period when staff involved in the underpinning research were employed by the submitting institution: 2013-present
Period when the impact occurred: 2017-present

1. Summary of the impact: Pain in the orofacial region is the outcome of different pathologies with a prevalence of 15 %. A national project for temporomandibular disorder was launched at Haukeland University Hospital in Bergen by the Health Directorate of Norway to set up an interdisciplinary investigation program. The patient group was characterized in clinical studies where national and international collaborators were involved. The impact of the project has increased quality of life for the patients by providing new knowledge, given insights into new mechanisms, sharpened diagnostic methods, offered novel treatments, and personalised rehabilitation programs. It has paved the way to strengthen interdisciplinary collaboration between odontology and medicine.

2. Underpinning research:

Pain in the orofacial region is the outcome of a range of different pathologies. The prevalence of orofacial pain (OFP) in the population is up to 15 %. The economic burden of OFP is estimated at £3,000 per year and patient, due to prescription charges, travel, and absenteeism. It has also been demonstrated that over the lifetime, OFP patients from age 25 y have a total expenditure of £27,317 and as a result only 17.5 y of perfect health.

For 15 years ago a national OFP project for temporomandibular disorder (TMD) was launched at Haukeland University Hospital in Bergen (HUH) by the Health Directorate (HD) of Norway to set up an interdisciplinary investigation program and an aim to characterize this patient group. A group of patients had established a patient association, to put their cause forward to the health authorities. They felt that the health care system did not take them seriously and was unable to provide sufficient treatment. They had typically undergone numerous investigations and interventions without success. Some of them sought healthcare abroad which was expensive and had limited effect. Due to lack of scientific documentation the social security system would not provide economic support. The interdisciplinary program was set up by the Department of Oral and Maxillofacial Surgery (OMS) and the Pain Clinic at HUH in Bergen led by the **Professors Trond Berge and Annika Rosèn** and the leader of the pain clinic **psychologist Borrik Schjødt**. The program was later evaluated by an external part with honest reviews (1). The Orofacial pain research group led by **Professor Annika Rosèn** at the Department of Clinical Dentistry, University of Bergen started to characterize the patient group (2). The interface between dentistry and medicine, improvement of mutual collaboration, diagnostics and treatments were urgent and needed to affect patients` safety and quality of life. During the years 2013-2018, 140 TMD patients were interdisciplinary investigated. A working group established by HD with members of our team rendered in National guidelines for TMD in 2017 (3). A National Unit for Orofacial Pain (NUOFP, Behandlingstjeneste) was launched in 2017 and has broadened the patient group with pain diseases and diagnostics (4). A learning and mastering course was created as one of the treatment solutions (5).

Results from our research group showed that TMD in children and adolescents was increasing. We joined a multicenter study, NorJIA (6), where we could study prevalence of TMD in juvenile idiopathic arthritis (JIA) and also sharpen the diagnostic tools for imaging the temporomandibular

joints (TMJ). In 2019, the Research Council of Norway BEHANDLING pre-project was achieved (7), and international collaborators could be included, from Karolinska Institutet, Sweden Associate Professor Carina Kruger Weiner and Massachusetts General Hospital/Harvard School of Dental medicine, Boston, USA Professor David Keith. The latter had been our mentors since 2013 when the interdisciplinary program was built. To combine clinical data with larger patient groups, health registers in Norway and Sweden were used. Work disability, morbidity, mortality and Quality of life among patients with TMD were analyzed.
Three theses were produced during the time frame. A general conclusion from thesis no. 1, is that patients with painful TMD suffered from high levels of psychological stress, including self-perceived cognitive deficits, anxiety, depression, rumination, pain-related catastrophizing and low QoL related to oral health. In thesis no. 2 it was shown that TMD was found in half of the participants with JIA, as compared to about one-fourth of their healthy peers. In thesis no. 3 with register-based data, causes and consequences of TMD in patients with joint diseases were presented. They have a strong development associated with mental and behavioral disorder and musculoskeletal and connective tissue disorder and with high work disability and disease burden in comparison to the general population. This increased dependency on social insurance benefits is strongly influenced by comorbidities.

3. References to the research

Thesis by Dr. Kordian Staniszewski at UiB 2023, with the title "Biological markers and cognitive function in painful temporomandibular disorder" (clinical research). Main supervisor Professor Annika Rosèn, co-supervisors Professors Anders Johansson, Åsa Hammar, Arne Tjølsen. Bergen Open Research Archive: Biological markers and cognitive function in painful temporomandibular disorder (uib.no)

Thesis by Dr. Johannes Fischer at UiB 2022, with the title “Subjective symptoms, clinical signs and imaging features related to temporomandibular disorder in juvenile idiopathic arthritis” (clinical research). Main supervisor Professor Annika Rosèn, co-supervisors Professors Marit Slåtterlid Skeie, Xieqi Shi, Karen Rosendahl. https://www.uib.no/nye-doktorgrader/156316/barn-og-unge-med-barneleddgikt-har-økt-risiko-tmd Bergen Open Research Archive: Subjective symptoms and clinical signs and imaging features related to temporomandibular disorders in juvenile idiopathic arthritis (uib.no)

Thesis by Dr. Adrian Salinas Fredricson at Karolinska Institutet (KI) Sweden 2023, with the title “Causes and consequences of temporomandibular joint diseases” (register research). Main supervisor Associate Professor Carina Kruger Weiner, co-supervisors Professors Annika Rosèn, Johanna Adami and Bodil Lund; Associate Professors Aron Naimi-Akbar and Britt Hedenberg-Magnusson; Dr Lars Fredriksson. Causes and consequences of temporomandibular joint diseases (ki.se)

4. Details of the impact:

Our research has provided new knowledge about OFP, given insights into new mechanisms, sharpened diagnostic methods, offered novel treatments, and personalised rehabilitation programs, and paved the way to strengthen interdisciplinary collaboration between odontology and medicine.

Characterization of the patient group: High levels of psychological stress, self-perceived cognitive deficits, anxiety, depression, rumination, pain-related catastrophizing and low QoL related were shown. Due to patients` comorbidities it is difficult to master chronic pain and common everyday tasks, suggested that they could be targeted in treatments and interventions. Prevalence of TMD in a JIA population was around 50% compared to about 25% of their healthy peers.

Sharpening the diagnostics: The diagnostic classification system for TMD (DC/TMD) was used, though in a modified version. Longitudinal evaluation on inter-examiner reliability study was made using the DC/TMD Examiner Protocol. Guidelines of diagnostics and treatments of TMD for clinicians was published by the HD in 2017 (3), which has been crucial for building the competence

in Norway. The consistency of the tested imaging modalities used for the assessment of TMJ growth disturbances differed, highlighting the importance of applying the most precise imaging markers under the premise of acceptable diagnostic accuracy, both at a patient level and for clinical trials. Further, there were no associations between painful TMD and CBCT-based pathology in children with JIA, which means that clinical symptoms and signs of TMD cannot predict TMJ deformity and vice versa which highlights the importance of right choice of methods to reach the right diagnosis. This is important when it comes to choosing treatments since there is a risk for serious opportunistic infections using biological immune modifying antirheumatics. From the National TMD project to the National Unit for orofacial pain broadened the pain diseases and diagnostics. A publication from the Boston group showed that there are underdiagnosed orofacial pain diseases that earlier have been mentioned as idiopathic pain (8). Using the recently published international diagnostic criteria for orofacial pain made it possible to increase the understanding of this patient group and classify them into different categories which make it easier to find the right treatment. A Scandinavian group of oral and maxillofacial surgeons was formed in 2016. The aim was to find different surgical treatment options for TMD patients. A disease focused classification system for surgical procedures was published in 2020 and is now available to use (9).

Tailored treatments: The impact of the research presented shows possibilities to increase QoL for OFP patients with improved diagnostics and tailored treatments. In thesis no. 1, a three year follow up study showed that high pain intensity is a risk factor for poorer recovery, but improved coping with painful TMD after an interdisciplinary investigation decreased pain intensity, pain catastrophizing and mandibular function. In thesis no. 3, findings emphasize how TMD patients are suffering from their condition and are strongly influenced by comorbidities, which increases the dependency on social insurance benefits. With optimized resources, by national guidelines designed by an interdisciplinary team both from the dental and medical fields, the work disability shown by our group will decrease, which the society gain benefits from with reduced economic burden on the social welfare system. The guidelines of diagnostics and treatments of TMD has been crucial for building the competence in Norway but also for supporting patients and their relatives. The diseased-focused surgical classification for TMD dysfunction (9) can be used as a tool for the systematic evaluation of patients and for promoting the evidence-based selection of TMJ surgical treatments. The interdisciplinary program for investigation, the learning and mastering course, a digital treatment program are all different types of tailored treatments that is ongoing and yearly reported to a national reference group for Treatment services (behandlingstjenester) in the health care system in Norway (10).

Strengthen interdisciplinary collaboration between odontology and medicine: The results have provided transfer values to other disciplines and brought knowledge to various professions within the primary health service (GP, physiotherapists, psychologists) and the dental health service (dentist), but also to the specialist health services. Improving the interaction at the intersection of medicine, dentistry, psychology, and physiotherapy facilitates patient safety in diagnostics, treatment, and rehabilitation and increases QoL throughout the entire patient pathway at various service levels. The results have increased the understanding of OFP and for the last 5 years, there have been no reports in the media from patient organizations that deal with facial pain, as it were a lot of for 10-15 years ago due to that this patient group was neglected by the healthcare system. Additionally, the results can serve as a reference for future research enabling studies for inter-clinical comparison, forming a basis for meta-analysis and solid evidence-based guidelines both nationally and internationally.

5. Sources to corroborate the impact

1. RAPPORT EVALUERING AV STRAKSTILTAKET FOR TMD (yumpu.com)

2. The Orofacial Pain research group, a section of the Oral Health research group which is part of the Center of Translational Oral Research (TOR) at University of Bergen: Smerter i ansikt og kjeve | Oral Helse | UiB
3. National guidelines for TMD: Temporomandibulær dysfunksjon – TMD - Helsedirektoratet
4. The National Unit for Orofacial Pain at Haukeland University Hospital, Bergen: Nasjonal behandlingsteneste for uavklarte smerter i ansikt og kjever - Helse Bergen HF (helse-bergen.no)
5. Learning and mastering course of orofacial pain and TMD at Haukeland University hospital, Bergen. Lærings- og mestringskurs for pasienter med uavklarte smerter i kjeve og ansikt | Den norske tannlegeforenings Tidende (tannlegetidende.no)
6. HOME (norjia.com)
7. Fundings from the Norwegian Research Council: Forskningsprosjekt på kjeve- og ansiktssmerter | Den norske tannlegeforenings Tidende (tannlegetidende.no)
8. Handa S, Keith D, Abou-Ezzi J, Rosèn A. Neuropathic orofacial pain: characterization of different patient groups using the ICOP 1st edition, in a tertiary level Orofacial Pain Clinic. Oral Surgery Oral Medicine Oral Pathology and Oral Radiology, 2021;132(6)653-661. DOI: 10.1016/j.oooo.2021.07.021
9. Lund B, Ulmner M, Bjørnland T, Berge T, Olsen-Bergem H, Rosèn A. A disease focused view on the temporomandibular joint: a Delphi process guided classification. Journal of Oral Science, Vol. 62, No. 1, 1-8, 2020. IF 1.556. http://doi.org/10.2334/josnusd.19-0128
10. Nasjonal behandlingstjeneste for uavklarte smerter i ansikt og kjeve - 2022 - Forskningsprosjekter (ihelse.net)

Department of Clinical Dentistry, University of Bergen - Case number 4

Institution: University of Bergen (UiB)
Administrative unit: Department of Clinical Dentistry (IKO)
Title of case study: Prosthetic rehabilitation of the edentulous
Period when the underpinning research was undertaken: 2012-2014
Period when staff involved in the underpinning research were employed by the submitting institution: 2012-present
Period when the impact occurred: 2014

1. Summary of the impact (indicative maximum 100 words)

Previously, edentulous patients were not entitled to reimbursement of cost for dentures. Based on research by Harald Gjengedal at the Institute of Clinical Dentistry, University of Bergen, it was shown that edentulous patients have significantly reduced oral function compared to dentate, with dire consequences such as pain, discomfort, severely reduced chewing ability, increased risk of oral infection and reduced dietary selection. In addition, edentulousness may have psychologic effects that may cause social isolation. Undoubtedly, this condition must be categorised as a major handicap. These findings impacted politically, resulting in public reimbursement by HELFO (The Norwegian Health Economics Administration) in 2014.

2. Underpinning research (indicative maximum 500 words)

As opposed to medical treatment, people over the age of 24 must basically bear the entire cost of dental treatment. There are a few exceptions to this rule for some specific medical and dental conditions, but before 2014, these did not include treatment for total edentulousness. From 2014, a new point (nr.14) was introduced in the regulations for reimbursement for treatment of patients with "loose prostheses/dentures". According to the provisions, benefits were to be "provided to people with a completely edentulous lower jaw who, due to stroke, general illness, anatomy or other conditions, were unable to use a loose-fitting prosthesis. Benefit should be provided for two intraosseous dental implants and a cover prosthesis (overdenture) attached to these implants". A necessary new prosthesis in the upper jaw should also be reimbursed. Importantly, the subjective opinion of the edentate patient was sufficient to trigger the provision.

These new provisions represented a radical change for edentulous patients wearing dentures. The introduction of these came as a direct result of work in the research group Oral Health. Research and a thesis highlighted the significant negative functional, psychological, and social consequences of being edentulous and using dentures. Most importantly, it demonstrated the radical improvement, both above aspects and the patients' oral quality of life after treatment. The treatment consists of inserting two intraosseous dental implants and an overdenture attached to them. This has the effect of fixating the lower denture during function – radically different from an ordinary denture that only relies on retention by the oro-facial muscles.

The patient material consisted of patients with a complete prosthesis in one or both jaws. The study was a survey of the denture wearers' experience with various aspects of denture use, general and oral health status, degree of satisfaction with the dentures, and a specific validated psychometric instrument that measures oral health-related quality of life (OHIP-20). Further, the patient material consisted of completely edentulous individuals who were dissatisfied with their mandibular prostheses. Both the latter articles were randomized clinical trials (RCTs) with a 2-year follow-up.

Even if our research did not directly study social consequences of edentulousness, convincing empirical knowledge indicates social stigma and frequent social isolation for denture wearers with possible wider consequences for mental and somatic health.

It was pointed out that edentulousness and its consequences fall well within the framework of the National Insurance Act's definition of disability, and that it was unreasonable that such a handicap was not publicly financed in the same way as a medical handicap of equivalent severity. Two newspaper chronicles with the same theme, published in the Norwegian newspaper Aftenposten, as well as a broad review of the research, directed public attention to the problem. The consequences of this were a significant public and political interest, and a new reimbursement scheme that was implemented from January 1st 2014.

3. References to the research (indicative maximum of six references)

1. Gjengedal H. Prosthetic rehabilitation of the edentulous. A randomized controlled trial comparing implant-retained mandibular overdentures and conventionally relined mandibular dentures. Dissertation, University of Bergen, 2012.
2. Gjengedal H, Berg E, Bøe OE, Trovik TI. Self-reported oral health and denture satisfaction in edentate and partially dentate. Int J Prosthodont, 2011;24:9-15.
3. Gjengedal H, Dahl L, Lavik A, Trovik TA, Berg E, Boe OE, Malde MK. Randomized clinical trial comparing dietary intake in patients with implant-retained overdentures and conventionally relined denture. Int J Prosthodont 2012;25:340-7.
4. Gjengedal H, Berg E, Grønningsæter AG, Dahl L, Malde MK, Boe OE, Trovik TA. The influence of relining or implant retaining existing mandibular dentures on health-related quality of life: a 2-year randomized study of dissatisfied edentulous patients. Int J Prosthodont 2013;26:68-78.
5. Berg E. Er tannløse pasienter oralt handikappet? Nor Tannlegeforen Tid 2012;122:760-6.
6. Berg E. Er ikke tannløses handicap like viktig som andres. Kronikk, Aftenposten 14/1 2013.

4. Details of the impact (indicative maximum 750 words)

The research by Gjengedal and the research group was the natural continuation of previous research conducted by staff at the sections of Prosthodontics and Odontophobia, Department of Clinical Dentistry largely in collaboration with staff from the Faculty of Psychology, both from the University of Bergen. Thus, between 1983 and 1989, 9 articles focussing on patient satisfaction with complete denture and 17 articles on odontophobia were published in international peer-reviewed journals. The former publications were authored by staff from the Prosthodontic section; some of these, in collaboration with staff from the Faculty of Psychology; the latter publications were authored by a team consisting of staff from the Prosthodontic and Pedodontic sections and Centre of Odontophobia from the School of Dentistry and staff from the Faculty of Psychology. A common denominator of all these publications was exploring patients' subjective reactions to dental treatment, specifically on patient satisfaction and health related quality of life (OHRQoL).

At the end of the 20th and the beginning of the 21st century, sections like Centre of Odontophobia, Community Dentistry and Gerodontology were established at School of Dentistry, University of Bergen and publicly financed, indicating a growing public and political interest in surveying oral health and needs of the community in general and oral health issues of elderlies in particular. A similar relevant political trend at the time was a growing focus on underprivileged groups that for some reason fall outside mainstream healthcare. This all prepared the ground for a political

decision deviating from the traditional separation between publicly funded medical and unfunded dental treatment.

The additions to the scientific environment of the fields of odontophobia, community dentistry and gerodontology to the already established cooperation with the Faculty of Psychology, constituted a fertile background for Gjengedal's studies and dissertation. These fell well within the mentioned trend of growing public interest and the dissertation no doubt triggered public funding for several reasons: His findings documented unequivocally such a significant and long-lasting improvement of OHRQoL of edentulous patients with a simple treatment, that it could not but attract a public interest. Also, the treatment concerned a typically socially underprivileged group such as the edentulous. Moreover, the obvious injustice that patients with severe problems associated with appearance, self-image, potential social dysfunction, often leading to social isolation, chewing, taste, dietary restrictions and frequent discomfort and pain, should not be publicly financed in line with comparable medical conditions, became politically untenable.

The treatment that made an impact on edentulous patients' OHRQoL and satisfaction with their dentures consisted of inserting two mandibular intraosseous dental implants which provide retention and support for a mandibular denture covering the implants (overdenture).

Conventional mandibular dentures are significantly more difficult for the patient to manage than maxillary ones. Both types of dentures, unaided by dental implants, are supported by the mucoperiosteum covering the maxillary and mandibular bones and retained during function, by the oro-facial muscles. The mandibular denture is exposed to three times more load than the maxillary one. It is also significantly more difficult to retain, being situated in contact with an active tongue and movable base of the mouth. This requires an ability to master and learn the required manual dexterity, which frequently is beyond the capability of many elderlies with dire consequences of OHRQoL.

The main reasons why public funding of the above treatment is limited to the mandibular denture, is because this is where the need is greatest. Similar treatment is not publicly funded for the maxillary denture. However, in a mandibular case treated as described above, a new maxillary denture (without dental implants) is also publicly funded to optimise the oral function.

The team behind Gjengedal's dissertation consisted of his supervisors with expertise in dental hygiene (Associate professor T.A. Trovik), prosthodontics (Professor emeritus Einar Berg), nutrition (Researchers M.K. Malde and L. Dahl) and statistics (Associate professor O.E.Bøe) and in addition, oral surgery (Associate professor A.G. Grønningsæter).

5. Sources to corroborate the impact (indicative maximum of ten references)

1. Gjengedal H. Prosthetic rehabilitation of the edentulous. A randomized controlled trial comparing implant-retained mandibular overdentures and conventionally relined mandibular dentures. Dissertation, University of Bergen, 2012.
2. Gjengedal H, Berg E, Bøe OE, Trovik TI. Self-reported oral health and denture satisfaction in edentate and partially dentate. Int J Prosthodont, 2011;24:9-15.
3. Gjengedal H, Dahl L, Lavik A, Trovik TA, Berg E, Boe OE, Malde MK. Randomized clinical trial comparing dietary intake in patients with implant-retained overdentures and conventionally relined denture. Int J Prosthodont 2012;25:340-7.
4. Gjengedal H, Berg E, Grønningsæter AG, Dahl L, Malde MK, Boe OE, Trovik TA. The influence of relining or implant retaining existing mandibular dentures on health-related

quality of life: a 2-year randomized study of dissatisfied edentulous patients. Int J Prosthodont 2013;26:68-78.
5. Berg E. Er tannløse pasienter oralt handikappet? Nor Tannlegeforen Tid 2012;122:760-6.
6. Berg E. Er ikke tannløses handicap like viktig som andres. Kronikk, Aftenposten 14/1 2013. http://www.aftenposten.no/meninger/kronikker/Er-ikke-tannloses-handicap-like-viktig-som-andres-7097477.html
7. Holtet E, Berg E. Jumbo i tannhelsehjelp. Kronikk, Aftenposten 18/6 2013. http://www.aftenposten.no/meninger/debatt/Jumbo-i-tannhelsehjelp-7233572.html
8. Galåsen TEE. Ny forskning endrer trygdereglene. Nor tannlegeforen Tid 2014; 124: 1-13.

Impact case guidelines

Each case study should include sufficiently clear and detailed information to enable the evaluation committee to make judgements based on the information it contains, without making inferences, gathering additional material, following up references or relying on members' prior knowledge. References to other sources of information will be used for verification purposes only, not as a means for the evaluation committee to gather further information to inform judgements.

In this evaluation, impact is defined as an effect on, change or benefit to the economy, society, culture, public policy or services, health, the environment or quality of life, beyond academia.

Timeframes

- The impact must have occurred between 2012 and 2022
- Some of the underpinning research should have been published in 2012 or later
- The administrative units are encouraged to prioritise recent cases

Page limit

Each completed case study template will be limited to **five pages** in length. Within the annotated template below, indicative guidance is provided about the expected maximum length limit of each section, but institutions will have flexibility to exceed these so long as the case study as a whole remains no longer than **five pages** (font Calibri, font size 11). Please write the text into the framed template under the sections 1–5 below. The guiding text that stands there now, can be deleted.

Maximum number of cases permitted per administrative unit

For up to 10 researchers: one case; for 10 to 30 researchers: two cases; for 30-50 researchers: three cases; for 50-100 researchers: four cases, and up to five cases for units exceeding 100 researchers.

Naming and numbering of cases

Please use the standardised short name for the administrative unit, and the case number for the unit (1,2,3, etc) in the headline of the case. Each case should be stored as a separate PDF-document with the file name: [Name of the institution and name of the administrative unit] [case number]

Publication of cases

RCN plans to publish all impact cases in a separate evaluation report. By submitting the case the head of the administrative units consents to the publication of the case. Please indicate below if a case may not be made public for reasons of confidentiality.

If relevant, describe any reason to keep this case confidential:

There is no need to keep it confidential.

University of Bergen (UiB), Department of Biomedicine (IBM) - case 1

Institution: University of Bergen
Administrative unit: Department of Biomedicine (IBM)
Title of case study: Startup **Pluvia Biotech (Pluvia)**
Period when the underpinning research was undertaken: Since 2007 (and before)
Period when staff involved in the underpinning research were employed by the submitting institution:
Period when the impact occurred:

1. Summary of the impact (indicative maximum 100 words)

The innovation and commercialization project on pharmacological chaperones (PCs) for phenylketonuria (PKU) originated from research in Prof. Aurora Martinez group, leading up to the founding of Pluvia in 2016 (www.pluviabiotech.com). Phenylketonuria (PKU) is a rare disease affecting ~1:10 000 and is detected by the newborn screening program. The standard treatment for these patients is a life-long and strict protein-free diet to avoid mental retardation caused by high phenylalanine levels. Pluvia was started to develop new oral medicine for PKU that targets the pathological mechanisms of PKU and increases the capacity to metabolize phenylalanine, allowing the patients to significantly increase the amount of proteins in their diet and possibly quit dietary treatment completely. The research group and Pluvia have worked complementary to understand mechanisms and develop disease modifying therapies, notably PCs, using advanced structural biology and biophysics, drug screening, cellular biology and animal models.

2. Underpinning research (indicative maximum 500 words)

The research of the group focuses on the investigation of the function, stability and regulation of proteins involved in inborn errors of metabolism, for which PKU is a paradigm for this class of disorders. PKU is associated with mutations in phenylalanine hydroxylase (PAH) – the enzyme that catalyzes the BH4-dependent conversion of phenylalanine (L-Phe) to tyrosine (L-Tyr) - leading to reduced activity and high, neurotoxic concentration of L-Phe.

Earlier investigations in the research group on genotype-phenotype correlations and experimental and computational analysis of PAH variants revealed that the main pathogenic mechanism in PKU, as later proved with other inborn errors of metabolism, was a decreased protein stability and increased misfolding caused by the mutations, often leading to decreased half-life of the functional conformation and loss of remaining activity (Pey et al. (2007) AJHG, DOI: 10.1086/521879; Wettstein et al. (2015), DOI: 10.1038/ejhg.2014.114). This understanding led the group to envision the potential of a PC-based therapy for PKU, and to select assays and protocols -notably differential scanning fluorimetry (DSF)- to screen large compound libraries (1-10K) for small molecules that bind to and stabilize PAH variants and counteract instability and misfolding. The primary hits selected in this pioneer work (especially Compounds III-IV) stabilized the functional tetrameric conformation of PAH and PKU associated variants and did not show substantial inhibition of activity. These compounds also significantly increased activity and steady-state PAH protein levels in cells transfected with either normal or variant PAH, providing proof-of-concept *in vitro* of the PC effect (Pey et al. (2008), DOI: 10.1172/JCI34355); Hole et al. (2015) DOI: 10.2174/1389450117666160307143512).

The group members at IBM with main contribution to this research until Pluvia was established for the development of a PC-based therapy for PKU were Jarl Underhaug, Oscar Aubi, Lars Skjerven, Knut Teigen and Ming Ying, besides A. Martinez. All became scientific founders of Pluvia early 2016

together with the Bergen Transfer Office (BTO, now VIS), with Torgeir Vaage as CEO and A. Martinez as CSO. Between 2017 and 2019, Underhaug, Aubi and Skjerven left the group to enter permanent positions outside IBM. Access to facilities at IBM was regulated through a Contract-research-agreement with UiB. From 2018 to 2022, when Pluvia received governmental and innovation funding from The Research Council of Norway (RCN) (See sections 4, 5), a Senior researcher (Ann Kari Grindheim), a researcher (Altanchimeg Altankhuyag), a part-time technician and an Industrial PhD, financed by both Pluvia and RCN (Karina S. Prestegård) were hired. In this period the long-awaited structure of full-length human PAH, relevant for structure-based drug derivatization, was solved by members of the research group and collaborators from CSIC, Madrid (Flydal et al. (2019); DOI: 10.1073/pnas.1902639116), followed by the determination of the structure of homologous tyrosine hydroxylase (TH) by Cryo-EM (Bueno-Carrasco et al. (2022) DOI: 10.1038/s41467-021-27657-y).

Prestegård investigated the proteostatic regulation of PAH, of relevance to understand PAH stability, and characterized a new mouse model of PKU, the *Pah-R261Q*, generated by CRISPR/Cas9 (Aubi, Prestegård et al. (2021), DOI: 10.1038/s41467-021-22107-1) that harbors one the most frequent human mutations. This mouse presented the expected hepatic PAH activity decrease and systemic L-Phe increase with consequent L-Tyr decrease, but also revealed a toxic aggregation of the PAH protein variant, leading to altered lipid metabolism and a metabolic profile indicative of oxidative stress. The work has resulted in a novel understanding of PKU not only as a loss-of-(PAH)-function disorder, but also as a gain-of-function disease, explaining comorbid conditions. Karina successfully defended her thesis in September 2022, and became a Senior researcher in Pluvia.

3. References to the research (indicative maximum of six references)

1. Pey AL, Ying M, Cremades N, Velazquez-Campoy A, Scherer T, Thöny B, Sancho J, Martinez A.
-Identification of pharmacological chaperones as potential therapeutic agents to treat phenylketonuria.
-2008
-J. Clin. Invest. 118(8):2858-67. DOI: 10.1172/JCI34355.
This paper was considered Best paper of year 2008 at the Faculty of Medicine, UiB.

2. Wettstein S, Underhaug J, Perez B, Marsden BD, Yue WW, Martinez A, Blau N.
-Linking genotypes database with locus-specific database and genotype-phenotype correlation in phenylketonuria.
-2015
-Eur J Hum Genet. 23(3):302-9. DOI: 10.1038/ejhg.2014.114.

3. Jung-Kc K, Himmelreich N, Prestegård KS, Shi TS, Scherer T, Ying M, Jorge-Finnigan A, Thöny B, Blau N, Martinez A
-Phenylalanine hydroxylase variants interact with the co-chaperone DNAJC12.
-2019
-Hum Mutat. 40(4):483-494. DOI: 10.1002/humu.23712.

4. Flydal MI, Alcorlo-Pagés M, Johannessen FG, Martínez-Caballero S, Skjærven L, Fernandez-Leiro R, Martinez A*, Hermoso JA*
-Structure of full-length human phenylalanine hydroxylase in complex with tetrahydrobiopterin.
-2019
-Proc. Natl. Acad. Sci USA. 116(23):11229-34. DOI: 10.1073/pnas.1902639116. *Co-corresponding.

5. Aubi O, Prestegård KS, Jung-Kc K, Shi TS, Ying M, Grindheim AK, Scherer T, Ulvik A, McCann A, Spriet E, Thöny B, Martinez A.
-The Pah-R261Q mouse reveals oxidative stress associated with amyloid-like hepatic aggregation of mutant phenylalanine hydroxylase.
-2021
-Nature Commun. 12(1):2073. DOI: 10.1038/s41467-021-22107-1.

6. Bueno-Carrasco MT, Cuéllar J, Flydal MI, Santiago C, Kråkenes TA, Kleppe R, López-Blanco JR, Marcilla M, Teigen K, Alvira S, Chacón P, Martinez A*, Valpuesta JM*.
-Structural mechanism for tyrosine hydroxylase inhibition by dopamine and reactivation by Ser40 phosphorylation.
-2022
-Nature Commun. 13(1):74. DOI: 10.1038/s41467-021-27657-y. *Co-corresponding.

4. Details of the impact (indicative maximum 750 words)

The results and knowledge obtained from research projects in the group of A. Martinez (section 2) have been crucial for the Innovation project "A pharmacological chaperone (PC) therapy for PKU". Since 2016 this work has been performed at Pluvia. Based on the acquired understanding on pathogenic mechanism for the majority of PKU mutations, causing instability and misfolding in the coded variants, we developed and implemented a screening cascade to select the compounds with best PAH-stabilizing effect and stimulation of functional enzyme. The workflow also assisted the rounds of medicinal chemistry (at Charnwood Molecular, UK) that were necessary to obtain selective hits with higher affinity and PC potential as oral therapy.

Central elements to the screening cascade have been the establishment of a cell line (HEK293) with permanent expression of a PAH mutant, as well as the PKU mouse harbouring the same mutation. There are reported more than 1500 PAH mutations, and selection of an appropriate and representative variant is therefore crucial. We chose the R261Q-PAH variant, one of the most prevalent PKU mutant (6% allele frequency worldwide), and it causes unstable and misfolded PAH protein (Wettstein et al. (2015), DOI: 10.1038/ejhg.2014.114). We thus prepared the HEK293-R261Q-PAH cell line for screening and support of the chemistry, followed by validation of efficacy for best leads in the *Pah-R261Q* mouse, which has been thoroughly characterized, revealing it as a robust model of human PKU (Aubi, Prestegård et al. (2021) DOI:10.1038/s41467-021-22107-1).

Using the HEK293- R261Q-PAH cell line we have developed screening assays and workflows both to identify stabilizers of PAH (by In-Cell Western) and to evaluate the increased consumption of L-Phe from cell culture medium (In-Cell functional PAH activity assay). After rounds of medicinal chemistry for hit expansion and lead optimization the molecule PBAS499 (and analogues) demonstrated large and optimal dose-dependent increases in PAH protein levels and L-Phe consumption, both in the cell line and in the *Pah-R261Q*. Based on efficacy data, ADME and PK parameters, we adjusted the in vivo protocol and obtained a reduction in blood Phe by up to 50% after treatment with PBAS499 at 20 mg/kg/dose, reaching non-PKU L-Phe concentrations.

The PC mechanism of the candidate drug was further confirmed by cellular and biophysical studies with isolated PAH protein, showing stabilization of the protein (wild-type (WT) and variant), protection from degradation and decreased aggregation. Notably, *in vitro* differential scanning fluorimetry (DSF) experiments, that provide the melting temperature (T_m) of the protein, have shown the increased thermal stability WT PAH and variant with bound PBAS499. On going structural analyses are confirming the binding mode that was predicted by molecular docking using the structure of full-length human PAH (Flydal et al. (2019) DOI: 10.1073/pnas.1902639116).

Available treatment options for children with PKU, i.e. low-Phe diet and supplementation with the cofactor (BH4) show low adherence and low efficacy, respectively, while the injected PEG-PAL therapy (Palynziq) is only approved for adults and leads to severe side effects. Also, these treatments are not satisfactory as they focus only on L-Phe reduction. This is effective in avoiding the neurological damage seen in untreated PKU patients but does not address the pathological mechanisms, such as instability and misfolding of mutant PAH, which certainly results in loss of PAH function but also cause amyloid-type aggregation in liver for some variants, such as R261Q-PAH (Aubi, Prestegård et al. (2021) DOI: 10.1038/s41467-021-22107-1). These additional clinical manifestations of PKU are not expected to disappear by palliative therapies focusing on L-Phe-reduction but rather by curative therapies, such as PCs, that correct both the loss-of-function and the toxic consequences of misfolding. Furthermore, it is recommended to stay on treatment (keep L-Phe levels low) throughout the patient's life, but this is not feasible due to lack of adherence to the strict and limiting diet, non-responsiveness to BH4 or the strong side-effects of Palynziq. Thus, PKU patients and their families would clearly benefit from a new treatment option.

PBAS499, showing good pre-clinical proof-of-concept in PKU models, clean safety profile, and PK properties supporting once daily oral dosing in humans, was selected as PC-candidate drug December 2022. This compound has the potential to correct unstable and misfolded PAH, increasing the levels of the functional enzyme in cell models and liver, and thereby directly addressing the pathological mechanisms of PKU in addition to enhance the metabolism of L-Phe. This will allow patients to significantly increase the amount of proteinaceous food in their diet and possibly go off dietary treatment completely. Results so far show that PBAS499 will be more effectful than BH4, both with respect to efficacy and mutation spectrum, and thus number of responsive patients, with an expected increased adherence to the treatment as well as improved quality of life.

In conclusion, there is an existing market with unmet need for novel PKU therapeutics. Pluvia plans to conduct first in man studies with PBAS499 in 2025. Oral administration and safety have been proven in *in vitro* and *in vivo* assays. PBAS499 is protected by patents and has been awarded Rare Pediatric Disease Designation (RPDD) by FDA (November 2023) (See section 5). Orphan Drug Designation (ODD) has been filed and filing of Investigational new drug (IND) application and Phase 1 clinical trials are being planned (Targeting a Series A round early 2024 to take the project through Phase 1 and clinical proof-of-concept).

5. Sources to corroborate the impact (indicative maximum of ten references)

1. January 2016, founding of Pluvia (pluviabiotech.com), a startup of UiB, with help from the Bergen Technology Transfer Office (BTO), now VIS. Pluvia develops oral pharmacological chaperones (PCs) to restore enzymatic activity as a novel therapy for PKU.

2. Present status of the company: October 2023, Progress and initiation of program aimed at showing clinical Proof-of- Concept in PKU patients, which ultimately could offer PKU patients a new oral therapy option for a life without dietary constraints. Willem van Weperen has been hired as new CEO (Pluvia Biotech progresses lead product for PKU and appoints Willem van Weperen as CEO | FirstWord Pharma). Pluvia has a small but very capable, well-connected team: A. Martinez (co-founder and CSO), A.K. Grindheim (Director, non-clinical drug development), K. Prestegård (Senior researcher), A. Altankhuyag (researcher), T.A. Kråkenes (part-time technician), Torgeir Vaage (CFO) and Mikael Thomsen (Consultant, clinical).

3. In 2017 Pluvia obtained relevant governmental and private seeding funds via Sarsia Seed. Pluvia attracts interest from new governmental seed funding | Biorecognition | UiB; Martinez krysser fingrene for såkornfondet (bt.no).

4. In 2018 Pluvia obtained a 4-years Project grant from the The Programme for User-driven Research-based Innovation (BIA), Research Council of Norway, which was matched with Investor funds from Sarsia Seed, Trond Mohn Fdn. (TMS) and Investinor. Pluvia - Giving PKU patients a shot at normal life | VIS (visinnovasjon.no)

5. In September 2022 Karina S. Prestegård defended and obtained an Industrial PhD, which was financed by The Research Council of Norway and Pluvia. Prøveforelesning og disputas: Karina Skjervheim Prestegård | Institutt for biomedisin | UiB

6. Rare Pediatric Disease Designation (RPDD) awarded for our candidate drug by FDA, November 2023 (# RPD-2023-758).

7. Fresh patent filed covering PBAS499 (Patent application to IPO, UK, Nr. 2312738.4), which is separate from the earlier awarded 2017 patent family: Hyperphenylalaninemia and treatments thereof (WIPO-PCT WO2017029202A1).

8. Patient involvement: Article in “kommunal landspensjonskasse” (KLP) on the work of Pluvia and the opinion of patients; https://www.klp.no/artikler/pluvia-et-helt-nytt-liv.

9. Patient involvement and sponsor activities: Organization of “Crossing Norway for a cure” in collaboration with National PKU Alliance (USA), to celebrate Asbjørn Følling’s discovery of PKU: https://www.uib.no/en/rg/martinez/131708/pku-ski-trek-event

10. Manuscript in preparation: Grindheim et al. (to be submitted spring 2024) “Pharmacological chaperones targeting variant phenylalanine hydroxylase, a disease-modifying therapy for PKU”, as a collaboration between UiB and Pluvia. A commercial licence has been obtained to publish this work using the *Pah-R261Q* mouse model.

Impact case guidelines

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In this evaluation, impact is defined as an effect on, change or benefit to the economy, society, culture, public policy or services, health, the environment or quality of life, beyond academia.

Timeframes

- The impact must have occurred between 2012 and 2022
- Some of the underpinning research should have been published in 2012 or later
- The administrative units are encouraged to prioritise recent cases

Page limit

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Naming and numbering of cases

Please use the standardised short name for the administrative unit, and the case number for the unit (1,2,3, etc) in the headline of the case. Each case should be stored as a separate PDF-document with the file name: [Name of the institution and name of the administrative unit] [case number]

Publication of cases

RCN plans to publish all impact cases in a separate evaluation report. By submitting the case the head of the administrative units consents to the publication of the case. Please indicate below if a case may not be made public for reasons of confidentiality.

If relevant, describe any reason to keep this case confidential:

There is no need to keep it confidential.

University of Bergen (UiB), Department of Biomedicine (IBM)- case 2

Institution: University of Bergen (UiB)
Administrative unit: Department of Biomedicine (IBM)
TITLE OF CASE STUDY: Intratumoral cypep-1 for the treatment of patients with advanced solid tumors
Period when the underpinning research was undertaken: 2012-2023
Period when staff involved in the underpinning research were employed by the submitting institution: 2012-2023
Period when the impact occurred: 2014 and 2021

1. Summary of the impact (indicative maximum 100 words)

The Translational Cancer Research Group (TCR) at IBM is conducting basic, translational, and clinical cancer research on malignant brain tumours. From basic research, we have developed a new therapeutic molecule (CyPep-1) that led to the establishment of a biotechnology company Cytovation ASA (www.cytovation.com). CyPep-1 is an engineered synthetic peptide with oncolytic properties. Since 2018, CyPep-1 has undergone a complete preclinical development pipeline that resulted in a phase I clinical trials at international centers. These clinical trials have now been completed (see https://clinicaltrials.gov/search?term=cytovation).

Based on positive therapeutic effects seen in several end-stage patients, Cytovation is now in the process of starting Phase II clinical trials. Cytovation is at present communicating with FDA aiming to obtain Orphan Drug Designation for selected cancers.

Since 2018, Cytovation has raised > 300MNOK towards its clinical programs. Cytovation also applied to the European Commission through the European EUROSTARS programme and the application was ranked number 14 out of 500 applications. Cytovation receives support from this programme.

2. Underpinning research (indicative maximum 500 words)

Rolf Bjerkvig in the TCR group receives support through the EUROSTARS programme to further understand the clinical effects seen following CyPep-1 treatment.

CyPep-1 is a first-in-class, non-viral oncolytic peptide. Thus far, oncolytic strategies have used viruses that infect tumour cells and subsequently cause them to lyse. However, oncolytic viruses have substantial drawbacks including patient immunity and off-target effects. CyPep-1 is a non-viral peptide that employs a unique mechanism: it assembles to form pores in the cell wall that causes cell lysis with the release of tumor neoantigens that creates an inflammatory environment, thereby triggering an immune response. The mechanism of action of CyPep-1 is based on a defence mechanism naturally used by cytotoxic T-cells, which has never been exploited in immunotherapy before. The revolutionary effect of CyPep-1 will turn non-responders to immune checkpoint inhibitors (ICIs) responsive, unleashing the full potential of ICI treatment. In fact, through preclinical treatment experiments in animals, we have shown that treatment using CyPep-1 in combination with ICI therapy enhances the therapeutic effects of CyPep-1 on immunological cold tumors. Based on these discoveries, Cytovation is at present collaborating with the pharma company MERCK.

We are currently working on finding a predictive biomarker profile in order to select patients who will respond to treatment. This is an important, unique new approach that will prevent over-treatment of non-responsive patients and increase the effectiveness of CyPep-1 treatment.

Key researcher affiliated with IBM:
Professor Emeritus Rolf Bjerkvig, PI and member of the TCR group.

3. References to the research

Szczepanski C, Tenstad O, Baumann A, Martinez A, Myklebust R, Bjerkvig R, Prestegarden L. Identification of a novel lytic peptide for the treatment of solid tumours. Genes Cancer 2014 May;5(5-6):186-200. doi: 10.18632/genesandcancer.18.

Pagan L, Yfanti C, Rijneveld R, Todd M, Jongste P, Feijen JJ, Klaassen ES, Bouwes Bavinck JN, Struik L, de Koning MNC, Prestegarden L, Niemeyer-van der Kolk T, van Poelgeest MIE, Rissmann R. Results of a randomized, placebo-controlled, first-in-human trial of topical CY-002 in patients with cutaneous warts. J Eur Acad Dermatol Venereol 2022 Oct;36(10):e773-e775. doi: 10.1111/jdv.18291.

4. Details of the impact (indicative maximum 750 words)

Cancer is the second leading cause of death in Europe, responsible for more than 1.9 million deaths in 2020. Activation of the immune system against the tumour, e.g. by Immune Checkpoint Inhibitors (ICIs) like PD-1/PD-L1 and CTLA-4 can reduce tumour size in a variety of cancer types. However, long-lasting benefits of ICIs are achieved in just a minority of patients. The success of ICIs is limited by immune escape of tumours, (so-called "cold" tumours). Moreover, a lack of predictive biomarkers to identify responsive patients hampers the success of ICI treatment. The Bjerkvig group within TCR has performed i*n vitro* experiments with multiple cancer cell lines and normal human cells. CyPep-1 exerted a rapid cytotoxic effect on cancer cells and scanning electron microscopy demonstrated a dose dependent membranolytic effect. The compound was further tested *in vivo* in a 4T1 murine breast cancer model. A significant reduction in tumour growth was observed in the tumours of the treatment group with an average volume of 1.1 cm^3, whereas the control tumours had grown to an average size of 3.5 cm^3 ($P<0.0001$) after 24 days (Szczepanski et al, 2014). The survival analyses showed that the animals assigned to the treatment group lived significantly longer (median survival: 32 days) than those of the control group (median survival: 20 days), indicating a clear treatment effect of CyPep-1 (Szczepanski et al, 2014). Similar results were observed in the B16-F10 melanoma and CT26 colorectal adenocarcinoma mouse models, where CyPep-1 administration alone or in combination with a specific anti-PD-1antibody led to significant decreases in tumour volumes and weight, and increased survival. Preliminary evaluation of the intratumoural lymphoid cell compartments of B16-F10 and CT26 tumours revealed significantly enhanced levels of CD45+ and CD8+ cells, and of the CD8/Treg ratio in the CyPep-1 injected vs the control groups. Following administration of CyPep-1, preliminary evaluation of the intratumoural myeloid cell compartment revealed an increase in CD11c+ dendritic cells levels, and in the ratios of CD8+ cells/M2-type immunosuppressive macrophages and CD8+ cells/myeloid derived suppressor cells (MDSCs). Lastly, preclinical studies in mice with B16-F10 melanoma tumours showed a significant reduction in both primary and contralateral tumour volumes, of which the primary tumours were injected with CyPep-1. The decrease in tumour volumes was enhanced when CyPep-1 was administered in combination with anti-PD-1 antibody. This highlights the capacity of CyPep-1, either alone or in combination with an anti-PD-1 antibody, to delay growth of both injected and non-injected tumours. No immunogenic effects were observed when CyPep-1 was administered in healthy animals.

5. Sources to corroborate the impact (indicative maximum of ten references)

https://www.cytovation.com

https://clinicaltrials.gov/search?term=cytovation

https://prosjektbanken.forskningsradet.no/en/project/FORISS/336799?Kilde=FORISS&distribution=Ar&chart=bar&calcType=funding&Sprak=no&sortBy=date&sortOrder=desc&resultCount=30&offset=0&Organisasjon.2=Næringsliv

The research has led to these patents:

Oligopeptide compounds and uses thereof (US9353156B2)

Combination therapy using a peptide (GB201810058DO)

Peptide-containing compounds for the treatment of neoplastic lesions (CN115003280A)

Treatment of cancers associated with beta-catenin (GB202314749DO)

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There is no need to keep it confidential.

University of Bergen (UiB), Department of Biomedicine (IBM) - case 3

Institution: University of Bergen
Administrative unit: Department of Biomedicine (IBM)
Title of case study: Expanding the knowledge and providing new targets of intervention for Neurodeveleopmental disorders
Period when the underpinning research was undertaken: 2012-2023
Period when staff involved in the underpinning research were employed by the submitting institution: 2012-2023
Period when the impact occurred: 2014 and 2021

1. Summary of the impact (indicative maximum 100 words)

Researchers at IBM are conducting basic, translational and clinical research. The latter aims to increase understanding, diagnosis and treatment of human diseases, including cancer, cardiovascular and neuropsychiatric disorders. The latter field includes research related to common conditions, including anxiety, depression, autism spectrum disorder, dementia, attention deficit hyperactivity disorder (ADHD). As an example, we highlight our work on ADHD and related neurodevelopmental disorders. These conditions have historically been subject to much controversy. There is a strong demand for scientifically well-founded diagnostic tests, prognostic tools and safe and efficient interventions. As detailed below, research performed at IBM during 2012-2022 has been important for developing new treatment guidelines in Norway and internationally.

2. Underpinning research (indicative maximum 500 words)

IBM has a strong research tradition in neurosciences. Different projects explore the structure and function of the nervous system from molecules to intact brain tissues and behavioural implications of cellular, molecular and genetic changes. Haavik and coworkers have investigated key enzymes involved in the synthesis of serotonin and catecholamine transmitters, demonstrated their involvement in human neurological and psychiatric disease and performed genome wide and targeted genetic studies of bipolar disorder and ADHD. They have characterized the active site structure, reaction mechanism, and regulation by phosphorylation and dephosphorylation of several human enzymes, including tyrosine hydroxylase, tryptophan hydroxylases and pyridoxal dependent decarboxylases, all key to neurotransmitter synthesis. They have performed clinical, epidemiological and MRI-imaging/biomarker studies of psychiatric disorders. By extensive international interdisciplinary collaboration, they have discovered of new risk genes and treatment targets across diagnostic boundaries and developed new animal models and shown how old drugs may be repurposed for new indications. As an example of this research, Haavik and his coworkers published 94 PubMed listed articles during 2012-2022 related to the genetics, brain imaging and clinical aspects of ADHD, mainly collected from Norwegian patients. Many of these projects and discoveries have only been possible through extensive international collaborations and pooling of data/resources. Among others, the results showed that ADHD has a strong genetic component, approx. 74% twin/based heritability, many genetic risk loci have been discovered, some of which are shared with other psychiatric disorders. Small but reproducible differences in brain structures have been demonstrated. Pre and perinatal risk factors and prenatal dietary risk factors have been discovered. Patterns of comorbidity have been found, molecular mechanisms have been explored and new treatment targets have been identified. Together, this information provided important scientific background data for the Norwegian clinical guidelines published in 2014 and updated in 2021. The main editor of the clinical guidelines also did her PhD in Haavik's group. This research has been communicated in journals, at scientific conferences, in the popular press/media and most importantly incorporated into many courses and training of clinicians throughout Norway and internationally.

Clinical guidelines in Norway and in other nations are strongly influenced by on published evidence from IBM and others and this has shaped clinical care for large patient groups in Norway and in other countries. These discoveries and published evidence have also decreased prejudice and use of non-evidence based treatments for these patients.

Key researcher affiliated with IBM:
Professor Jan Haavik, PI and member of Neuroscience group.

2. References to the research (indicative maximum of six references)

Cannon Homaei S, Barone H, Kleppe R, Betari N, Reif A, Haavik J. ADHD symptoms in neurometabolic diseases: Underlying mechanisms and clinical implications.
Neurosci Biobehav Rev. 2022 doi: 10.1016/j.neubiorev.2021.11.012

Hegvik TA, Waløen K, Pandey SK, Faraone SV, Haavik J, Zayats T. Druggable genome in attention deficit/hyperactivity disorder and its co-morbid conditions. New avenues for treatment.
Mol Psychiatry. 2021. doi: 10.1038/s41380-019-0540-z

Cross-Disorder Group of the Psychiatric Genomics Consortium. Genomic Relationships, Novel Loci, and Pleiotropic Mechanisms across Eight Psychiatric Disorders. Cell. 2019. doi: 10.1016/j.cell.2019.11.020.

Demontis et al. Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. Nat Genet. 2019 doi: 10.1038/s41588-018-0269-7.

Hoogman et al. Subcortical brain volume differences in participants with attention deficit hyperactivity disorder in children and adults: a cross-sectional mega-analysis. Lancet Psychiatry. 2017 doi: 10.1016/S2215-0366(17)30049-4.

Halmøy A, Klungsøyr K, Skjærven R, Haavik J. Pre- and perinatal risk factors in adults with attention-deficit/hyperactivity disorder. Biol Psychiatry. 2012, DOI: 10.1016/j.biopsych.2011.11.013

4. Details of the impact (indicative maximum 750 words)

Psychiatric disorders in general and ADHD in particular have been subject to much controversy and stigma. Increased scientific knowledge is important for prevention, to aid correct identification and improve treatment of these conditions and to reduce stigma. The research in this field was conducted locally at IBM at University of Bergen (we conducted the first GWAS of ADHD in Norway) but also as parts of large international collaborative efforts. The group was involved in six different European consortia and have collaborated in multiple international consortia where clinical samples are pooled and meta/analyzed and new methods are developed in collaboration, including the ENIGMA consortium and the PGC consortium. It was shown that routine electroencephalographic (EEG) or radiological MRI examination does not provide added diagnostic information in this condition. Previously reported commercial neuropsychological test batteries or commercial genetic testing had limited value. In contrast, we found robust evidence for multiple environmental and molecular genetic risk factors and have summarized the research in the field in meta-analyses and guidelines. Some of the results of the research have been incorporated into concrete clinical guidelines published by clinical competence centres and The Norwegian Directorate of Health among others. The Norwegian Directorate of Health applies and interprets legislation and regulations into national clinical guidelines. Such guidelines are important for harmonization of clinical care. Research at IBM has been important for providing knowledge base for several such guidelines, e.g. management of ADHD, that was considered experimental and in principle illegal for adults in Norway until 2005. The official Norwegian clinical guidelines were published in 2014 and updated in 2021: https://www.helsedirektoratet.no/retningslinjer/adhd

5. Sources to corroborate the impact (indicative maximum of ten references)

Norway:
https://www.helsedirektoratet.no/retningslinjer/adhd
UK:
https://www.nice.org.uk/guidance/qs39

UiB, The Faculty of Psychology (DPF), Case number 1

Institution: University of Bergen (UiB)
Administrative unit: The Faculty of Psychology (DPF)
Title of case study: Perceived Risk and Precautions during a Pandemic Outbreak (PANDRISK)
Period when the underpinning research was undertaken: 07.01.2020 - 30.06.2023
Period when staff involved in the underpinning research were employed by the submitting institution: Both researchers in the project were employed at UiB both before and after the project
Period when the impact occurred: winter 2020 - ongoing

1. Summary of the impact (indicative maximum 100 words)

The project collected, analysed and disseminated research about public reactions to and behaviour during the ongoing pandemic. We emphasized fast presentation of results to stakeholders, decision-makers, fellow researchers, and the general public. We had extensive popular science dissemination about how people responded to the pandemic. We collaborated with stakeholders such as FHI to share our preliminary results, and to direct our further research towards research questions they were interested in. We emphasized fast turnaround to provide information that could guide policy decisions, guide further research and intervention studies. We made several extensive datasets public within months of collection.

2. Underpinning research (indicative maximum 500 words)

When:
The PANDRISK was funded by NRC's "emergency call" for COVID-19 projects (see funded dates on top of the report). Data collection for the underpinning research was done from March 2020 until June 2022. Collaborations with other researchers and stakeholders began at the start of data-collection. Popular science dissemination and preprints began in May 2020. The first peer-reviewed papers were published in 2021, with other papers currently in review and future papers planned. The project aimed to provide actionable knowledge and to adjust the research to a continuously developing situation. The PANDRISK project measured variables related to how people were affected by and made decisions related to the COVID-10 pandemic.

What:
We focused on investigating how individuals perceived the ramifications of the pandemic and how this perception influenced factors such as: behavioural patterns, susceptibility to infection, potential to transmit the virus, concerns about contracting the virus, levels of anxiety, and mental well-being. The project also aimed to examine how personality traits like coping mechanisms, optimism, and motivation could account for the variations in how individuals responded to a pandemic outbreak.

Outline of research:
At nine time-points over the course of 18 months, a representative Norwegian sample from the "Norwegian Citizen Panel" (N up to = 5,541) answered questions about the pandemic. In addition to descriptive survey studies, confirmatory associations between responses were tested, and survey experiments were performed. In-depth interviews were conducted to delve into participants' experiences related to risk perception, coping strategies, and adherence to quarantine measures. Attitude and behaviour were measured for COVID-19 patients undergoing

medical follow-up and from people seeking COVID-19 testing. A smartphone application was also employed to collect real-time information about day-to-day encounters and the psychological consequences of the pandemic outbreak.

Key findings:
Among the project's main findings, were that the Norwegian public were to track the Norwegian public's assessment of risk, their attitudes and compliance to infection control measures (keeping physical distance, wearing facemask, vaccination) throughout the first 18 months of the pandemic. We found that risk perception was mainly realistic, and compliance was very high in the beginning of the pandemic, although falling somewhat as time went on, but responding to surges in infection numbers. In contrast to most previous research, we did not find a strong association between how people saw the risk and their willingness to comply with infection control measures. Instead, we found that motivation to protect others was a stronger predictor. We measured the level of fatigue people had towards infection control measures, and their reasons for not following them, and found that a social drive was important for both. We found that different ways of phrasing the message had some effect on people's willingness to vaccinate, which may have consequences for public health messaging. We found that the public mostly disliked infection control measures that restricted their social life, and stated social reasons for not following the measures.

By whom:
The project was managed by professor Bjørn Sætrevik, and day-to-day work on materials, data-collection, analysis and later dissemination was headed by Sebastian Bjørkheim (now PhD candidate on an associate project). All key researchers are at the Department of Psychosocial Science, Faculty of Psychology, UiB.

3. References to the research (indicative maximum of six references)

- Sætrevik, B. (2021). Realistic Expectations and Prosocial Behavioural Intentions to the Early Phase of the COVID-19 Pandemic in the Norwegian Population. *Collabra: Psychology, 7*(1): 18698. https://doi.org/10.1525/collabra.18698
- Sætrevik, B., Bærøe, K., Carlsen, B., & Bjørkheim, S.B. (2021). Nordmenn stolte på offentlig håndtering, informasjon og råd i koronapandemiens første måneder. *Tidsskrift for Velferdsforskning 24*(2), 1-16. https://doi.org/10.18261/issn.2464-3076-2021-02-06
- Bjørkheim, S., & Sætrevik, B. (2022). Manipulating risk of infection and appeal to public benefit increase compliance with infection control measures in a hypothetical pandemic scenario. *PLOS ONE, 17*(11), e0274024. https://doi.org/10.1371/journal.pone.0274024
- Gregersen, T., Doran, R., Böhm, G., & Sætrevik, B. (2022). Did concern about COVID-19 drain from a 'finite pool of worry' for climate change? Results from longitudinal panel data. *The Journal of Climate Change and Health, 100144.* https://doi.org/10.1016/j.joclim.2022.100144
- Sætrevik, B., & Bjørkheim, S. (2022). Motivational factors were more important than perceived risk or optimism for compliance to infection control measures in the early stage of the COVID-19 pandemic. *PLOS ONE 17*(9). https://doi.org/10.31234/osf.io/njhvu
- Friehs, M. T., et al. (2022). Warmth and competence perceptions of key protagonists are associated with containment measures during the COVID-19 pandemic: Evidence from 35 countries. *Scientific Reports, 12*(1), 21277. https://www.nature.com/articles/s41598-022-25228-9

4. Details of the impact (indicative maximum 750 words)

The aim of the project was to continuously describe the changes in the ongoing pandemic, to interpret the developments based on past research and theory, and to quickly make available the underlying datasets for other researchers. A further aim was to provide support and liaison with

national and regional agencies and stakeholders, to provide scientific knowledge to base decisions on.

To achieve this impact, we had a fast turnaround from planning, data-collection, preliminary analysis and dissemination. Throughout the project period we reached out and accepted invitations to collaborate with governmental and municipal agencies, public health and first line medical care, and NGOs. This served to continuously adjust our research focus to adjust to the ongoing situation, to explore under-researched areas, and to respond to specific knowledge gaps that was needed to adapt to the situation.

To disseminate to and initiate collaborations with the scientific community, we participated in, accepted invitations to talk at, and coordinated a number of conferences, seminars and meetings. These activities are listed on the project website (https://www.uib.no/en/pandrisk/158878/presentations). One of our impacts have been to collaborate with FHI and other researchers to plan and design additional data-collections about the current and future health crisis. Further, we have work along with the UiB pandemic centre towards synthesizing the extensive and idiosyncratic research that has been generated on this topic.

The scientific publication from the project has attempted to balance between emphasizing speed in disseminating findings from a time-sensitive issue against the more meticulous process of peer-reviewed scientific journals. The approach has been to publish open access preprint manuscripts once they have been internally reviewed, and to invite feedback on these from the scientific community. These manuscripts have later been submitted to peer review at established open-access scientific journals.

We see as one of the main impacts of the project to curate and make available the collected datasets. The most important of these are the online panel survey datasets from a representative sample of adult Norwegians, where the same people can be traced at nine time-points throughout the pandemic (N up to 5,541). These and other datasets have been posted publicly at the "Open Science Framework" as quickly as they could be verified, in order to be made available to others researching this time-critical issue. The datasets can be found here:

- Bjørkheim, S., & Sætrevik, B. (2022, November 17). *Datasets from representative surveys.* Retrieved from https://osf.io/s46ax/.

To inform stakeholders and the general public about our findings, we emphasized popular science dissemination in the early phase of the pandemic. This took the form of feature articles, interviews, opinion pieces and essays in national and regional online, print and broadcast media. See list of appearances below:

- NRK TV: Interview at national news broadcast, 03.05.20.
- Bergensavisen and Haugesunds Avis: Overraskende mange sier de gjør sitt beste for å følge rådene, 03.05.2020.
- Regional newspaper (Bergen Tidende): Folk har realistiske tanker om det som skjer nå, 25.04.2020.
- Regional newspaper (Bergensavisen, BA) feature about the retrospective patient survey: De første koronasmittede fulgte i mindre grad smittevernrådene, 15.01.21.
- National radio P4 interview about perceived load of infection control measures, 06.01.22.
- Popular science website «Forskning.no» about perceived load of infection control measures: Forskere advarer om at folk begynner å bli lei noen av koronatiltakene, 08.01.22.

- National newspaper (Aftenposten online): Vi følger smitteverntiltak hvis vi ser andre rundt oss gjøre det, 01.02.22.
- National newspaper (Aftenposten print edition, front page): «Hjemmekontor struper det sosiale livet» 02.02.22.
- National newspaper (Aftenposten print edition): «Vi følger smitteverntiltak hvis vi ser andre gjør det» 03.02.22.

Additional impacts of the project have been to train an early career researcher in theoretical, methodological, analytical, and dissemination of the relevant research. The project has also had the impact of securing additional funding for a PhD project (the POSTRISK project), which will be used to continue the analysis and publication of the data collected in the PANDRISK project, and to extent the research in direction of long-lasting effects of the COVID-19 pandemic on how the public perceives risk and responds to health crises.

5. Sources to corroborate the impact (indicative maximum of ten references)

At the Norwegian Institute of Public Health: Marit Knapstad, Simon Øverland, Christine Holst.
At Bergen Emergency Health: Dagrun Waag Linchausen.
At Haukeland University Hospital: Rebecca Cox.
At the UiB Pandemic Centre: Esperanza Dias.

UiB, The Faculty of Psychology (DPF), case number 2

Institution: University of Bergen (UiB)
Administrative unit: The Faculty of psychology (DPF)
Title of case study: Cognitive training and brain stimulation for auditory hallucinations in schizophrenia
Period when the underpinning research was undertaken: 2012-2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2012-2022
Period when the impact occurred: 2012-2022

1. Summary of the impact (indicative maximum 100 words)

The impact comes from two back-to-back ERC Advanced Grant research projects in the evaluation period (2012-2022) headed by Professor Kenneth Hugdahl. Impact has been two new treatment/training approaches for reduction of frequency of hallucinatory experiences, based on a neurobiological model which identifies underlying mechanisms for auditory hallucinations. These approaches are development of a smartphone app for daily use by the patient to train attention focus, and application of brain stimulation technique for inhibiting the onset of a hallucinatory episode.

2. Underpinning research (indicative maximum 500 words)

Auditory hallucinations, the experience of "hearing voces" in the absence of an external speech source, is a severe symptom of schizophrenia. As such it distorts the reality view of the patient, leading to withdrawal and isolation. Up to 80% of all individuals with a schizophrenia diagnosis also experience auditory hallucinations, and although drug treatments helps, there is a large proportion of patients for which it does not help, and side-effects are common for those it does help. An issue with current treatments for schizophrenia is that they affect across symptoms, not considering the specific symptom profile. The ERC projects had a focus on the symptom, rather than the diagnosis, with the aim to map out the underlying neurobiological mechanisms of the disorder. The primary method for this purpose was magnetic resonance imaging of the brain, and particularly functional magnetic resonance imaging (fMRI). The research resulted in the formulation of a theoretical model in 2015 and further expanded in 2016 which views auditory hallucinations as caused by spontaneous neuronal hyperactivity (bottom-up) originating in the language areas in the temporal lobe which is not inhibited (top-down) due to frontal lobe hypoactivity. Thus, the normal balance between excitatory and inhibitory neuronal processes are therefore set out of play in auditory hallucinations. From this model two hypothesis were derived; a) that the imbalance could be restored by dampening activity in the temporal lobe while at the same time increasing activity in the frontal lobe, which would prevent initiation of an episode, b) use cognitive training to improve cognitive control over their voices, facilitate listening to outer voices, and at the same time inhibit listening to inner voices. The first hypothesis could be achieved by developing a clinically relevant brain stimulation technique, transcranial DC stimulation (tDCS) which would induce neuronal excitation at frontal lobe sites and neuronal inhibition at temporal lobe site. The second hypothesis could be achieved by developing a smart-phone app to be implemented on a device the patient holds, which would re-focus attention away from the inner "voices" to the outer real voices. In this way patients would learn how to ignore the "voices" and attend to the social environment around them.

Key researchers; Kenneth Hugdahl, professor 2012-2022, Marco Hirnstein (postdoc/professor 2012-2022), Josef Bless (postdoc 2012-2018), Iris Sommer (professor 2012-2022), Erik Johnsen (psychiatrist, 2012-2020); Lin Lilleskare, research nurse (2016-2022)

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3. References to the research (indicative maximum of six references)

Hugdahl, K. (2015). Auditory hallucinations: A review of the ERC "VOICE" project. World Journal of Psychiatry, 5, 193-209. https://doi.org/10.5498/wjp.v5.i2.193

Visser, L., Sinceviciute, I., Sommer, I., Bless, J. (2018). Training switching focus with a mobile-application by a patient suffering from AVH, a case report, Scandinavian Journal of Psychology, 2018, 59, 59-61, DOI:10.1111/sjop.12415

Bless, J., Hjelmervik, H., Torsheim, T., Gudmundsen, M., Larøi, F., Holma, I., Arola, A, Korkila, J., Hirnstein, M., Marquardt, L., Kusztrits, I., Smelror, R. E., Agartz, I., Hugdahl, K. (2020). Temporal signatures of auditory verbal hallucinations: An app-based experience sampling study. Schizophrenia Research, 215, 442-444, doi: 10.1016/j.schres.2019.11.020

Marquardt, L., Craven, A.R., Hugdahl, K., Johnsen, E., Kroken, R.A., Kusztrits, I., Specht, K., Thomassen, A.S., Weber, S., Hirnstein, M. (2022**).** Pilot-RCT finds no evidence for modulation of neuronal networks of auditory hallucinations by transcranial direct current stimulation. Brain Sciences, 12, 1382. https://doi.org/10.3390/brainsci12101382

4. Details of the impact (indicative maximum 750 words)

The research which underpinned the dichotic listening part of the impact case took place within the ERC Advanced Grant "VOICE" project between 2012 and 2016 and followed-up in the ERC Advanced Grant "ONOFF" project between 2016-2021. The research was focused on understanding neurocognitive and neurobiological factors behind auditory hallucinations in schizophrenia. The research had led to the development of a theoretical model for this which view auditory hallucinations as the result of an imbalance between excitatory and inhibitory processes at the neuronal level. This has the consequence that cognitive factors, like attention, is focused on the inner "voices" at the expense of the patient not being able to attend to and interact with the outer world. The project PI professor Kenneth Hugdahl had for other purposes developed a cognitive test paradigm based on presentation of auditory speech sounds to manipulate focus of attention to the left or right side of auditory space. An idea now came up in the ERC project that this could be used as a cognitive treatment for auditory hallucinations, but by applying the test to re-direct attention focus from the inner "voices" to the outer voices. A young PhD student, Josef Bless, suggested that instead of having the patient come to the laboratory many times to be tested (which would be problematic considering the nature of the disorder), one could make the test into an iPhone app. This was not immediately met with approval because at that time the use of smart-phone apps was something new and untested in psychiatry and psychological treatment, unlike today when such tools are abundant for both diagnostic and treatment purposes. However, Bless did not give in and finally had his way that this was the way to go and an app was developed out of Hugdahl's original dichotic listening test around 2012 and implemented into clinical testing a few years later. The app was later used in the "Voices Clinic" at the Utrecht medical University Center, Netherlands headed by Professor Iris Sommer. The app is today in use for patients after referral and is typically administered by a nurse.

The tDCS brain stimulation part of the impact case came out the same theoretical model for the understanding of auditory hallucinations as excitatory/inhibitory imbalance at the neuronal, brain, level of explanation. The model was a direct consequence of the research that had been conducted in the two ERC Advanced Grant projects mentioned above. The transition from research to an impact case came when a former Postdoc on the ERC projects, Marco Hirnstein

suggested that perhaps the imbalance could be reversed by implementing a simple brain stimulation technique, known as trans-cranial DC stimulation, or tDCS. The tDCS apparatus utilises a common battery with two electrodes connected to the poles of the battery, one to the anode (-) and one to the cathode (+). Current over the anode lowers the threshold for a neuron firing, while current over the cathode increases the threshold. An idea was then formed, and Hirnstein established his own research project in 2016 with own funding based on the idea, that applying tDCS over the temporal and frontal regions of the brain could be a way of restoring the imbalance which caused auditory hallucinations. The nurse administering the tDCS treatment would fasten the anode electrode over frontal brain regions and the cathode over temporal brain regions. Training with tDCS would then occur for a period of weeks. The tDCS application has proven not to work for all patients handicapped with auditory hallucinations, but for a selected sub-sample, and we currently do not know why. Similar results are seen also in international studies.

5. Sources to corroborate the impact (indicative maximum of ten references)

Visser, L., Sinceviciute, I., Sommer, I., Bless, J. (2018). Training switching focus with a mobile-application by a patient suffering from AVH, a case report, Scandinavian Journal of Psychology, 2018, 59, 59-61, DOI:10.1111/sjop.12415

Marquardt, L., Craven, A.R., Hugdahl, K., Johnsen, E., Kroken, R.A., Kusztrits, I., Specht, K., Thomassen, A.S., Weber, S., Hirnstein, M. (2022**).** Pilot-RCT finds no evidence for modulation of neuronal networks of auditory hallucinations by transcranial direct current stimulation. Brain Sciences, 12, 1382. https://doi.org/10.3390/brainsci12101382

UiB, The Faculty of Psychology (DPF), Case number 3

Institution: University of Bergen (UiB)
Administrative unit: The Faculty of Psychology (DPF)
Title of case study: Therapy Light rooms / Innovative Light solutions to improve health and quality of life
Period when the underpinning research was undertaken: 2017-present day
Period when staff involved in the underpinning research were employed by the submitting institution: 2017-present day
Period when the impact occurred: 2017-present day

Summary of the impact

This impact case highlights a groundbreaking **randomized controlled trial** and associated research examining the impact of a dynamic ceiling-mounted **light therapy** on nursing home patients with dementia. The results demonstrated **immediate benefits**, improving **sleep,** and reducing **neuropsychiatric symptoms**, especially **depression**. Beyond individual benefits, the project influenced **public policy** and services, prompting a heightened focus on enhancing lighting in both the light and health industries. The adoption of advanced LED technology not only proves **economically and environmentally advantageous** but also holds the potential to **decrease reliance on costly medications** for sleep and behavioural issues. Ongoing research aims to pinpoint how light can enhance cognitive functioning in older adults and those with dementia.

2. Underpinning research

This impact case is based on a body of work spanning from 2017 until present day, mainly comprising the scientific project "Therapy Light Rooms for Nursing Home Patients with Dementia: Designing Diurnal Conditions for Improved Sleep, Mood and Behavioural Problems" (DEM.LIGHT, 2017-2020, NCT03357328, Public Sector Scheme, RCN 259987), but also paving the way for the FRIPRO funded project "Exploring New and optimal Light conditions for improved memory and mood" (ENLIGHT, 2020-present, RCN 275305). Previous research has demonstrated that Behavioral and Psychological Symptoms of Dementia (BPSD) and disturbed sleep affect most people with dementia, and that psychotropic drug therapy, antipsychotics in particular, has limited efficacy and potentially serious side effects. In addition to adequate pain treatment, **non-pharmacological, person centered,** therapy is essential for a person with dementia's **health and quality of life**[1,2].

The 24-week randomized controlled DEM.LIGHT trial (RCT lasting 2017-2018, last PhD completed 2021) included 79 nursing home patients with dementia. We hypothesized that light therapy would have a positive effect on sleep, circadian rhythm and BPSD. The intervention units received a ceiling mounted dynamic LED light solution, emulating a natural variation in light intensity and wavelength, with a peak in melanopic equivalent daylight illuminance mid-day; accentuating the light-dark cycle that entrains human circadian rhythms. The DEM.LIGHT project also included dementia units at all municipal nursing homes in Bergen, in a baseline mapping of existing light conditions compared to industrial and scientific standards for optimal lighting for human circadian regulation[3]. In addition, an extensive systematic review of the literature covering light therapy for people with dementia was performed[2].

The baseline mapping demonstrated that light conditions in nursing home dementia units were below the industrial standards, regardless of season, and not suitable according to scientific standards to support a robust circadian rhythm[3]. The review found that light is a promising

intervention, yet there were large methodological discrepancies between studies, with mixed and at times contradicting results, calling for better-quality RCTs[2].

The trial demonstrated improvements in sleep[4], BPSD[5], depression[5] and circadian rhythms[6], with the strongest effects being evident in depression symptoms mid-winter (trial week 16)[5].

The output of the DEM.LIGHT project prompted the need to conduct experimental paradigms (ENLIGHT 2020-present day, post pandemic lab opening late 2021), including old adults and people with dementia, to investigate the acute day-time effects of different light conditions on cognition and mood. There is a need to untangle how light may be used most beneficially for this population, as it is possible that acute effects on alertness, cognitive performance and mood is just as important as the effects on sleep and circadian rhythms to **optimize health, functioning and quality of life.** Moreover, recent advances suggest differential neural pathways for the acute effects of light on affect, as well as a differential effects of light wavelength in older adults. By including young healthy controls, the ENLIGHT project aims to advance further knowledge on unique effects of light in older adults and people with dementia. (ENLIGHT, RCN 275305).

DEM.LIGHT Project Management Committee, Faculty of Psychology, UiB

- Prof. Elisabeth Flo-Groeneboom (PI, Dept. Clinical Psychology, Faculty of Psychology, UiB)
- Prof. Emerita Inger Hilde Nordhus (Dept. Clinical Psychology, Faculty of Psychology, UiB)
- Prof. Ståle Pallesen (Dept. Psychosocial Psychology, Faculty of Psychology, UiB)

DEM.LIGHT Employees, Faculty of Psychology, UiB

- Gunnhild Hjetland (PhD, Dept. Clinical Psychology, Faculty of Psychology, UiB)
- Eirin Kolberg (PhD, Dept. Clinical Psychology, Faculty of Psychology, UiB)
- Eirunn Thun (Postdoc, Dept. Clinical Psychology, Faculty of Psychology, UiB)

ENLIGHT Management Committee, Faculty of Psychology, UiB

- Prof. Elisabeth Flo-Groeneboom (PI, Dept. Clinical Psychology, Faculty of Psychology, UiB)
- Prof. Emerita Inger Hilde Nordhus (Dept. Clinical Psychology, Faculty of Psychology, UiB)
- Prof. Lin Sørensen (Dept. Biological and Medical Psychology, Faculty of Psychology, UiB)
- Assoc. Prof. Endre Visted (Dept. Clinical Psychology, Faculty of Psychology, UiB)
- Assoc. Prof. Berge Osnes (Dept. Clinical Psychology, Faculty of Psychology, UiB)

ENLIGHT Employees, Faculty of Psychology, UiB

- Louise Bruland Bjerrum (PhD, Dept. Clinical Psychology, Faculty of Psychology, UiB)
- Oda Bugge Kambestad (PhD, Dept. Clinical Psychology, Faculty of Psychology, UiB)
- Malika Elise Hansen (PhD, Dept. Clinical Psychology, Faculty of Psychology, UiB)

4. References to the research

1. Husebo, B. S., Achterberg, W., & Flo, E. (2016). Identifying and managing pain in people with Alzheimer's disease and other types of dementia: a systematic review. *CNS drugs*, *30*, 481-497. doi: https://doi.org/10.1007/s40263-016-0342-7

2. Hjetland, G. J., Pallesen, S., Thun, E., Kolberg, E., Nordhus, I. H., & Flo, E. (2020). Light interventions and sleep, circadian, behavioral, and psychological disturbances in dementia: A systematic review of methods and outcomes. Sleep Medicine Reviews, 52, 101310. doi: https://doi.org/10.1016/j.smrv.2020.101310

3. Kolberg, E., Pallesen, S., Hjetland, G. J., Nordhus, I. H., Thun, E., & Flo-Groeneboom, E. (2022). Insufficient melanopic equivalent daylight illuminance in nursing home dementia units across seasons and gaze directions. *Lighting Research & Technology*, *54*, 163-177. doi: https://doi.org/10.1177/1477153521994539

4. Hjetland, G. J., Kolberg, E., Pallesen, S., Thun, E., Nordhus, I. H., Bjorvatn, B., & Flo-Groeneboom, E. (2021). Ambient bright light treatment improved proxy-rated sleep but not sleep measured by actigraphy in nursing home patients with dementia: a placebo-controlled randomised trial. BMC Geriatrics, 21, 1-15. doi: https://doi.org/10.1186/s12877-021-02236-4

5. Kolberg, E., Hjetland, G. J., Thun, E., Pallesen, S., Nordhus, I. H., Husebo, B. S., & Flo-Groeneboom, E. (2021). The effects of bright light treatment on affective symptoms in people with dementia: a 24-week cluster randomized controlled trial. BMC Psychiatry, 21, 1-16. doi: https://doi.org/10.1186/s12888-021-03376-y

6. Kolberg, E., Pallesen, S., Hjetland, G. J., Nordhus, I. H., & Flo-Groeneboom, E. (2021). The Effect of Bright Light Treatment on Rest–Activity Rhythms in People with Dementia: A 24-Week Cluster Randomized Controlled Trial. Clocks & Sleep, 3, 449-464. doi: https://doi.org/10.3390/clockssleep3030032

4. Details of the impact

As demonstrated in the above mentioned literature[2-6], the research results showed an **immediate benefit** for the included participants, as the light therapy **improved sleep** as observed by the nursing home staff and **neuropsychiatric symptoms**, in particular **depression**. Additionally, the use of new and improved LED technology is more **economic** and **environmentally** friendly with less power consumption. In the long run, the use of dynamic and human centric lighting may potentially reduce the use of costly medications related to sleep and behavioural and psychological symptoms.

The project also has had **clinically relevant impact** for nursing home patients and other patient groups as there has been an increased focus and prioritizing both in the light industry as well as in the health industry to improve lighting not only for optimal vision, but also to attain the proven health benefits. With our research results, we aimed to impact prioritizing and implementation of better light solution as part of **public services** through a targeted **dissemination to public policy makers,** the **general public, health worker** and **users.** Before, during and after the project period, researchers have disseminated relevant knowledge through various channels aiming to facilitate implementation of innovative light solutions. This included talks to politicians, municipal and health trust leaders and staff[7,8,9], inclusion of staff in international workshops (digital)[10], media coverage[11], Hosting of popular science research nights[12], as well as talks to light industry engineers and entrepeneurs[12].

Importantly, the DEM.LIGHT project leader arranged a meeting with the **health minister** Bent Høie, together with the staff of one of the included nursing home, municipal leaders, the UiB rector Dag Rune Olsen of UiB, and press (22.06.2017)[9]. In addition to listening to a scientific talk about light, and an experience-based talk from the nursing home staff, the health minister met with and talked with nursing home residents living in the unit equipped with the innovative light solution.

More recently, the DEM.LIGHT primary investigator, PI, Flo-Groeneboom, was a guest at the Lindmo talkshow (25.03.2022), talking about sleep and light therapy. Lindmo is a Norwegian talk show hosted by Anne Sandvik Lindmo. The program runs on Friday evenings and is considered the most popular/seen talk show in Norway[11].

Flo-Groeneboom curated and hosted the 2023 Researcher Night in Bergen (22.09.2023). The show called “The Power of Sleep”, invited leading researchers and users to talk about sleep through the

lifespan with a particular focus on the use of light therapy. The Show had an audience of approx. 200 people and was also turned into a podcast[12].

Although it is difficult to obtain clear cut data on **societal impact**, the project's industry partner Glamox ASA has reported a notable change in municipality- and state led building projects that develop dynamic human centric lighting. Glamox ASA reported an increase of over 4000% from 2016 until 2022. The technical advances is soon ahead of research, inviting more scientific projects to investigate the overall impact on public **health and quality of life** when an increasing number of public buildings (Hospitals, schools, nursing homes and more) provide improved lighting conditions.

5. Sources to corroborate the impact

7. https://www.facebook.com/events/scandic-bergen-city/olaviken-konferansen-2019/347410905973268/
8. https://www.bergen.kommune.no/politikere-utvalg/api/fil/bk360/5847913/Framstilling-Statusmelding-Plan-for-forskning-innovasjon-og-utdanning-i-de-kommunale-helse-og-omsorgstjenestene-2016-2019 (see «offentlig PhD»)
9. https://www.uib.no/psyfa/108945/lysere-tider-demenspasienter
10. https://ageoflightinnovations.com/curating/
11. https://tv.nrk.no/serie/lindmo/2022/MUHU15001122
12. https://alrekhelseklynge.no/arrangementer/alrekdagene2023-forskernatt-sovn/

UiB, The Faculty of Psychology (DPF), Case number 4

Institution: University of Bergen (UiB)
Administrative unit: The Faculty of Psychology (DPF)
Title of case study: The Bergen 4-day Treatment (B4DT)
Period when the underpinning research was undertaken: 2012 - current
Period when staff involved in the underpinning research were employed by the submitting institution: From 1992 and 2012
Period when the impact occurred: 2012 – current

1. Summary of the impact (indicative maximum 100 words)

In this case study, the specific impact being described is the Bergen 4-Day OCD Treatment (B4DT), developed by professors Gerd Kvale and Bjarne Hansen. While traditional therapy for Obsessive-Compulsive Disorder (OCD) typically requires several months to yield positive results, the B4DT has been demonstrated to effectively treat OCD in a significantly shorter timeframe, specifically within just four days. For this work the developers were recognized by Time Magazine as among the "50 Most Influential in Health 2018," (Time Magazine, 50 most influential in health 2018). The B4DT has had major impact for treatment dissemination, treatment development and research into basic mechanisms of OCD and anxiety related disorders.

2. Underpinning research (indicative maximum 500 words)

Bergen 4-day treatment (B4DT) is an innovative approach has been widely implemented, with 54 Norwegian clinics certified to deliver B4DT, reaching almost 2000 patients in Norway in 2023. Our research encompasses a broad spectrum of clinical studies, particularly focusing on Obsessive-Compulsive Disorder (OCD), panic disorder (PD), and social anxiety disorder (SAD). The research of the format and the network established, have had large impact on clinical research, but also in the field of genetics, epigenetics and fMRI.

From January 1, 2020, to January 1, 2023, a substantial cohort of 3577 patients consented to participate in our clinical studies. This period marks significant progress in our research endeavors, yielding valuable insights into these disorders and their treatment. The versatility of B4DT has been a key finding, demonstrating clinical efficacy across various disorders, clinics, therapists, and cultural contexts.

Our research has been particularly important in the genetic and epigenetic understanding of OCD. Collaborating in the largest Genome-Wide Association Study (GWAS) on OCD, our team contributed to the identification of 30 genomic loci associated with the disorder. Moreover, an epigenome-wide analysis of 400 participants revealed differentially methylated regions that correlate with treatment response, even at baseline. This finding is crucial for understanding the biological underpinnings of OCD and improving treatment strategies.

In addition to OCD, our research has extended to include clinical data and saliva samples from 438 patients with PD and 293 with SAD. Neuroimaging data has also been collected from 66 patients, both pre- and post-treatment, as well as during follow-up sessions. This comprehensive data collection is instrumental in advancing our understanding of these disorders and their treatment.

The richness of the data accumulated has led to an increase in scientific publications and presentations at prominent international conferences, such as the World Congress of Psychiatry

Genetics. Our findings not only contribute to the academic understanding of these disorders but also hold practical implications for treatment approaches. The ongoing analyses, including biomarker identification and genetic x epigenetic studies, are set to revolutionize our understanding of brain structure changes in response to treatment.

This body of work represents a significant contribution to the field of psychological disorder treatment and research. Our findings underscore the importance of integrated approaches that combine clinical, genetic, and neuroimaging data to advance treatment strategies and patient care.

Our clinical research on the Bergen 4-day treatment (B4DT) for psychological disorders has been the core component of the research. This framework is very suitable also for combining the clinical research with research in the field of genetics, epigenetics and fMRI. Our research have been greatly enriched by a comprehensive network of both national and international collaborators. These experts, with their diverse specializations in genetics, epigenetics, brain imaging, and clinical psychology, have played pivotal roles in advancing our understanding and treatment of disorders such as Obsessive-Compulsive Disorder (OCD), panic disorder (PD), and social anxiety disorder (SAD).

Key Researchers and Their Contributions:
Based on the B4DT, several institutions collaborated in establishing the Bergen Center for Brain Plasticity (BCBP). The Centre is currently directed by Professor Bjarne Hansen, with Associate Professor Kristen Hagen as co-director. The aim of the centre is to build on the large clinical infrastructure to enhance further clinical dissemination, combined with research organized in the following work packages:

Clinicial Psychology:
Ass. Prof. Kristen Hagen, NTNU and BCBP, Norway, Prof. Stian Solem, NTNU, Norway, Prof. Gerd Kvale, University of Bergen, Norway, Prof. Emeritus Lars-Göran Öst, University of Stockholm, Sweden, and Assoc. Prof. Thröstur Björgvinsson, MacLean Hospital, Boston, USA: Their expertise in clinical psychology enriched our knowledge of B4DT's adaptability and efficacy in diverse clinical settings.

Genetics:
Prof. Jan Haavik, University of Bergen, Norway: Crucial in the genetic studies, particularly in the GWAS identifying genomic loci associated with OCD.
Assoc. Prof. James A. Crowley, University of Chapel Hill, NC, USA: Integral to exploring genetic factors related to OCD and other disorders.

Epigenetics:
Prof. Stephanie le Hellard, University of Bergen, Norway: Led the epigenome-wide analysis, identifying differentially methylated regions correlating with treatment response.
Prof. Kerry A Ressler, MacLean Hospital/ Harvard Medical School, Boston: Provided extensive knowledge in epigenetics, enhancing our understanding of epigenetic modifications and treatment outcomes.

Brain Imaging:
Assoc. Prof. Olga Therese Ousdal, University of Bergen, Norway: Oversaw the neuroimaging components, facilitating insights into brain structure and functional changes post-treatment.
Prof. O.A. van den Heuvel, VUMC, Netherlands: Aided in neuroimaging studies, contributing to analyses of brain structure changes related to treatment response.
Clinical Psychology:

The collaboration with these eminent researchers has not only provided a multidisciplinary approach to our research but also highlighted the importance of combining national and international expertise in advancing scientific understanding and treatment methodologies in the field of psychological disorders. Their contributions, both in their specialized fields and to the overarching goals of our research, have been indispensable to the progress and impact of our studies.

3. References to the research (indicative maximum of six references)

Hansen, B., Hagen, K., Öst, L. G., Solem, S., & Kvale, G. (2018). The Bergen 4-Day OCD Treatment Delivered in a Group Setting: 12-Month Follow-Up. Frontiers in Psychology, 9, 639. doi:10.3389/fpsyg.2018.00639.

Hansen, B., Kvale, G., Hagen, K., Havnen, A., & Ost, L. G. (2019). The Bergen 4-day treatment for OCD: four years follow-up of concentrated ERP in a clinical mental health setting. *Cognitive behaviour therapy, 48*(2), 89-105. doi:10.1080/16506073.2018.1478447

Launes, G., Hagen, K., Sunde, T., Öst, L-G., ,Klovning, I., Laukvik, I-L., , Himle, J.A., Solem, S., , Hystad, S.W., Hansen, B. and Kvale, G. (2019) A randomized controlled trial of concentrated ERP for obsessive-compulsive disorder: The Bergen 4-day treatment. Frontiers in Psychology, DOI: 10.3389/fpsyg.2019.02500

Kvale, G**.,** Hansen, B., Hagen, K., Abramowitz, Børtveit, T., Crase, M., Franklin, M. E., Haseth, S., Himle, J.A., Hystad, S., Kristensen, U.B., Launes, G., Lund, A., Solem, S., Öst, L-G (2020) Effect of D-Cycloserine on the Effect of Concentrated Exposure and Response Prevention in Difficult-to-Treat Obsessive-Compulsive Disorder: A Randomized Clinical Trial. *JAMA Network Open* 3(8):e2013249 DOI: 10.1001/jamanetworkopen.2020.13249

Mataix-Cols, D., Hansen, B., Mattheisen, M., Karlsson, E. K., Addington, A. M., Boberg, J., ... & Crowley, J. J. (2020). Nordic OCD & Related Disorders Consortium: rationale, design, and methods. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 183(1), 38-50. DOI: 10.1002/ajmg.b.32756

Thorsen, A. L., de Wit, S. J., Hagland, P., Ousdal, O. T., Hansen, B., Hagen, K., ... & van den Heuvel, O. A. (2020). Stable inhibition-related inferior frontal hypoactivation and fronto-limbic hyperconnectivity in obsessive–compulsive disorder after concentrated exposure therapy. NeuroImage: Clinical, 28, 102460. DOI:10.1016/j.nicl.2020.102460

4. Details of the impact (indicative maximum 750 words)

The Bergen 4-Day Treatment (B4DT) and The Bergen Center for Brain Plasticity (BCBP) have made remarkable contributions to mental health care, both in Norway and internationally. This impact is rooted in innovative research, collaborative efforts, and the effective dissemination of findings. The evidence and narratives provided herein outline the distinct and material contributions of this research to mental health practices, policy formation, and scientific advancements.

1. Impact Through Dissemination and Clinical Application:
The Bergen 4-Day Treatment (B4DT), formulated by the Obsessive-Compulsive Disorder (OCD) research team at Haukeland University Hospital (HUS), has notably advanced the therapeutic landscape for OCD. This innovative treatment approach, exhibiting a remarkable long-term recovery rate, has been systematically implemented across all Norwegian health regions, showcasing the transformative impact of research in enhancing mental health care.

The integration of B4DT into the national healthcare system was a multifaceted process. It encompassed rigorous training programs for clinicians, assimilation into healthcare protocols, and a

strategic dissemination campaign. This holistic strategy facilitated the extensive adoption of B4DT, positioning it as a primary therapeutic modality for anxiety disorders within Norway.

In 2018, the significant contributions of Professor Bjarne Hansen and Professor Gerd Kvale in accelerating therapy processes were internationally acknowledged by Times Magazine, listing them among the top 50 most influential figures in health. This distinction highlights the global recognition of their innovative contributions to mental health treatment.

Subsequently, in 2022, the Norwegian Research Council awarded Professors Hansen and Kvale the Innovation Prize, further endorsing their work's substantial impact both nationally and internationally. This accolade underlines the significance and innovation of their research in the field of mental health.

Presently, efforts are underway to adapt the B4DT for broader applications, including other mental disorders. This expansion is indicative of an ongoing commitment to enhancing the efficiency and scope of treatment methodologies. The progression and adaptation of B4DT reflect a continual pursuit of clinical innovation and effectiveness in mental health interventions.

2.International Dissemination of the Bergen 4-Day Treatment (B4DT): Global Reach and Integration into Healthcare Systems

The Bergen 4-Day Treatment (B4DT) has achieved significant international dissemination, with its adoption in countries including Iceland, Germany, the USA, Singapore, Sweden, and Finland. These countries have not only trained and certified clinics in the B4DT method but also integrated it into the routine care of major healthcare institutions, indicating its global applicability and effectiveness in treating anxiety disorders.

Further expansion of B4DT is underway, with training programs planned for Ecuador and Kenya, demonstrating the treatment's adaptability to diverse cultural and healthcare contexts. This global expansion is supported by a strong academic foundation, with numerous papers published and more in the pipeline, highlighting the efficacy and implementation of B4DT across different populations.

The enthusiasm and positive feedback from healthcare institutions using B4DT underscore plans for its wider dissemination. The ongoing research and plans for expansion reflect a commitment to making this innovative treatment approach accessible to a broader patient population worldwide, contributing significantly to global mental health care.

3. Advancements in Scientific Understanding through BCBP:

Established in 2019, BCBP has significantly contributed to the understanding of brain plasticity. By integrating clinical, genetic, epigenetic, and neuroimaging data, the center has positioned itself at the forefront of mental health research. This multidisciplinary approach has facilitated the identification of predictors of treatment response and disease risk, promising to revolutionize treatment strategies for OCD and other mental disorders.

4. Extending Impact Through International Collaboration:

The center's active engagement in global consortia and collaborations with leading institutions worldwide has amplified its impact. By sharing data, biological samples, and research methodologies, the center has contributed to a broader understanding of mental health disorders. These international partnerships not only bolster the global knowledge base but also enhance the generalizability and applicability of the B4DT and related research findings across diverse cultural contexts.

5. Fostering Research and Clinical Excellence:
The BCBP's structured approach to research, encompassing various work packages and objectives, has nurtured a rich environment for scientific inquiry and clinical innovation. This structured approach has facilitated the development of more effective treatment regimens and a deeper understanding of mental disorders at a molecular level. The recruitment of early-stage researchers and the establishment of a research forum underscore the center's commitment to academic excellence and the cultivation of future leaders in mental health research.

6. Internationalization and Future Directions:
The center's focus on international research cooperation and the formation of a global clinical consortium demonstrate an unwavering commitment to advancing mental health care worldwide. Participation in consortia like ENIGMA and collaborative projects with international researchers and institutions highlight the center's role in driving global advancements in mental health research.

5. Sources to corroborate the impact (indicative maximum of ten references)

Time Magazine: Time Magazine, 50 most influential in health 2018

The Norwegian Research Council: Norwegian research council, Innovation of the year 2022

New York Times: https://www.nytimes.com/2018/08/13/health/ocd-concentrated-therapy-cbt.html
https://www.youtube.com/watch?v=ZRSExyZ3GPg&t=32s

The Norwegian Broadcasting Corporation: https://www.youtube.com/watch?v=_0iNr2G2VQA

German television: https://clinical-neuropsychology.de/zwang-kompaktbehandlung/?fbclid=IwAR1x7wTevQHjvVlqdPILXnA-rfHXZIXdyPwmF_7Q01yv3zKtTQCIIjCUst0

Swiss television: #tocs et #thérapies intensives - 36.9° - YouTube

UiB, The Faculty of Psychology (DPF), Case number 5

Institution: University of Bergen (UiB)
Administrative unit: The Faculty of Psychology (DPF)
Title of case study: Health Behaviour in School-aged Children (HBSC)
Period when the underpinning research was undertaken: 2012-2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2012-2022
Period when the impact occurred: 2012-2022

1. Summary of the impact (indicative maximum 100 words)

The SIPA group has since its origin worked closely with national and local educational and health authorities by sharing our national and international findings from the HBSC study through reports. Lately also digital reports have been sent to all participating schools. The national authorities have been invited to request inclusion of measures in questionnaire to meet national monitoring needs for adolescent health. We have further shared our measures with the educational authorities to be used in their own monitoring studies on psychosocial school environment. Finally, we have been represented on national policy boards and participated at public health and educational conferences.

2. Underpinning research (indicative maximum 500 words)

The *Health Behaviour in School-aged Children study. A WHO Collaborative Cross-national survey* (HBSC) was established in 1983 by researchers from England, Finland, and Norway. Today the network includes 52 countries. The HBSC network collects nationally representative data on 11-, 13-, and 15-year-olds every four years, with the last survey undertaken in 2021/2022. Thus, the study offers a 40-year trend perspective and unique cross-national data on to young people's health and well-being. Data are collected on social context (relations with family, peers, school, and online communication), health outcomes (subjective health, health complaints, overweight and obesity, and injuries), health behaviours (patterns of eating, physical activity and toothbrushing) and risk behaviours (use of tobacco, alcohol and cannabis, sexual behaviour, fighting and bullying) relevant . While risk behaviours have been reduced over the last years, health complaints and stress perceptions in school have increased, in particular among 15-year-old girls. Staff in the current research group SIPA was part of the establishment in 1983 and has continued to be involved in the scientific and data quality development of the study. Since 1985 the International Data Management Centre of the study has been at the Faculty of Psychology and from June 2024 the International Coordination Centre will also be placed at the Faculty of Psychology. SIPA at the Department of Health Promotion and Development is the responsible unit for these centres. SIPA is also responsible for the Norwegian data collection.

SIPA staff has published numerous scientific publications on the data during the reporting period (see examples in section 3, Fismen et al., 2019; Langøy et al., 2019; Melkevik et al., 2015).

After each survey round SIPA is involved in the production of both an international as well as a Norwegian national report that are shared widely. SIPA is also responsible for the data cleaning and quality checking of all national files, before they are merged into an international data file. Further, SIPA undertakes all the data analyses for the international reports and take part in the writing of the reports. In the period 2012-2022 two international reports have been published (see section 3, where the latest is included, Inchley et al., 2020). The international reports are

published as World Health Organization (WHO) publications, with high level press coverage and reports being sent to educational and health authorities in all participating countries.

The national report is written as a joint effort within SIPA. In the period 2012-2022 three national reports have been published (see section 3, where two are referenced Haug et al., 2020; Samdal et al., 2016). The national report is sent to all county national level educational and health authorities, as well as to participating schools. In SIPA's experience the reports are widely used by politicians and practitioners at both local and national level (see section 4).

Members of the SIPA group have a continuous dialogue with local and national policy makers and practitioners where we share data and provide perspective on science-based policy development. In the reporting period we have written two theory-based report commissioned by the Directorate of Health, where one on stress and mastery is referenced in section 3 (Samdal et al., 2017).

Names of the key researchers

The project is managed by professor Oddrun Samdal. All key researchers are at the Department of Health Promotion, Faculty of Psychology, UiB:

- Oddrun Samdal – Professor
- Bente Wold – Professor
- Torill Larsen – professor
- Ellen Haug – Associate Professor
- Trond Helland – researcher
- Frida K. S. Mathisen – research assistant and Phd student
- Catharina Robson-Wold – research assistant

3. References to the research (indicative maximum of six references)

Fismen, A-S.; Smith, O. R. F.; Helleve, A.; **Haug**, E. M. M.; Chatelan, A.; Kelly, C.; Dzielska, A.; Nardone, P.; Melkumova, M.; Ercan, O.; Kopcakova, J.; Lazzeri, G.; Klepp, K. I.; **Samdal,** O. (2022). Cross-national variation in the association between family structure and overweight and obesity: Findings from the Health Behaviour in School-aged children (HBSC) study. SSM - Population Health 2022 ;Volum 19. s.

Haug, E., **Robson-Wold**, C., **Helland**, T., **Jåstad**, A. **Torsheim**, T., Fismen, A.S., **Wold**, B. & **Samdal,** O.. (2020). Barn og unges helse og trivsel: Forekomst og sosial ulikhet i Norge og Norden. HEMIL-rapport. Institutt for helse, miljø og likeverd – HEMIL Universitetet i Bergen. https://www.uib.no/sites/w3.uib.no/files/attachments/hevas_rapport_v10.pdf

Inchley,J. Currie, D. Budisavljevic, S.,**Torsheim**, T., **Jåstad**, A., Cosma, A. Kelly,C., Arnarsson, AM & **Samdal,** O. (2020). Spotlight on adolescent health and well-being. Findings from the 2017/2018 Health Behaviour in School-aged Children (HBSC) survey in Europe and Canada. International report. Volume 2. Key data. Copenhagen: World Health Organization. https://hbsc.org/publications/reports/spotlight-on-adolescent-health-and-well-being/

Langøy, A., Smith, O. R., **Wold**, B., **Samdal**, O., & **Haug**, E. M. (2019). Associations between family structure and young people's physical activity and screen time behaviors. BMC public health, 19(1), 433.

Melkevik, O., **Haug,** E., Rasmussen, M., **Fismen,** A.S**., Wold**, B., **Torsheim**, T., Borrachino, A., Sigmund, E., Balazsi, R., Bucksch, J., Inchley J., Gaspar de Matos, M., **Samdal** O. (2015). Are associations between electronic media use and BMI different across levels of physical activity? A cross-national investigation in 30 countries. *BMC Public Health, 15(1),* 497

Samdal, O.; **Mathisen**, F.K.S.; **Torsheim**, T.; **Diseth**, Å.; **Fismen**, A.S.; **Larsen**, T.; **Wold**, B. & **Årdal**, E. (2016). Helse og trivsel blant barn og unge. Resultater fra den landsrepresentative spørreundersøkelsen "Helsevaner blant skoleleelver. En WHO-undersøkelse i flere land". HEMIL-rapport 1/2016. Bergen: HEMIL-senteret, Universitetet i Bergen. https://issuu.com/universitetet_i_bergen/docs/hemil-rapport2016

Samdal, O., **Wold**, B., Harris, A. & **Torsheim**, T. (2017). Stress og mestring. Rapport 08/2017. Oslo: Helsedirektoratet. https://www.helsedirektoratet.no/rapporter/stress-og-mestring/Stress%20og%20mestring.pdf/_/attachment/inline/11df8af9-831e-4535-aaef-43178fa9b389:faf7b30a63b6004ff91eb7d4bbf2c6a89c4d4718/Stress%20og%20mestring.pdf

4. Details of the impact (indicative maximum 750 words)

SIPA has over the years of publishing the national HBSC reports as well as contributing to the international reports observed that reports are much more used for policy documents than scientific papers. We have therefore given priority to the production of these reports. Given the close and continuous dialogue we have with policy makers in the national educational and health authorities we always give priority to share data to be used in policy documents.

In section 5, nine examples of Norwegian policy documents are listed, showing the year of the impact. The examples represent different forms of policy documents with the main ones being green papers (NOU), white papers (St.Meld, Meld.St), public health monitoring reports, action plans, and financial propositions. In these policy documents national and international HBSC data have been presented and used by national educational and health authorities as basis for policy proposals, monitoring of action plans, and financial propositions.

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SIPA members have also been representatives in national boards for development of policies for tobacco and physical activity since the origin of such boards in 1999. In the reporting period Wold was a member of the Board for physical activity in 2012-2016. A typical outcome of the activities in such boards is the development or revisions of action plans in the fields.

In the continuous dialogue with national authorities, we also invite them to suggest topics to be covered in the next national HBSC study. When SIPA applied to become the next Coordinating Centre for the HBSC study the Ministry of Health provided a declaration to support our emphasis and competence in contribution to policy development as one strength of our profile.

WHO Europe has a range of collaborating centres across Europe specialising in providing support for WHO activities. SIPA has through the whole reporting period been a WHO Collaborating Centre (Samdal is the director of the centre). The WHO Collaborating Centre role is primarily related to our function as Data Management Centre for the HBSC study, but also includes providing advice on policies and actions for health promotion initiative in European schools.

Through both the WHO Collaborating Centre and the HBSC Data Management Centre SIPA representatives have during the reporting period met with WHO staff four times or more per year. These are important encounters to promote the use of the data for policy development as well as encouraging WHO to support HBSC countries that are struggling to raise funds for their national data collection. This way we can ensure that we maintain data across participating countries also

for the purposes of publishing trends, which will be a main focus for the coming years, given the 40-year history of the HBSC study. WHO give high priority to publish the international reports and data from the HBSC study, as can be seen from this website: https://www.who.int/europe/initiatives/health-behaviour-in-school-aged-children-(hbsc)-study

The WHO reports that the HBSC data are systematically used in all international meetings with WHO national contact points and ministerial conferences, making the HBSC a key reference study for policy development not only nationally in Norway as documented in section 5, but also internationally. Other international organisations, like the OECD and UNICEF also systematically use the HBSC data for their monitoring and policy development of adolescent health, as seen in reference 1 in section 5 (UNICEF Innocenti, 2020).

5. Sources to corroborate the impact (indicative maximum of ten references)

International publication with use of international HBSC data

1. UNICEF Innocenti, 'Worlds of Influence: Understanding what shapes child well-being in rich countries', Innocenti Report Card 16, UNICEF Office of Research – Innocenti, Florence, 2020. https://www.unicef-irc.org/publications/pdf/Report-Card-16-Worlds-of-Influence-child-wellbeing.pdf

National impact publications with use of national and international HBSC data

2. Utviklingen i norsk kosthold (2023). Annual update of Norwegian population's food and drink consumption. Norwegian HBSC data included for 15-year-olds: https://www.helsedirektoratet.no/rapporter/utviklingen-i-norsk-kosthold-2023/matvareforbruk/brus-mineralvann-sjokolade-og-sukkervarer

3. Folkehelserapporten (Public Health Report) (2022). Annual update of report by use of Norwegian data from the HBSC study. Last update 23rd June 2022. https://www.fhi.no/he/folkehelserapporten/samfunn/barn-oppvekst/?term=

4. Nasjonal handlingsplan for bedre kosthold (2017-2023). National action plan to improve diet (2017-2023). Norwegian HBSC data are used as a basis for monitoring through quantitative measures, Nasjonal handlingsplan for bedre kosthold (2017–2021) - regjeringen.no, with change reported in mid-term evaluation of the national action plan: Midtveisevaluering av Nasjonal handlingsplan for bedre kosthold (2017-2021) - FHI

5. NOU 2015: 2 - Å høre til. Green paper «To belong» - actions to promote a safe psychosocial school climate. Oslo: Ministry of Education. Danish HBSC data are referenced as starting point for bullying intervention program. https://www.regjeringen.no/no/dokumenter/nou-2015-2/id2400765/?q=HBSC&ch=4#match_0

6. NOU 2019: 3 - Nye sjanser – bedre læring. Green paper: New chances – better learning. Gender differences in school achievement and educational tracks. Oslo: Ministry of Education. Norwegian HBSC data are presented showing gender differences in perceived school pressure, with reference comparison to international HBSC data.

7. NOU 2019: 8. Særavgiftene på sjokolade- og sukkervarer og alkoholfrie drikkevarer. Green paper on taxation of chocolate and sugar products and soft drinks where prevalences on adolescent intake of these products are reported using the Norwegian HBSC data. NOU 2019: 8 - regjeringen.no

8. NOU 2023: 1 - Kvalitetsvurdering og kvalitetsutvikling i skolen. Green paper on Quality assessment and quality development in compulsory schooling. Oslo: Ministry of Education. Reference is given to international and national HBSC data providing measures on the topic.

9. Meld. St. 21 (2016–2017) - Lærelyst – tidlig innsats og kvalitet i skolen. White paper on Motivation for learning - early intervention and quality in school. Norwegian HBSC data on perceived school stress are presented.

10. Prop. 1 S (2017–2018) - For budsjettåret 2018 under Kunnskapsdepartementet. Budget proposition for 2018 from Ministry of Education including presentation of Norwegian HBSC data for perceived stress among 15-year-olds.

IGS. Case number 1.

Institution: University of Bergen (UiB)
Administrative unit: Department of Global Public Health and Primary Care (IGS)
Title of case study: Post-discharge malaria prevention in children (PDMC)
Period when the underpinning research was undertaken: 2014-2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2014-2022
Period when the impact occurred:2020-2022

1. Summary of the impact

Children under 5 years who were treated for severe anaemia are at high risk of malaria-related readmission or death during the months after their hospital discharge. A decade ago, evidence supporting post-discharge malaria chemoprevention (PDMC) for these children was lacking. Since 2014, our international consortium produced interdisciplinary research confirming PDMC's safety, efficacy, acceptability, and cost-effectiveness. We presented this evidence to the WHO, who – in response - adopted PDMC in its 2022 malaria control guidelines for endemic settings. Beyond the WHO interaction, we engaged national decision makers from the start and tailored our research to their information needs. This contributed to some sub-Saharan countries' implementing and scaling-up of PDMC immediately following the WHO recommendation. Further supporting this impact, UiB-IGS plays a leading role in ongoing international research projects to advise and evaluate these national implementation processes, and to expand the successful concept to other vulnerable child populations.

2. Underpinning research and UiB-IGS contribution

Annually, approximately 130,000 children in Africa experience severe hospitalized anaemia. In 2014, the Research Council of Norway funded an international consortium, led by IGS-UiB, to explore the use of post-discharge malaria chemoprevention (PDMC). The overall objective was to assemble a comprehensive evidence package to enable the WHO to evaluate PDMC and, provided the evidence supported this, recommend PDMC as the new standard of care for the sub-Saharan Region. This multidisciplinary evidence package covered the following areas.

Safety and Efficacy

In a randomized controlled trial in Kenya and Uganda, 3 months of post-discharge malaria chemoprevention with dihydroartemisinin–piperaquine significantly lowered the incidence of readmission or death from week 3 to 14 by 70%, compared to a placebo treatment. Beyond week 14, the benefits did not persist. No serious adverse events were linked to dihydroartemisinin–piperaquine. This suggested a strong potential for PDMC to prevent adverse outcomes in high-transmission areas during the vulnerable post-discharge period. These efficacy and safety results were at the core of the WHO recommendation. The trial development started 2014, data was collected between 2016 and 2018. In 2020, these results were published in NEJM (Impact factor 176), Professor Bjarne Robberstad (BR), IGS, co-authored the article (Kwambai et al, 2020).

In addition, in a meta-analysis, the consortium examined the effectiveness of PDMC, likewise in children recovering from severe anaemia in malaria-endemic areas. Three trials with 3663 children were included. Chemoprevention resulted in a 77% reduction in mortality and a 55% reduction in all-cause readmissions, compared to placebo, during the intervention period. The protective effect was temporary and not sustained after drug effects diminished. Monthly sulfadoxine–pyrimethamine, artemether–lumefantrine, and dihydroartemisinin–piperaquine were used. Limited trials hindered a thorough assessment of heterogeneity and publication bias. These

results, published recently with co-authorship of BR in Lancet Global Health (IF 34.3), confirmed the potential benefit of different antimalarials used post-discharge in this high-risk populations (Phiri et al, 2024).

Delivery and acceptability

Simultaneously, prioritizing implementation questions from the start, the consortium conducted a PDMC delivery trial in Malawi. With the same inclusion criteria as the efficacy trial in Kenya and Uganda, this cluster-randomized study identified "community-based delivery", especially with village health worker support, as the optimal approach, i.e. achieving the caregivers' highest adherence to PDMC. The results were published in PLOS One (IF 3.7) (Gondwe et al, 2021). Aside from informing the WHO expert panels, these findings significantly influenced the Malawian and Ugandan governments' technical working groups for malaria control, guiding their initial evaluations of PDMC, and informing initial delivery designs.

The delivery research was accompanied by qualitative studies assessing the caregivers' acceptability and the feasibility of delivering PDMC with support of village health teams (VHT). They identified the preference of caregivers to obtain full PDMC treatment courses at discharge, and to remember and administer the antimalarials independently at home. VHT' perspectives were explored, and they confirmed the feasibility of a supporting role to the households; however, their limited resources and coverage caused caregivers' not wanting to rely on VHT for drug delivery or reminders of PDMC. Both studies were published in BMC Health Services Research (IF 2.8); only one is referenced below (Svege et al, 2018).

Cost-Effectiveness and Modelling PDMC Impact

Combining data from the trials in Kenya, Uganda, and Malawi, IGS-UiB led a cost-effectiveness-study of PDMC for these countries, focusing on the delivery strategies tested in Malawi. It showed that both community-based and facility-based PDMC were cost-saving, in each country, compared to standard care. This means they are less costly, if the incidence of adverse health events is included, and more effective in increasing health-adjusted life expectancy of children. Community-based PDMC was found to be less costly and more effective than facility-based PDMC. The estimated incremental cost savings per child treated ranged from US$22.10 in Malawi to US$38.52 in Kenya. These findings, confirmed in different sensitivity and scenario analyses, suggested with high certainty that PDMC is a cost-effective strategy for implementation in malaria-endemic southeastern African settings. Preliminary results were submitted to WHO in early 2022 and played an important role in the decision to recommend PDMC for the sub-Saharan Region. The full study was published the same year in Lancet eClinicalMed (IF 15.1) (Kühl et al, 2022).

Alongside, in a mathematical model developed on the basis of a clinical trial, ATM and co-authors projected the health impact of PDMC, both for the African Region and 30 malaria-endemic sub-Saharan countries. If all eligible children in the Region had access to PDMC, 38,600 (range 16,900–88,400) malaria-associated readmissions could be prevented, annually. Realistically, implementing PDMC could thus prevent thousands of malaria-associated readmissions and deaths every year in this highly vulnerable population. In the 20 highest-burden countries, giving PDMC to 2–5 children could prevent one hospitalised malaria episode, and treating less than 100 children could prevent one death. Results were submitted as preprint to the WHO in early 2022, and published later on in Nature Communications (IF 16.4) (Okell et al, 2023).

UiB-IGS employees in the PDMC Project (2014-2022) and in the global PDMC Consortium (until 2022):

- Prof. Bjarne Robberstad (BR): 2014-present
- Amani Thomas Mori (ATM), post-doctoral fellow and senior researcher: 2017-present
- Ulrikke Voltersvik, PhD fellow 2016-2017
- Thandile Nkosi-Gondwe (TNG), PhD fellow: 2016-2021
- Sarah Svege, research track student, then PhD-fellow: 2016-present

- Melf-Jakob Kühl (MJK), PhD fellow and researcher: 2017-present

BR was the project leader and grant manager from the outset of the project, and co-principal investigator to the trials presented here. He was supported by post-doctoral fellow ATM. PhD-students and research-track students joined the project subsequently in 2015 (TG, UV) and 2017 (SS, MJK). Their contribution included their developing project-specific study designs and research tools, collecting data or managing the collection, publishing their results, and supporting other analyses within the consortium. Notably, research from each UiB-IGS-led PhD project was represented in the key evidence package presented here, and to WHO in 2022.

3. References to the research

1 Kwambai TK, Dhabangi A, Idro R, *et al.* Malaria Chemoprevention in the Postdischarge Management of Severe Anemia. *N Engl J Med* 2020; **383**: 2242–54. **BR** co-authored this paper. ,

2 **Nkosi-Gondwe T**, **Robberstad B**, Mukaka M, *et al.* Adherence to community versus facility-based delivery of monthly malaria chemoprevention with dihydroartemisinin-piperaquine for the post-discharge management of severe anemia in Malawian children: A cluster randomized trial. *PLoS One* 2021; **16**. DOI:10.1371/JOURNAL.PONE.0255769. In addition to TNG and BR, **MJK** co-authored this paper.

3 **Svege S**, Kaunda B, **Robberstad B, Nkosi-Gondwe T**, Phiri KS, Lange S. Post-discharge malaria chemoprevention (PMC) in Malawi: Caregivers' acceptance and preferences with regard to delivery methods. *BMC Health Serv Res* 2018; **18**. DOI:10.1186/s12913-018-3327-z.

4 **Kühl M, Gondwe T**, Dhabangi A, *et al.* Cost-effectiveness of post-discharge malaria chemoprevention among preschool children with severe anaemia in Malawi, Kenya, and Uganda. WHO, 2022 DOI:10.5281/ZENODO.6559953. **BR** was the last author to this paper.

5 Okell LC, Kwambai TK, Dhabangi A, *et al.* Projected health impact of post-discharge malaria chemoprevention among children with severe malarial anaemia in Africa. *Nat Commun* 2023; **14**. DOI:10.1038/s41467-023-35939-w. **BR** and **MJK** co-authored this paper, **ATM** was last author.

6 Phiri KS, Khairallah C, Kwambai TK, *et al.* Post-discharge malaria chemoprevention in children admitted with severe anaemia in malaria-endemic settings in Africa: a systematic review and individual patient data meta-analysis of randomised controlled trials. *Lancet Glob Heal* 2024; **12**: e33–44. **BR** co-authored this paper.

Note: The last two references are from 2023 and 2024; however, the results from both studies were included, as pre-print and unpublished study, in the evidence submitted to the WHO, in 2022. In spite of their later publication, both studies were therefore important to the impact we report until 2022.

3. Details of the impact

Upon invitation by the WHO Global Malaria Programme, the political engagement group in our consortium summarized and compiled, in January 2022, the above described studies, and other research relevant to evaluate PDMC. On June 3, 2022, upon thorough review of this evidence package, the responsible expert panels in the WHO issued revised Malaria Guidelines and declared:

"WHO is issuing today a recommendation in favour of post-discharge malaria chemoprevention (PDMC). This is a strategy aimed at preventing malaria among children with severe anemia living in areas of moderate-to-high transmission after they are discharged from a hospital, when they are at high risk of re-admission or death. Through PDMC, children are given a full antimalarial treatment course at regular intervals."

In summary, it defines PDMC broadly, independent of the antimalarial and delivery strategy used. The recommendation endorses PDMC for children residing in regions characterized by moderate-to-high malaria transmission, de facto this includes most sub-Saharan countries. The recommendation encompasses practical facets such as antimalarial medication particulars, age-specific considerations, optimal dosage determination, frequency considerations, and diverse delivery approaches. Evidence underscores PDMC's efficacy in diminishing re-admission and mortality risks during the intervention period. Community-based delivery emerges as a favourable strategy owing to its cost-effectiveness and heightened adherence. Although uncertainties persist regarding the potential impact of PDMC on drug resistance, its overall feasibility and acceptability among key stakeholders are acknowledged. The recommendation assumes a conditional stance, emphasizing nuanced implementation in tandem with contextual considerations. Continuous monitoring for safety, efficacy, and plausible drug resistance is advised, with comprehensive insights expected to be expounded upon in forthcoming implementation guides.

This recommendation was issued directly, upon the first evaluation of evidence for PDMC. The expert group evaluated the certainty of the evidence presented by the consortium across all critical outcomes as «moderate to high». It concluded with a categorical recommendation that in malarious areas «PDMC should be given even when the cause(s) of severe anaemia in an individual cannot be identified. » By means of this recommendation, we have achieved the successful conversion of IGS-UiB-produced research, mostly only just published in and after 2020, to a policy-relevant treatment recommendation for the largest part of sub-Saharan Africa, in effect from June 2022. In WHO Guideline practice, such a fast conversion pace is rare.

Beyond the interaction with the WHO, the consortium's policy-engagement group had also been involving national decision-makers throughout the research period, especially in the countries hosting research sites. This enabled countries to swiftly evaluate the WHO Guidelines and translate them directly into implementation models to be tested. Malawi, Kenya, Uganda, and Benin have progressed the furthest with this. However, these ongoing processes depended directly on the Guideline issuing date and, therefore, they have largely not manifested themselves before 2023. Nonetheless, as some processes began earlier, we present exemplary the process of policy and program development in Malawi, starting as early as 2020. It serves as an example for fast national adoption of PDMC by closely informed national decision-makers who could anticipate the recommendation and champion its rapid implementation.

In Malawi, the discussion of adopting PDMC by the Ministry of Health (MoH) intensified in 2021, after our consortium presented preliminary evidence surrounding PDMC to members of the National Malaria Control Program (NMCP) in 2020. PDMC is today in the final stage of becoming policy, after it was endorsed by the MoH Technical Working Group in October 2023. The drafting and review of official documents to be used in community and in hospital settings, when providing PDMC as routine care, was completed in 2023. This was done in collaboration with the NMCP and the Integrated Management of Childhood Illness (IMCI) department. In parallel, PDMC adaptation workshops with the NMCP, and separately with IMCI, were conducted, and implementation

guidelines for nurses, clinicians and pharmacy personnel were developed. Training materials for the information and capacity building of community healthcare workers were developed and integrated into existing training schedules.

Below, we share a list of documents that were co-developed and adopted by the Ministry of Health in the process towards full implementation of PDMC. The MoH plans to scale PDMC up to the entire country by the end of 2024 or early 2025. An implementation schedule by MoH for this process, and all other documents listed below, are available upon request.

5. Sources to corroborate the impact

Global and regional impact (SSA): WHO adopting PDMC in new guidelines:

1. The WHO World Malaria Report summarizes trends in the global malaria burden and developments in malaria control efforts. The 2022 report summarizes evidence and the new recommendation for PDMC (search "PDMC"). It's available on the WHO's website:

   World Health Organization. World malaria report 2022 (8 December 2022). https://www.who.int/teams/global-malaria-programme/reports/world-malaria-report-2022. (search: PDMC; the 2023 report is also available)

2. *The 2022 WHO Malaria Guidelines* are superseded by a 2023 update in the WHO system, which can be found here: https://www.who.int/teams/global-malaria-programme/guidelines-for-malaria. In the PDMC-section, the folder "evidence to decision" summarizes our evidence package, and links to the versions of our research used to formulate the recommendation in 2022, for example: the economic evaluation: https://zenodo.org/records/6559953.The original 2022 Guidelines can still be found here: https://reliefweb.int/report/world/who-guidelines-malaria-3-june-2022

National Impact, the process of PDMC implementation in Malawi:

Malawi's Ministry of Health has initiated and championed the process of adopting PDMC since 2020. This list of documents, for use within the health system to train personnel in the implementation of PDMC and plan and operationalize the scale-up, is available upon request:

3. *Documentation of MoH PDMC Training and Capacity Building:*
   PDMC Training guidelines for health service personnel, incl. facilitator manuals and training schedules; information and training material for training participants, evaluation tools.

4. *Documentation of MoH Operationalization of PDMC:*
   National implementation plan for PDMC 2025, updated Village Health Worker Manual (draft), updated registrar and adherence monitoring tool for Health Centres, updated referral sheets for VHT, and monthly reporting sheets for Health Centres.

University of Bergen (UiB), Department of Global Public Health and Primary Care (IGS), Case 2

Institution: University of Bergen
Administrative unit: IGS
Title of case study: CVDNOR - Cardiovascular Disease in Norway 1994-2014
Period when the underpinning research was undertaken: 2012-2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2012-2022
Period when the impact occurred: 2013-2022

1. **Summary of the impact** (indicative maximum 100 words)

The CVDNOR project was initiated to study burden and trends over time in CVD occurrence and prognosis, provide CVD endpoints for national and regional health surveys conducted throughout Norway, and facilitate studies of the impact of known and potentially new risk factors in CVD occurrence. The project provided for the first time unique, nationwide data on CVD over two decades in Norway (1994-2014). Between 2013 and 2023, 88 papers using data from the CVDNOR project have been published in international peer-reviewed journals and 11 PhD dissertations were based on this project. Further, the data were used to develop a Norwegian risk model for acute cerebral stroke and myocardial infarction which is implemented in national guidelines for primary prevention of CVD. The project was also a cornerstone for the development of a national CVD register.

2. Underpinning research (indicative maximum 500 words)

Background and aim

Cardiovascular mortality has decreased substantially in Norway during the last decades. Still, it remains a major contributor to both morbidity and mortality, second only to cancer (from 2016) and posing a great financial burden to society. The CVDNOR project was initiated to address the absence of a national Norwegian health registry on cardiovascular disease (CVD). A precursor to the project was the Western Norway Cardiovascular Registry (WENOCARD), which was established as a research project with regional data from three counties in Western Norway covering the years 1972-2006.

The CVDNOR project's main objectives were to offer the opportunity to a) study the burden and time trends in CVD occurrence and prognosis, b) provide CVD endpoints for national and regional health surveys conducted throughout Norway and c) facilitate studies of the impact of several known and potentially new risk factors in CVD occurrence.

How research was developed

The project began as a collaboration between the University of Bergen and the Norwegian Knowledge Centre for the Health Services (now part of the National Institute of Public Health (NIPH)). Using a system called FS (Forskning i Sykehus = Research in hospitals) developed by Tomislav Dimoski at the NIPH, the project extracted retrospectively information on all hospital stays with a CVD, diabetes or congenital malformations of the circulatory system code diagnoses, as well as all related procedures (diagnostic or treatment) performed from Patient Administrative Systems (PAS) from all Norwegian somatic hospitals from 1994 (the year from which all hospitals adopted an electronic PAS) through 2009. Later the data were expanded with data from the Norwegian Patient Registry from 2009 to 2014.

The core group of researchers included epidemiologists, statisticians, cardiologists, clinicians, and experts in data manipulation. The project also involved PhD candidates with diverse backgrounds, such as cardiology and statistics, who were recruited at an early stage of the project. Under the

guidance of senior members of the core group, the PhD candidates developed algorithms for definitions of clinical endpoints and did extensive programming tasks to facilitate data for research. A web page was created to provide information about the CVDNOR project and to guide interested parties about possibilities for research based on the data. For each subproject, hospital data were linked to various data sources, such as Norwegian health registers (cancer registry, birth registry, cause of death registry), health surveys, a registry for congenital heart defects, and Statistics Norway. All subprojects were pre-approved by REK before they could proceed.

Project output
A total of 88 papers published in international, peer-reviewed journals used data from the CVDNOR project. The project has also served as the basis for 11 PhD dissertations, seven of which were conducted at EPISTAT between 2013 and 2021. Additionally, reports and descriptive papers were published.

Societal contribution
The CVDNOR core group played a key role in establishing a national CVD register. They actively promoted the need for a national register through meetings, professional advice, and media articles. Later, they served as members of the advisory scientific steering committee of the national CVD registry. Additionally, several scientific publications were discussed in the media.

The project webpage provides an overview of the project's scientific and media contributions.

Key researchers (included subproject leaders from IGS)

- Grethe S. Tell (Principal Investigator), Professor in epidemiology IGS
- Stein Emil Vollset (-2018), Professor in medical statistics IGS
- Gerhard Sulo (-2017, 2022-), PhD/Post doc IGS, Associate professor in epidemiology IGS
- Jannicke Igland, PhD IGS, Associate professor in medical statistics IGS
- Marta Ebbing, Cardiologist, Leader of the national CVD registry, now Director of Research and Development, Haukeland University Hospital
- Ottar Nygård, Professor UIB/Cardiologist Haukeland University Hospital
- Tomislav Dimoski, Senior engineer Norwegian Knowledge Centre for the Health Services (now part of Norwegian Institute of Public Health)
- Nina Øyen (Principal Investigator of Congenital heart defects in Norway, with four subprojects 2011-2024), professor in epidemiology IGS
- Anne Kjersti Daltveit (Principal Investigator of one subproject 2014-2018), professor in epidemiology IGS

3. References to the research (indicative maximum of six references)

1. **Sulo G**, **Igland J**, **Tell GS**Cardiovascular Disease in Norway /CVDNOR), 1994-2014 Project: An overview of data use and publications. Hjerteforum N° 3/ **2020**/ vol 33.
2. Selmer R, **Igland J**, Ariansen I, Tverdal A, Njølstad I, Furu K, **Tell GS**, Klemsdal TO. NORRISK 2: A Norwegian risk model for acute cerebral stroke and myocardial infarction. Eur J Prev Cardiol. **2017** May;24(7):773-782. doi: 10.1177/2047487317693949. Epub 2017 Feb 16. PMID: 28206819.
3. Rabanal KS, Selmer RM, **Igland J**, *Tell GS*, Meyer HE. Ethnic inequalities in acute myocardial infarction and stroke rates in Norway 1994-2009: a nationwide cohort study (CVDNOR). BMC Public Health. **2015**;15:1073. Doi: 10.1186/s12889-015-2412-z
4. **Igland J**, **Vollset SE**, Nygard OK, **Sulo G**, **Sulo E**, Ebbing M, et al. Educational inequalities in 28 day and 1-year mortality after hospitalisation for incident acute myocardial infarction--

a nationwide cohort study. Int J Cardiol. **2014**;177(3):874-80. Doi: 10.1016/j.ijcard.2014.10.045

5. **Sulo G**, **Igland J**, Nygård O, **Vollset SE**, Ebbing M, **Tell GS**. Favourable trends in incidence of AMI in Norway during 2001-2009 do not include younger adults: a CVDNOR project. Eur J Prev Cardiol. **2014** Nov;21(11):1358-64. doi: 10.1177/2047487313495993. Epub 2013 Jul 11. PMID: 23847184.
6. Leirgul E, **Fomina T**, Brodwall K, Greve G, Holmstrøm H, **Vollset SE**, **Tell GS**, **Øyen N**. Birth prevalence of congenital heart defects in Norway 1994-2009--a nationwide study. Am Heart J. 2014 Dec;168(6):956-64. doi: 10.1016/j.ahj.2014.07.030. Epub 2014 Aug 10. PMID: 25458661.

4. Details of the impact (indicative maximum 750 words)

We highlight three impacts of the project:

i) The project provided unique nationwide data on the occurrence and prognosis of cardiovascular disease over two decades in Norway and served as an valid endpoint register for many national and regional population-based health surveys and clinical studies

The CVDNOR project was the first to collect information and publish on incidence, prevalence and recurrence of main CVD sub entities. To put things in context, the actual national CVD registry includes information on CVD from 2012 (partially) and from 2013 at the national level. The CVDNOR data were linked to many other data sources, contributing to identify new, potential risk factors/markers of CVD, study prognosis and effect of interventions/medications among individuals with established cardiometabolic conditions.

The CVDNOR project has been instrumental in advancing our understanding of cardiovascular disease and its risk factors in Norway and beyond. Examples of research that have been addressed using these data are:

-Burden and time trends, gender differences, socioeconomic and ethnic gradients n AMI, stroke, and heart failure.
-The blood pressure lowering effect of candesartan in the acute phase of stroke and whether it can lead to long-term benefits (RCT).
-Risk of stroke in genetically verified familial hypercholesterolemia.
-Health anxiety and risk of ischemic heart disease.
-Congenital heart disease in Norway – a nation-wide cohort study with 3 PhD dissertations on national figures for birth prevalence, maternal morbidity, follow-up and mortality in childhood and one ongoing PhD on pregnancy and delivery outcomes in women with congenital heart disease.
-Hypertensive pregnancy disorders and later cardiovascular disease in women.

ii) The project provided data to develop a Norwegian risk model for acute cerebral stroke and myocardial infarction.
International guidelines for the prevention of cardiovascular disease (CVD) recommend the estimation of an individual's total risk of CVD to determine the extent of interventions that are needed. Prior to the CVDNOR-project, general practitioners in Norway used a prediction model developed to predict CVD mortality (NORRISK), because of lack of data on non-fatal events. Survival after CVD events has improved substantially in the last decades because of better treatment, but the disease burden is still high, and prediction models which only predicts mortality are therefore not optimal as a tool in primary prevention to identify persons in need of treatment.

By linking data on cardiovascular risk factors from population-based health surveys in Norway to data on hospitalizations and death from CVDNOR it was possible to develop a prediction model which predicted both non-fatal and fatal events of myocardial infarction and stroke (NORRISK2). This model is currently included in the Norwegian guidelines for primary prevention of cardiovascular disease as a recommended tool to identify high-risk individuals. The model has later been validated and recalibrated to improve prediction among different immigrant groups and persons with diabetes.

iii) The project was a cornerstone for the development of a national CVD register.
The CVDNOR project contributed substantially to the development of the national CVD registry. Several scientists involved in the CVDNOR project contributed with their expertise to the national CVD registry. Further, operational definitions, comparable to those used internationally that were established in the context of the CVDNOR project were 'transferred' to the national CVD registry. The core members of the CVDNOR project have further contributed internationally (publication in Circ: Cardiovascular quality and Outcomes) by discussing technicalities related to definitions used in CVDNOR and their potential impact on CVD trends. Lastly, key persons from the CVDNOR project core group have been in the advisory scientific board of the CVD registry since the registry was established.

5. Sources to corroborate the impact (indicative maximum of ten references)

Project web page: https://cvdnor.w.uib.no/

Lie M, Iversen SG, **Tell GS**, Njølstad I. På høy tid med et nasjonalt hjerte- og karregister [Time to establish a national registry of cardiovascular diseases]. Tidsskr Nor Laegeforen. **2004** Feb 5;124(3):367-8. Norwegian. PMID: 14963514.

Øyen N, Nygård O, **Igland J**, **Tell GS**, Nordrehaug JE, **Irgens LM**, Cooper JG, Langørgen J, **Vollset SE**. Sykehusinnleggelser for hjerte- og karsykdom i Helse Vest i perioden 1992-2001 [Hospital admission rates for cardiovascular diseases in Western Norway, 1992-2001]. Tidsskr Nor Laegeforen. **2008** Jan 3;128(1):17-23. Norwegian. PMID: 18183051.

Hornslien AG, Sandset EC, **Igland J**, Terént A, Boysen G, Bath PM, Murray GD, Berge E. Effects of candesartan in acute stroke on vascular events during long-term follow-up: results from the Scandinavian Candesartan Acute Stroke Trial (SCAST). Int J Stroke. **2015** Aug;10(6):830-5. doi: 10.1111/ijs.12477. Epub 2015 Mar 22. PMID: 25808741.

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Brodwall K, Leirgul E, Greve G, Vollset SE, Holmstrøm H, **Tell GS**, **Øyen N**. Possible Common Aetiology behind Maternal Preeclampsia and Congenital Heart Defects in the Child: a Cardiovascular Diseases in Norway Project Study. Paediatr Perinat Epidemiol. **2016** Jan;30(1):76-85. doi: 10.1111/ppe.12252. Epub 2015 Oct 19. PMID: 26479038.

Berge LI, Skogen JC, **Sulo G, Igland J**, Wilhelmsen I, **Vollset SE, Tell GS**, Knudsen AK. Health anxiety and risk of ischaemic heart disease: a prospective cohort study linking the Hordaland Health Study (HUSK) with the Cardiovascular Diseases in Norway (CVDNOR) project. BMJ Open. **2016** Nov 3;6(11):e012914. doi: 10.1136/bmjopen-2016-012914. PMID: 27810977; PMCID: PMC5129078.

Sulo E, Nygård O, **Vollset SE**, **Igland J**, **Sulo G**, Ebbing M, **Egeland GM**, Hawkins NM, **Tell GS**. Coronary angiography and myocardial revascularization following the first acute myocardial infarction in Norway during 2001-2009: Analyzing time trends and educational inequalities using data from the CVDNOR project. Int J Cardiol. **2016** Jun 1;212:122-8. doi: 10.1016/j.ijcard.2016.03.050. Epub 2016 Mar 19. PMID: 27043059.

Norwegian Institute of Public Health, report: hjerte--og-karregisteret.-rapport-for-2012-2016.pdf (fhi.no). **2018.**

Sulo G, **Igland J**, **Vollset SE**, Ebbing M, **Egeland GM**, Ariansen I, **Tell GS**. Trends in incident acute myocardial infarction in Norway: An updated analysis to 2014 using national data from the CVDNOR project. Eur J Prev Cardiol. **2018** Jul;25(10):1031-1039. doi: 10.1177/2047487318780033. Epub 2018 May 29. PMID: 29808757.

Svendsen K, Krogh HW, **Igland J**, **Tell GS**, Mundal LJ, Holven KB, Bogsrud MP, Leren TP, Retterstøl K. 2.5-fold increased risk of recurrent acute myocardial infarction with familial hypercholesterolemia. Atherosclerosis. **2021** Feb;319:28-34. doi: 10.1016/j.atherosclerosis.2020.12.019. Epub 2020 Dec 21. PMID: 33465659.

Riise HKR, **Igland J**, **Sulo G**, Iversen MM, Graue M, Eskild A, **Tell GS**, **Daltveit AK**. Is the risk of cardiovascular disease in women with pre-eclampsia modified by very low or very high offspring birth weight? A nationwide cohort study in Norway. BMJ Open. **2022** Apr 26;12(4):e055467. doi: 10.1136/bmjopen-2021-055467. PMID: 35473727; PMCID: PMC9045054.

University of Bergen (UiB), Department of Global Public Health and Primary Care (IGS), Case 3

Institution: University of Bergen
Administrative unit: Department of Global Public Health and Primary Care (IGS)
Title of case study: Continuity in general practice as predictor of mortality, acute hospitalisation, and use of out-of-hours care: a registry-based observational study in Norway.
Period when the underpinning research was undertaken: 2020-2021
Period when staff involved in the underpinning research were employed by the submitting institution: Professor Steinar Hunskaar and Professor Øystein Hetlevik were employed in the whole evaluation period 2012-2022, Jesper Blinkenberg affiliated as PhD candidate during this work
Period when the impact occurred: 2021 and further

1. Summary of the impact (indicative maximum 100 words)

This study shows an association between continuity of care measured by year with the same GP and reduced use of acute hospital admissions, out-of-hours services and mortality. The study has received extensive publicity outside of academia and its main impact has been on is based on referring to the study when debating policy debates on how to the organization of primary care. Especially in the UK where the continuity of care in general practice has been declining over the last recent decades, this paper has been used actively in policy development at the national level and the last author was invited as an expert to a government committee. BMJ covered the article as follows: "Continuity saves lives! We should trumpet this from the rooftops."

2. Underpinning research (indicative maximum 500 words)

A health care system based on a first-line primary care service taking care of a broad range of health issues is well accepted as the best way of organizing health care at a national level. According to prior studies, continuity of care in general practice is shown to increase patient satisfaction, improve health, and contribute to more efficient use of total health care. However, when holding different policy goals against each other in recent decades, access has often been prioritized over continuity of care. This has been an international policy trend, and questions have been raised about the value of continuity of care with a personal relationship between a GP and the patients.

In our research environment, we have had a focus on the utilization of health care with continuity of care as one main pillar. As a part of this research, we presented the paper "Continuity in general practice as predictor of mortality, acute hospitalisation, and use of out-of-hours care: a registry-based observational study in Norway" authored by Hogne Sandvik, Øystein Hetlevik, Jesper Blinkenberg and Steinar Hunskaar (Br J Gen Pract 2021 (published online 4 Oct). doi:10.3399/BJGP.2021.0340).

In this study, we aimed to increase knowledge regarding continuity of care and analysed the association between longitudinal continuity with a named regular general practitioner (RGP) and.

The duration of the RGP-patient relationship (I.e. being listed to the same RGP) in the period from the Norwegian list patent systems was established in 2001 to 2017 was used as an explanatory variable for the use of OOH services, acute hospital admission, and mortality in 2018. Several patient-related (sex, age, educational level, country of birth, Charlson score,

centrality, mean number of consultations per year) and RGP-related covariates (RGP's sex, RGP's age, general practice specialist, list size, vacant list capacity) were included in the analyses by linking high-quality national registries. Duration of RGP–patient relationship was categorised as 1, 2–3, 4–5, 6–10, 11–15, or >15 years. Results are given as adjusted odds ratio (OR) with 95% confidence intervals (CI) resulting from multilevel logistic regression analyses.

Compared with a 1-year RGP–patient relationship, the OR for use of OOH services decreased gradually from 0.87 (95% CI = 0.86 to 0.88) after 2–3 years' duration to 0.70 (95% CI = 0.69 to 0.71) after >15 years. OR for acute hospital admission decreased gradually from 0.88 (95% CI = 0.86 to 0.90) after 2–3 years' duration to 0.72 (95% CI = 0.70 to 0.73) after >15 years. OR for dying decreased gradually from 0.92 (95% CI = 0.86 to 0.98) after 2–3 years' duration, to 0.75 (95% CI = 0.70 to 0.80) after an RGP–patient relationship of >15 years.

We conclude that the length of the RGP-patient relationship shows a dose–response relationship with the use of out-of-hours (OOH) services, acute hospital admission, and mortality, indicative of a causal relationship. This study indicates a potential reduction of 30% in the use of OOH services, 28% in acute hospital admissions, and 25% lower mortality when comparing those with the same RGP in 15 years or more to those who have a relationship below one year.

Professor Steinar Hunskaar and Professor Øystein Hetlevik have been employed by the Section for General Practice at IGS 2012-2022, with Jesper Blinkenberg affiliated as PhD the last years of this period and he also has a leading position at the National Centre for Emergency Primary Health Care, NORCE Norwegian Research Centre AS (NKLM) where Hogne Sandvik has a position as senior researcher.

3. References to the research (indicative maximum of six references)

Sandvik H, Hetlevik Ø, Blinkenberg J, Hunskaar S. Continuity in general practice as predictor of mortality, acute hospitalisation, and use of out-of-hours care: a registry-based observational study in Norway. Br J Gen Pract. 2022 Jan 27;72(715):e84-e90. doi: 10.3399/BJGP.2021.0340. PMID: 34607797; PMCID: PMC8510690.

4. Details of the impact (indicative maximum 750 words)

This research has been extensively used in the debates about organising primary as an argument for primary care with a stable staff of GPs and organising the services to build the ground for achieving continuity of care.

The study was published in the British Journal of General Practice, the highest-ranked journal in this field. The paper was first published online in October 2021. The editor judged this an important paper, and it was promoted as such when published. This resulted in immediate response in different media, especially in the UK and Spain. When BJGP published a list of "Top 10 research most read and published in 2021" to bring together high-profile primary care research and clinical innovation, this paper on continuity of care was ranked as number one.

The study has been covered in social media and news media worldwide throughout 2021-22, primarily on Twitter from Europe, and North and South America. It has also been covered in many news outlets. In Norway, there have been reports on NRK, TV2, and all major national newspapers. There have also been many reports in England. In addition, we have registered mentions in about

15 other countries. BMJ covered the article as follows: “Continuity saves lives! We should trumpet this from the rooftops.”

In the UK, after the article was mentioned in The Times and other newspapers, it was quickly picked up by politicians in the British House of Lords and House of Commons. Former Health Minister (current Chancellor of the Exchequer) Jeremy Hunt mentioned it in several speeches in Parliament. In the fall of 2022, the Health and Social Committee in Parliament issued a report on British general practice with several proposals to increase continuity between doctors and patients in the UK. The study was used as an argument several times in the report, and Steinar Hunskaar (senior author) was invited to take part in a hearing with experts. This report has since been included as an important decision basis for the government’s work on the development of the English general practitioner scheme.

The article has also had important political implications in Spain, where the government proposed changes that would weaken continuity. Doctors protested and demonstrated in the streets, referring to the article. The Minister of Health believed that the emphasis on continuity was “old-fashioned,” which led to the Medical Association demanding the Minister of Health’s resignation for unscientific attitudes. In Spain, a poster has also been made about the findings from the article, which is used for the public in waiting rooms at doctor’s offices, health stations, etc.

Also in Norway, this paper has been often cited in news media when primary care questions are discussed. Also in the other Nordic countries, the results of the article are referred to and used in policy papers. Researchers and the Medical Association have given several presentations where the article has been presented. There are ongoing debates also here about the organisation of primary care with challenges in recruiting GPs, resulting in increased use of fragmented private health care. The Medical Associations are very active in presenting the results of the article in many contexts to underpin the usefulness of a well-organised list patient system with er personal GP. The state administration, municipalities, county doctors, and other stakeholders have become more familiar with the concept of continuity. However, there are also here diverging priorities in policy and in that debate, the value of continuity is challenged.

Overall, this article has put Norwegian general practice research and the Bergen research community on the map nationally and internationally at a whole new level. The research group has published important continuity data since before 2015. A doctoral thesis is in its conclusion, with findings that show both very high continuity for patients with chronic illness, and also effects on mortality in patients with serious chronic illness.

In conclusion, the study has inspired important discussions about the organisation of primary care and the role of GPs, which might have a further impact on population health, according to this study. However, such impacts are difficult to measure during the first year after publication, as is the scope of this evaluation report.

5. Sources to corroborate the impact (indicative maximum of ten references)

An overview of impact in media and policy is indicated by the Altmetric scores:
https://www.altmetric.com/details/112657744#score

Presentation from BJGP of the top 10 research most read and published in 2021:
https://www.youtube.com/watch?v=7G27wEqX4Lc

A press release from the University of Bergen including links to other media:

https://www.uib.no/med/148555/ny-uib-studie-%C2%ABtar-av%C2%BB-i-utlandet-%E2%80%93-dette-har-truffet-en-nerve

Report to the Government in UK from The House of Commons, Health and Social Care Committee: The future of general Practice. Fourth Report of Session 2022–23 (See sectio 2 on continuity of care) :
https://publications.parliament.uk/pa/cm5803/cmselect/cmhealth/113/report.html

The article has had an impact in the British Parliament, with repeated mentions in both the Upper House, Lower House and the Health Committee. Here is an example where former health minister (current finance minister) Jeremy Hunt recommends the article as sparkling summer reading for the health minister:
https://www.facebook.com/watch/?v=332709702410246

Example of impact on advice given from medical expertise:
“Exploring innovation in General Practice” – a Policy document from British Medical Association:
https://www.bma.org.uk/media/vbabuy3n/exploring-innovation-in-general-practice-design-final.pdf

According to Google Scholar were there 65 citations of this paper in 2021-2022, here is one example used to underpin the value of GP practice organization with a personal list:

Gray, Denis Pereira, Kate Sidaway-Lee, and Philip Evans. "Continuity of GP care: using personal lists in general practice." *British Journal of General Practice* 72.718 (2022): 208-209.

University of Bergen (UiB), Department of Global Public Health and Primary Care (IGS), Case 4

Institution: University of Bergen
Administrative unit: Department of Global Public Health and Primary Care (IGS)
Title of case study: Kangaroo Mother Care to enhance the survival of low birth weight infants
Period when the underpinning research was undertaken: 2014 - 2021
Period when staff involved in the underpinning research were employed by the submitting institution: 2014 - 2021
Period when the impact occurred: 2019 and onwards

1. Summary of the impact

Our randomized controlled trial in India indicated that promoting home-based (or community-initiated) kangaroo mother care (ciKMC) to babies with low birth weight can substantially and equitably increase their survival over the first 6 months of life. Being by far the largest of its kind, this high-quality trial contributed the most important evidence to a systematic review and meta-analysis which constituted the base for the new 2022-WHO recommendations for care of preterm and other low-birth-weight infants. If scaled up to 80% coverage, ciKMC has the potential to prevent ¼ million low birth weight babies' deaths every year.

In addition to increasing survival, ciKMC reduced the risk of severe infant illness and the risk of maternal post-partum depressive symptoms. Health economic evaluations indicated that ciKMC can substantially reduce the cost of care-seeking, the risk of impoverishment of households, and may thus offer financial risk protection.

2. Underpinning research

In many South Asian countries, including India, approximately 1 in 4 babies are born with a birth weight of less than 2.5 kg. These low birth weight (LBW) babies are born small for gestational age (SGA) and/or too early (preterm) and face a disproportionately high risk of severe illness and death as well as developmental impairments, including of physical growth. Globally, they make up nearly 80% of all infant deaths. Enhancing their survival chances would accordingly substantially reduce child mortality in South Asia and low- and middle-income countries (LMICs) in other regions.

When we in year 2013 started to plan for our research on kangaroo mother care (KMC), hospital studies had shown that keeping LBW babies close to their mothers' chest, providing them with easy access to breast milk as well as better temperature regulation, could substantially enhance their survival probabilities. The World Health Organization (WHO) had accordingly identified KMC in birth facilities as being one of the most promising interventions for promoting neonatal and infant survival, particularly in low-resource situations. However, in deprived settings, a high proportion of births happen outside of health facilities and, although more and more women do have institutional births, they are often discharged to their homes early, i.e. within a day, even if their babies have LBW.

Learning whether KMC initiation at home, i.e. community-initiated KMC (ciKMC), would be safe and effective would therefore importantly inform the development of both national (South Asian) and global (WHO) guidelines on whether the existing recommendation could be extended to the home-born babies and those discharged from birth facilities early, the ones probably at highest

risk of dying. Our main study question was accordingly if providing these babies with KMC at home, whether initiated there or after a too short stay in a birth facility, would give them a substantial survival benefit. Such information would fill an important gap in the then available guidelines for preterm and other LBW babies.

Our research team at the Society for Applied Studies in India (https://sas.org.in) and the Centre of Excellence for Intervention Science in Maternal and Child Health (CISMAC; www.cismac.org) at the Department of Global Public Health and Primary Care (https://www.uib.no/en/globpub) went through a careful process of defining a suitable population and then launching a very large randomized controlled trial of ciKMC in Haryana, India. The process included in depth formative research (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5833044/pdf/12889_2018_Article_5197.pdf), developing and publishing a protocol (https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-017-1991-7) and, once resources had been dedicated by CISMAC, launching the study in 2015. It was completed already in 2018, followed by rapid analysis and publication in 2019 (https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(19)32223-8/fulltext).

The findings revealed that promoting ciKMC can substantially improve survival in LBW infants up to 6 months of age, after which there are good reasons to believe that the survival benefits are sustained. Moreover, our studies showed that ciKMC also reduced the risk of severe infant illness and that the survival benefits induced by ciKMC showed some tendency of enhancing equity in survival (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8709992/pdf/12939_2021_Article_1605.pdf), that promoting ciKMC can substantially reduce the cost of care-seeking and the risk of impoverishment for households and may thus offer financial risk protection (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9668036/pdf/bmjgh-2022-010000.pdf). Moreover ciKMC reduced the prevalence of post-partum depressive symptoms among the mothers of these LBW infants (https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2779045).

Names of the key researchers and what positions they held at the **Department of Global Public Health and Primary Care**, the University of Bergen (IGS-UiB):

- Nita Bhandari, Adjunct professor, Centre for International Health, IGS-UiB
- Tarun Choudhary, PhD student, Centre for International Health, IGS-UiB
- José Martines, Scientific coordinator, CISMAC, IGS-UiB
- Halvor Sommerfelt, Director, Centre for intervention Science in Maternal and Child Health (CISMAC) and Professor at the Centre for International Health IGS-UiB

3. References to the research

(These references are also included as weblinks in section two above, to ease access while reading).

Mazumder, S., R. P. Upadhyay, Z. Hill, S. Taneja, B. Dube, J. Kaur, M. Shekhar, R. Ghosh, S. Bisht, J. C. Martines, R. Bahl, H. Sommerfelt, and N. Bhandari. 2018. Kangaroo mother care: using formative research to design an acceptable community intervention. BMC Public Health. 18:307. doi: 10.1186/s12889-018-5197-z.

Mazumder, S., S. Taneja, S. K. Dalpath, R. Gupta, B. Dube, B. Sinha, K. Bhatia, S. Yoshida, O. F. Norheim, R. Bahl, H. Sommerfelt, N. Bhandari, and J. Martines. 2017. Impact of community-initiated Kangaroo Mother Care on survival of low birth weight infants: study protocol for a randomized controlled trial. Trials. 18: 262. doi: 10.1186/s13063-017-1991-7.

Mazumder S., S. Taneja, B. Dube, K. Bhatia, R. Ghosh, M. Shekhar, B. Sinha, R. Bahl, J. Martines, M. K. Bhan, H. Sommerfelt, and N. Bhandari. 2019. Effect of community-initiated kangaroo mother care on survival of infants with low birthweight: a randomized controlled trial. The Lancet. 394: 1724–36. 10.1016/S0140-6736(19)32223-8

Sinha, B., H. Sommerfelt, P. Ashorn, S. Mazumder, S. Taneja, D. More, R. Bahl, and N. Bhandari. 2021. Effect of community-initiated kangaroo mother care on postpartum depressive symptoms and stress among mothers of low-birth-weight infants. Jama Netw. Open. 4(4):e216040. doi:10.1001/jamanetworkopen.2021.6040.

Choudhary, T. S., S. Mazumder, Ø. A. Haaland, S. Taneja, R. Bahl, J. Martines, M. K. Bhan, K. A. Johansson, H. Sommerfelt, N. Bhandari, and O. F. Norheim. 2021. Health equity impact of community-initiated kangaroo mother care: a randomized controlled trial. Int J Equity Health. 2021; 20: 263. doi: 10.1186/s12939-021-01605-0.

Choudhary, T. S., S. Mazumder, O. A. Haaland, S. Taneja, R. Bahl, J. Martines, M. K. Bhan, O. F. Norheim, H. Sommerfelt H, N. Bhandari, K. A. Johansson KA. 2022. Effect of kangaroo mother care initiated in community settings on financial risk protection of low-income households: a randomised controlled trial in Haryana, India. BMJ Glob Health 2022 Nov;7(11):e010000; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9668036/pdf/bmjgh-2022-010000.pdf

4. Details of the impact

The large sample size and high quality of the trial described in section 2 were key features to ensure that its findings carried a very high weight in defining the summary effects of the meta-analysis (https://gh.bmj.com/content/bmjgh/8/6/e010728.full.pdf). This meta-analysis provided the evidence base for WHO to issue an updated guideline in year 2022 (https://iris.who.int/bitstream/handle/10665/363697/9789240058262-eng.pdf?sequence=1). As a result, these WHO recommendations for care of the preterm or low-birth-weight infant now state that "KMC can be initiated in the health-care facility **or at home** …" (our boldface). The WHO summary of the evidence considers this a strong recommendation, based on high-certainty evidence (WHO recommendations for care of the preterm or low-birth-weight infant. Web Supplement; https://iris.who.int/bitstream/handle/10665/363699/9789240060050-eng.pdf).

To amplify the ownership of the trial findings and ensure that future users' concerns were addressed, the government of the State of Haryana in India, the Central Government in India as well as the WHO were closely involved throughout the process from study conceptualization, undertaking through to publication of main findings. The WHO estimated at the time that if implemented with 80% coverage, ciKMC would prevent 250,000 infant deaths per year globally (please see slide #8 in https://www.healthynewbornnetwork.org/hnn-content/uploads/Slides-for-launch_16May2023-2.pdf).

5. Sources to corroborate the impact

(Except for the paper in eClinical medicine, these references are also referred to in the section two as clickable weblinks for ease access while reading).

Sivanandan, S. and Mari J. Sankar. 2022. Kangaroo mother care for preterm or low birth weight infants: a systematic review and meta-analysis. BMJ Global Health 2023; 8:e010728. https://doi:10.1136/bmjgh-2022-010728.

Care of Preterm or Low Birthweight Infants Group. New World Health Organization recommendations for care of preterm or low birth weight infants: health policy. eClinicalMedicine 2023;63: 102155. https://www.thelancet.com/action/showPdf?pii=S2589-5370%2823%2900332-2.

The World Health Organization. 2022. WHO recommendations for care of the preterm or low-birth-weight infant. ISBN 978-92-4-005826-2 (electronic version); https://iris.who.int/bitstream/handle/10665/363697/9789240058262-eng.pdf?sequence=1

The World Health Organization. 2022. WHO recommendations for care of the preterm or low-birth-weight infant. Evidence base. Web supplement. ISBN 978-92-4-006005-0 (electronic version). https://iris.who.int/bitstream/handle/10665/363699/9789240060050-eng.pdf

Dr Anshu Banerjee published presentation https://www.healthynewbornnetwork.org/hnn-content/uploads/Slides-for-launch_16May2023-2.pdf during WHO's launch of Kangaroo Mother Care Global Position Paper and Implementation Strategy 16th of May 2023.

University of Bergen (UiB), Department of Global Public Health and Primary Care (IGS), Case 5

Institution: University of Bergen
Administrative unit: Department of Global Public Health and Primary Care (IGS)
Title of case study: Disease Control Priorities – Ethiopia (DCP-E)
Period when the underpinning research was undertaken: 2016 - 2021
Period when staff involved in the underpinning research were employed by the submitting institution: 2016 - 2021
Period when the impact occurred: 2019 - 2020

1. Summary of the impact (indicative maximum 100 words)

DCP-E, funded by the Bill and Melinda Gates Foundation (BMGF), successfully delivered on its two objectives:

- DCP-E provided input, through research and evidence led by Ethiopian researchers, to the revision of the Essential Health Services Package (EHSP) for the Ethiopian health sector. In November 2019, the Minister of Health Dr. Amir publicly launched the report, an event widely covered by the media in Ethiopia.
- BCEPS, Bergen Centre of Ethics and Priority Setting, through this project, helped develop priority-setting capacity in Ethiopia through 7 master's degrees and 2 PhD degrees for civil servants recruited from and for the Health Economics and Financing Case Team in the Ministry of Health.

2. Underpinning research (indicative maximum 500 words)

Setting priorities to control diseases around the world

The Disease Control Priorities Network (DCPN) was first funded by BMGF in 2009. The programme is now in its 4th edition. Its aim is to summarize and synthesize evidence of the effectiveness of global health interventions and provide comparative economic evaluation of policies to implement those interventions.

The three organisations IGS, Harvard TH Chan School of Public Health and Ethiopia's Ministry of Health had worked together since 2015 to strengthen the health economics and priority-setting capacity of researchers and decision-makers in Ethiopia and thereby contribute to better and fairer priority setting in the Ethiopian health services. The BMGF funding made it possible to train more individuals in these skills. The DCP-E project trained Ethiopian researchers and policymakers in health economics, decision sciences, and priority setting. This enabled participants to generate an evidence base that informed the development, design, and recommendations for Ethiopia's current essential health services package.

The essential health services package

In addition to all the evidence generated, the process to revise the EHSP included 35 consultative workshops with experts and the public to define the scope of the revision, develop a list of health interventions, agree on the prioritization criteria, gather evidence and compare health interventions. The aim was to establish a participatory, inclusive and evidence-based prioritization process. Seven prioritization criteria were accepted after deliberation and a policy process:

disease burden, cost effectiveness, equity, financial risk protection, budget impact, public acceptability and political acceptability. The candidate list of interventions included more than 1000 services to either prevent or treat diseases. The interventions included in the EHSP were comprehensive and were assigned to health care delivery platforms and linked to financing mechanisms.

Evidence to policy

The underlying research analyzed costs and impact on health, poverty and inequity of the various health interventions studied. Examples include: Catastrophic out-of-pocket expenditure related to seeking health services for cardiovascular disease, estimating cancer incidence to improve cancer control programs and coverage; economic burden of malaria for rural households; cost-effectiveness analysis of prevention and treatment of cardiovascular diseases, maternal and neonatal health interventions; and health gains and financial protection provided by scaling up neuropsychiatric services in Ethiopia.

Research findings were then communicated through policy briefs and regular meetings in and with the Ministry on topics such as: Measuring progress towards universal health coverage: National and subnational analysis in Ethiopia; Supporting decision makers to save lives: Cost-effectiveness analyses for priority setting in Ethiopia; The Potentially large health and financial risk protection benefits of universal public finance.

Key researchers

- Ole F. Norheim, Professor UiB/BCEPS, PI
- Stéphane Verguet, Ass Professor, Department of Global Health and Population, Harvard TH Chan School of Public Health, Co-PI.
- Seblewongel Yigletu, Researcher, Harvard TH Chan School of Public Health
- Kjell Arne Johansson, Ass professor, UiB/BCEPS.
- Mieraf Taddese Tolera, Senior researcher, ACEPS
- Solomon Memirie, Senior researcher, ACEPS
- Alemayehu Hailu, Senior researcher, seconded to MoH
- Mizan Kiros, Master's student, later PhD.
- Getachew Teshome Eregeta (PhD)
- Lelisa Fekadu (PhD)
- Seven master students.

3. References to the research (indicative maximum of six references)

Reports and publications

Ministry of Health. Essential health services package of Ethiopia. Ethiopian Federal Ministry of Health, November 2019, Addis Ababa, Ethiopia.

1. Verguet, Stéphane; Hailu, Alemayehu; Eregata, Getachew Teshome; Memirie, Solomon Tessema; Johansson, Kjell Arne; Norheim, Ole Frithjof**. Toward universal health coverage in the post-COVID-19 era**. *Nature Medicine*; 15 March 2021.
2. Assebe, L. F., Kwete, X. J., Wang, D., Liu, L., Norheim, O. F., Jbaily, A., Verguet, S., Johansson, K. A., & Tolla, M. T. (2020). Health gains and financial risk protection afforded by public financing of selected malaria interventions in Ethiopia: An extended cost-effectiveness analysis. *Malaria Journal*, *19*(1), 41–41. PubMed. https://doi.org/10.1186/s12936-020-3103-5

3. Eregata, Getachew Teshome; Hailu, Alemayehu; Stenberg, Karin; Johansson, Kjell Arne; Norheim, Ole Frithjof; Bertram, Melanie Y. Generalised cost-effectiveness analysis of 159 health interventions for the Ethiopian essential health service package. *Cost Effectiveness and Resource Allocation* 19, 2 (2021). 6 January 2021.
4. Hailu, Alemayehu; Eregata, Getachew Teshome; Stenberg, Karin; Norheim, Ole Frithjof. Is Universal Health Coverage Affordable? Estimated Costs and Fiscal Space Analysis for the Ethiopian Essential Health Services Package. *Health Systems & Reform* 7:1; 19 March 2021.
5. Alemayehu Hailu, Getachew Teshome Eregata, Amanuel Yigezu, Melanie Y. Bertram, Kjell Arne Johansson, Ole F. Norheim. Contextualization of cost-effectiveness evidence from literature for 382 health interventions for the Ethiopian essential health services package revision. *Cost Effectiveness and Resource Allocation*19, 58 (2021); 14 September 2021.
6. Norheim, O. F. (2018). Disease Control Priorities Third Edition Is Published: A Theory of Change Is Needed for Translating Evidence to Health Policy. International Journal of Health Policy and Management, 7(9), 771–777. https://doi.org/10.15171/ijhpm.2018.60

4. Details of the impact (indicative maximum 750 words)

BCEPS researchers worked closely with MoH officials, technical advisors from World Health Organization, and other partners throughout the whole process of revising the essential health service package. All documents and documentation published were led by our Ethiopian researchers in the team. It is too early and difficult to document the impact of priority setting policies on patients and citizens of a country of more than 110 million people. The policies were aimed to improve health, reduce health inequities and reduce poverty though financial protection. After the project ended, the country was hard hit by the pandemic and civil war.

DCP-E has had societal impact by concretely shaping key policies and four policy documents (2019-21) in Ethiopia:

- DCP-E researchers advised and supported implementation of the EHSP revision through the revisions of the Ethiopian Health Extension Program 2020-2035 and the Health Sector Transformation Plan II 2020-25.
- DCP-E researchers have been contributing to discussions around maintaining essential health services in low- and middle-income countries (including Ethiopia) during the COVID-19 pandemic, in close partnership with the MoH and its National COVID-19 Response.
- The MoH developed a "Roadmap for Optimizing the Ethiopian Health Extension Program 2020-2035". During this process, DCP-E researchers were involved as members of a technical working group and of the steering committee. DCP-E contributed to a situation analysis, including local and international (virtual) benchmarking, projections, and modelling, as well as a costing and budget impact analysis for the roadmap.
- DCP-E researchers provided technical support for aligning and tailoring the EHSP with the essential benefits package to be covered by Ethiopia's Community-Based Health Insurance (CBHI) under the leadership of Deputy Director General Muluken Argaw, Ethiopian Health Insurance Agency (EHIA). DCP-E team members Memirie, Norheim, Tolla, and Verguet are part of an advisory committee to the EHIA on the matter. As such, they contribute to regular teleconference calls and analytical exercises conducted by the EHIA. The final report will be completed by spring 2024.

Beyond the policy impact, most of the researchers trained in this project are back in Ethiopia and hired in key positions within the Ministry of Health. One is at Harvard doing a PhD, one is a senior researcher at the Health Economic and Financing Program at Africa CDC, one is a director of Addis Centre for Ethics and Priority Setting, Addis Ababa University. Capacity development may be the

most important impact of research and training of this type. Developing expertise and capacity to develop fair and efficient health policies remains a key goal for BCEPS.

5. Sources to corroborate the impact (indicative maximum of ten references)

- Ministry of Health Ethiopia. Press release, Nov 2019.
- UiB/BCEPS Project page.
- Meet Some Capacity Builders. BCEPS web news.
- Harvard TH Chan School of Public Health Project page.
- Federal Ministry of Health, Ethiopia.

University of Bergen, Department of Clinical Medicine

Institution: University of Bergen (UiB)
Administrative unit: Department of Clinical Medicine
Title of case study: Clinical nutrition
Period when the underpinning research was undertaken: 2012-2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2012-22
Period when the impact occurred: 2012-22

Description of the impact

The Nutrition group´s research in nutrition epidemiology and clinical nutrition which also included innovative research as part of the Haukeland university hospital's (HUH) Nutritional strategy have shaped nutritional policy decisions at national levels. We created the first Norwegian nutritional register for hospitalised patients and a large case-control study at HUH. Thereby, we identified nutritional key factors and discovered associations to increased morbidity, mortality, length of stay/health care costs. This led to the development of clinical routines and tools. Our innovative solutions include patient surgical checklist (PASC) and a decision support system. Our research has contributed to the definitions on ICD-10-codes for malnutrition in Norway.

Our research and innovative projects, which has been recognised for its substantial contributions to effective identification of malnutrition and a deeper understanding of how to identify, prevent and treat the disease-related malnutrition, are rooted in the following projects:

- HUH nutritional register (2008-2018), prevalence surveys on hospitalised patients, n=20.000 (3 phd, 3 MSc). (funded by the Western Norway Health Authority)
- Malnutra (2018-2023), case-control study on risk of malnutrition, n=350 (1 phd, 5 MSc). (funded by the Western Norway Health Authority and the Mohn Nutrition Research Laboratory)

Our innovative projects include:

- PASC innovation project: Development and implementing **patients surgery checklist** in a step-wedge cluster-randomized RCT (quantitative) n=2500 and feasibility study (quality) (2 phd, 3 post-doc). (funded by the RCN)
- MyFood innovation project: Development and evaluation of a decision support system to prevent and treat disease-related malnutrition (1 phd) (South-East Norway Health Authority)

Our contribution to national strategies, national guidelines and the patient safety programme has impacted the national nutritional routines in hospitals, nursing homes and home-dwelling patients:
1) National guidelines to prevent and treat malnutrition in hospitals, nursing homes and home-dwelling patients (steering board, reference board)
2) National Patient Safety Programme, work package: Disease-related Malnutrition (expert panel)
3) Education: e-courses in clinical nutrition, Kosthåndboken (editors and contributors)
4) National Advisory Unit on Disease-related Malnutrition (leader)

References:

1. **Trollebø M**, **Skeie E**, Revheim I, Stangeland H, Erstein MAH, Grønning M, **Tangvik R**, Morken M, Nygård, Eagan T, **Rosendahl-Riise H, Dierkes J.** Comparison of nutritional risk screening with NRS2002 and the GLIM diagnostic criteria for malnutrition in hospitalized patients. Sci Rep. 2022; 12: 19743. Published online 2022 Nov 17. doi: 10.1038/s41598-022-23878-3

2. Folven K, **Tangvik RJ,** Nilsen RM, Beck AM, Hetlevik Ø, and Biringer E: Nutritional Risk Is Associated with Earlier Death in Older Service Users with Common Chronic Diseases Curr Dev Nutr. 2022 Jun; 6 (Suppl 1): 19. Published online 2022 Jun 14. doi: 10.1093/cdn/nzac047.019. PMCID: PMC9193744

3. **Tangvik RJ, Skeie E,** Haugen A, Harthug S, Harris K: Routine screening by healthcare workers do not identify elective surgical patients who think they are "at risk of malnutrition" prior to admission. Under submission

4. **Skeie E,** Sygnestveit K, Nilsen RM, Harthug S, Koch AM, **Tangvik RJ.** Prevalence of patients "at risk of malnutrition" and nutritional routines among surgical and non-surgical patients at a large university hospital during the years 2008-2018. Clin Nutr. 2021 Jul;40(7): 4738-4744.doi: 10.1016/j.clnu.2021.05.029.

5. **Olsen MN, Tangvik RJ**, Halse AK. Evaluation of nutritional status and methods to identify nutritional risk in rheumatoid arthritis and spondyloarthritis. Nutrients Nov 2020. Nov 21;12(11):3571. doi: 10.3390/nu12113571. PMID: 33233336

6. **Rivelsrud M,** Paur I, Sygnestveit K, Nilsen RM, **Tangvik RJ.** Nutritional treatment is associated with longer survival in patients with pancreatic disease and concomitant risk of malnutrition. Clin Nutr. 2020 Oct 1:S0261-5614(20)30509-4. doi: 10.1016/j.clnu.2020.09.037. PMID: 33059912

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8. **Skeie E, Tangvik RJ,** Nymo LS, Harthug S, Lassen K, Viste A. Weight loss and BMI criteria in GLIM's definition of malnutrition is associated with postoperative complications following abdominal resections - Results from a National Quality Registry. Clin Nutr. 2020 doi: 10.1016

9. Paulsen MM, Varsi C, Paur I, **Tangvik RJ**, Andersen LF. Barriers and Facilitators for Implementing a Decision Support System to Prevent and Treat Disease-Related Malnutrition in a Hospital Setting: Qualitative Study. JMIR Form Res. 2019 May 9;3(2): e11890. doi: 10.2196/11890

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11. Kårstad KÅ, Sygnestveit K, **Tangvik RJ:** Ernæringsmessig risiko. Norsk tidsskr sykepleierforskning 2018

12. **Skeie E,** Koch AM, Harthug S, Fosse U, Sygnestveit K, Nilsen RM, **Tangvik RJ.** A positive association between nutritional risk and the incidence of surgical site infections: A hospital-based register study. PLoS One. 2018 May 15;13(5):e0197344. doi: 10.1371/journal.pone.0197344. eCollection 2018. PMID: 29763425

13. **Tangvik RJ,** Torheim LE, Henriksen C. Bedre ernæringspraksis – til det beste for pasientene. Tidsskr Nor Laegeforen. 2018 Apr 17;138(7). doi: 10.4045/tidsskr.18.0159. PMID: 29663770

14. Juul H, Nilsen H, Paur I, Thoresen L, **Tangvik RJ:** Ernæring og pasientsikkerhet. Norsk tidsskrift for ernæring, 2017 nr 3 s 54-57.

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16. Nilsen H, Juul H, Paur I, Thoresen L, **Tangvik RJ:** Nutrition Day er revidert og bedre egnet til å evaluere kvalitet på ernæringsbehandlingen. Norsk tidsskrift for ernæring, 2017 nr 3 62-64.

17. **Tangvik RJ,** Smedshaug G. Ernæring og pasientsikkerhet. Nordisk Nutrition, okt 2016.

18. Birkeland ES, Stokke G, **Tangvik RJ,** Torkildsen EA, Boateng J, Wollen AL, Albrechtsen S, Flaatten H, Trovik J: Norwegian PUQE (Pregnancy-Unique Quantification of Emesis and nausea) identifies patients with hyperemesis gravidarum and poor nutritional intake; a prospective cohort validation study. PLoS One. 2015 Apr 1;10(4):e0119962. doi: 10.1371/journal.pone.0119962. eCollection 2015.

19. **Tangvik RJ,** Tell GS, Guttormsen AB, Eisman JA, Henriksen A, Nilsen RM, Ranhoff AH Nutritional risk profile in a university hospital population. Clin Nutr. 2014 Aug 12. pii: S0261-5614(14)00205-2. doi: 10.1016/j.clnu.2014.08.001. [Epub ahead of print]. PMID: 25159298

20. **Tangvik RJ,** Tell GS, Eisman JA, Guttormsen AB, Henriksen A, Nilsen RM, Øyen J, Ranhoff AH. The nutritional strategy: four questions predict morbidity, mortality and health care costs. Clin Nutr. 2014 Aug;33(4):634-41. doi: 10.1016/j.clnu.2013.09.008. Epub 2013 Sep 18. PMID: 24094814

21. **Tangvik RJ,** Tell GS, Guttormsen AB, Ranhoff AR: Implementation of nutritional guidelines in a university hospital monitored by repeated point prevalence surveys. Eur J Clin Nutr. 2012 Mar;66(3):388-93. doi: 10.1038

Institution: University of Bergen (UiB) and Haukeland University Hospital, Helse Bergen (HB)
Administrative unit: Section of Nephrology and Urology, Department of Clinical Medicine (K1), UiB, and Section of Nephrology, Department of Medicine, and Department of Pathology, Haukeland University Hospital, HB
Title of case study: Digitization of the Norwegian Kidney Biopsy Registry and kidney pathology services
Period when the underpinning research was undertaken: 2012-2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2012-2022
Period when the impact occurred: 2012-2022

1. Summary of the impact

The Norwegian Kidney Biopsy Registry's digital infrastructure, established in 2012 by the Renal Research Group (RRG), led by the visionary Bjarne Iversen, has catalysed significant advancements in kidney research, education, and pathology services. This innovative initiative, further guided by key researchers like Hans-Peter Marti and Sabine Leh, has become an invaluable tool for research within the RRG, fostering collaboration, innovation, and a deeper understanding of chronic kidney diseases. We also played an important role in driving impactful regional and national digital pathology projects as well as resonated globally. Finally, the foundation of the digital infrastructure in 2012 paved the way for the third revolution in pathology, the development and implementation of AI tools as well as its key prerequisite enabling several omics technologies established by the RRG.

2. Underpinning research

The Renal Research Group (RRG) has a longstanding track record performing high quality research at the University of Bergen and Haukeland University Hospital. Bjarne Magnus Iversen founded the RRG in the mid 1970s and its focus has been basic science and translational research as well as nationwide registry studies. The foundation of the Norwegian Kidney Biopsy Registry (NKBR) as early as in 1988 was a consequent step to further improve research possibilities both for the RRG but also for any researcher who want to work with this data. The registry serves several purposes including preserving rare biopsy materials, setting national standards for nephrology-pathology collaboration, fostering interdisciplinary interactions, and conducting clinical and epidemiological research. The registry, jointly operated by the Nephrology Section and the Pathology Department at Haukeland University Hospital maintains comprehensive clinical and pathological data from all non-tumour and non-transplant kidney biopsies in Norway.

The advent of digital technology with the development of digital slide scanners presented a transformative opportunity for the field. Digitizing histological sections, akin to colour images, but at higher resolutions, allowed for evaluation histologic glass slides on computer screens rather than through traditional microscopes. Bjarne Iversen saw the potential of this new technology and initiated a project to purchase a digital slides scanner for digitization of non-neoplastic kidney biopsies. With the support of Trond Mohn’s donation the acquisition of a digital slide scanner, an image database and a viewing program with image analysis tools became a reality.

This technological leap in 2012 marked a significant milestone, ensuring the preservation of colour quality, eliminating dependence on microscopes, and facilitating centralized storage on a server, thus enabling novel collaborative approaches and enhanced accessibility.

In 2012 a scanning facility was established at the pathology department. From that time all kidney biopsies examined at the pathology department were scanned and stored, as well as histologic kidney biopsy slides from other pathology departments if they were registered in the Norwegian Kidney Biopsy Registry.

The initial objectives at that time point were creating a searchable image database, supporting interdisciplinary conferences on kidney biopsies, and setting the groundwork for teaching and research tasks. Not surprisingly with this fascinating new technology, the digital slides were then

also used quite quickly for the primary diagnosis of all kidney biopsies at the HUS pathology department.
The digital infrastructure with a multipurpose image database supported the work of the "Norwegian Renal Registry (NRR) where NKBR is included, in multiple ways. The development of advanced omics techniques on formalin fixed paraffin embedded kidney biopsies by Hans-Peter Marti and Øystein Solberg Eikrem would not have been possible without being able to use digital slides for identification of structures and lesions to investigate.
In the following years it became more and more clear that digitization of histological sections is the necessary precondition for development and application of AI tools which is now considered the third revolution in pathology and a major paradigm shift.
To summarize and conclude regarding the major societal impact of this, establishment of the digital infrastructure for kidney biopsies was indeed a revolutionary step in 2012, setting the stage for ongoing advancements both in pathology diagnostics, kidney research and student teaching. The innovation was largely the work of Bjarne Iversen, the leader of the Renal Research Group at the time. He had the foresight to realise, how useful this digital technology would be for further research work. Tragically Bjarne did not live long enough to see the realisation of his vision. He died six months before the implementation of the slide scanner he had worked so successfully to acquire.

Names of the key researchers and what positions they held at the administrative unit
Hans-Peter Marti (Professor in Nephrology, Leader of the Renal Research Group), Sabine Leh (Nephropathologist and leader of non-neoplastic kidney biopsy laboratory at the Department of Pathology, Haukeland University Hospital, Associate professor UiB), Bjørn Egil Vikse (Professor and former Professor at UiB), Øystein Solberg Eikrem (Consultant Nephrologist and Postdoctoral fellow), Einar Svarstad (Guest Researcher UiB), Camilla Tøndel (Professor, UiB), Jessica Furriol (former Postdoctoral fellow and now researcher at the RRG) and Hrafn Weishaupt (Postdoctoral fellow at Department of Pathology)

3. References to the research (indicative maximum of six references)
In the context of our case study, the section referred to as "underpinning research" is more appropriately described as "Foundational Research Infrastructure." This distinction is important as our focus lies not in presenting specific research findings but in detailing the critical establishment of the digital infrastructure that supports and enhances research endeavours. Specific references are therefore not provided in this section.

4. Details of the impact

Digital pathology fuelling research endeavours by the Renal Research Group

Advanced omics technologies from archival FFPE tissue

FFPE tissues are by far the mostly used tissue preservation method for archiving and preserving tissues for diagnostical purposes and the archives at the pathology departments worldwide are vast. Until recently these tissues were inaccessible to advanced omics technologies that has been available only the last decade. In comparison, the Human genome project took over a decade to complete in 2013. After its completion, the introduction of next generation sequencing has been a game changer. The RRG has made great contributions in method development of both proteomics and RNA sequencing in FFPE tissues. In these research projects, tissue selection is imperative and digitalized sections and annotations are of great help. In a current project the RRG is also performing automated single cell extraction of certain cell types from digitalized sections for RNA sequencing purposes.

Fabry Disease

What particularly characterises the research group for Fabry disease and for which it is internationally renowned is its intensive work with kidney biopsies. These biopsies are for example used, to demonstrate the effects of treatment. Scoring systems are here applied to quantify effects. The application of these systems and the documentation of the results would be considerably more difficult without digital slides. Research related to Fabry disease has so far led

to the publication of more than 40 scientific articles. Led by Camilla Tøndel and Einar Svarstad the Fabry research group has not only advanced scientific knowledge but has also left a lasting impact by shaping evidence-based treatment guidelines. Given the significant cost of enzyme replacement therapy, these guidelines, supported by meticulous analyses of digital histological slides, are vital in ensuring effective and economically sound patient care.

Digital pathology fuelling research endeavours by other research groups

The digital pathology system, which was put into operation in 2012, was not only intended to be used for scanning of kidney biopsies, but also enable interested research groups in general to work with digital sections. This opportunity has been taken up by research groups from a variety of backgrounds. The research section of the database contains 36 projects, 24 of which are not related to renal research.

Digital slides for student teaching

With the possibility to digitize histological slides, digital pathology was gradually introduced into student teaching, witnessing significant advancements with the advent of web-based applications. The pivotal moment for widespread acceptance among teaching staff occurred during the Covid pandemic, when the pathology teaching programme was converted to digital microscopy within weeks. The success of this transition was possible because of years of accumulated experience and a robust system already in place. In 2021, a more sustainable funding solution was secured through the allocation of infrastructure funds ("Vestlandslegen").

Helse Vest is at the forefront of development of applied digital pathology

Digitization of the Norwegian Kidney Biopsy Registry and kidney diagnostics at Haukeland University Hospital marked the inception of transformative projects within Helse Vest:

The national project digital pathology investigated solutions on a national level. The project run from 2016 – 2023 and published a couple of reports covering various topics such as “Storage of blocks, slides and digital slides in the era of digital pathology”. The project also established a solution for exchange of digital slides across health regions for teaching, quality assessment and consultation purposes.

The regional project digital pathology established full digitization of all histologic slides the 4 pathology departments in Helse Vest in 2022. With this, Helse Vest is one of the few regions worldwide with regional digitized pathology services and thus also at the forefront of implementation of KI tools for pathology diagnostics. With one focus on applied nephropathology it was possible to acquire strategic funding for development of AI tools in 2020 as well as funding for an innovation project for procurement of commercial AI solutions in 2022.

Impact beyond national borders

Sabine Leh's engagement in regional and national digitization projects, coupled with presentations sharing experiences, resulted in a significant role as a board member in the European Society for Digital and Integrative Pathology (ESDIP). In this capacity, Sabine contributes to fostering collaboration, disseminating knowledge, and promoting innovative practices within the European pathology community.

5. Sources to corroborate the impact

Advanced omics technologies from archival FFPE tissue

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Systems analyses of the Fabry kidney transcriptome and its response to enzyme replacement therapy identified and cross-validated enzyme replacement therapy-resistant targets amenable to drug repurposing. Kidney International, 2023. https://doi.org/10.1016/j.kint.2023.06.029

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Mariell Rivedal, Håvard Mikkelsen, Hans-Peter Marti, Lili Liu, Krzysztof Kiryluk, Thomas Knoop, Rune Bjørneklett, Yngvar Lunde Haaskjold, Jessica Furriol, Sabine Leh, Flavia Paunas, Janka Bábíčková, Andreas Scherer, Camille Serre, Oystein Eikrem, Philipp Strauss
Kidney International, 2023. https://doi.org/10.1016/j.kint.2023.12.010

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Fabry Disease

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Digital pathology fueling research endeavours by other research groups - examples

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Student teaching with digital slides – example

Projects digital pathology

Website Nasjonal digital patologi
Solution for exchange of images across health regions (cytomine)
Regional project digital pathology
Strategic funding "Patologi i Vest – et senter for anvendt digitalisering i patologitjenesten»
Renal Research Group, Nephropathology Projects

Impact beyond national borders

European society of digital and integrative pathology

Institution: Haukeland University Hospital (HUH), and University of Bergen (UiB)
Administrative unit: Dep. of Neurology, and Dep of Clinical Medicine
Title of case study: High-efficacy multiple sclerosis therapy to a sustainable cost to the society
Period when the underpinning research was undertaken: 2008-2024 (2012-2022)
Period when staff involved in the underpinning research were employed by the submitting institution: 2008-2024 (2012-2022)
Period when the impact occurred: 2018-2023

1. **Summary of the impact**

One of the main objectives for the Bergen MS-Research Group is to provide improved and tailored treatment in multiple sclerosis (MS). Since the early 1990's, when the first approved medication for MS were launched, our group has participated in industry- or academic sponsored clinical trials in MS. The group has facilitated Norwegian participation in more than fifty clinical trials, and pioneered early implementation of new therapies, such as mitoxantrone, natalizumab, rituximab and haematopoietic stem cell transplantation (HSCT). For a decade, the group has pioneered the use of high-efficacy off-label rituximab to a low and societal sustainable cost, in parallel with performing scientific quality control of clinical practice use of the therapy. In that way, we have implemented rituximab in national treatment guidelines (https://www.helsedirektoratet.no/retningslinjer/multippel-sklerose) and made it accessible for a large number of newly diagnosed patients. Latest update (2022) indicates that 96% of newly diagnosed patients receive early high-efficacy therapy – most of them rituximab to a low cost for the society (www.norskmsregister.no).

We have also contributed to the MSIF's (https://www.msif.org/) initiative to include MS therapies, including rituximab, on the WHO's list of essential medicines – to promote world-wide access to MS-therapies.

2. **Underpinning research**

The Bergen MS-Research Group has since the early 1990's been the leading Norwegian MS research group, especially in clinical trials in MS. The group has participated in different trials of most of the new therapeutic developments of more than twenty different substances in about fifty different trials. It started out with modest-efficacy interferon-beta injections to the current high-efficacy B-cell depleting therapies. The group has also been central in performing academic trials in Norway and Scandinavia – searching for improved treatment strategies of available therapies. When the first reports of B-cell depletion with rituximab appeared in 2008 (https://pubmed.ncbi.nlm.nih.gov/18272891/), the group started out using this off-label therapy for single patients with breakthrough disease on standard approved medications. The surprising high efficacy from the treatment, led to gradual increase in the use, along with systematic implementation of dosing and dosing interval recommendations, in collaboration with Swedish colleagues (https://pubmed.ncbi.nlm.nih.gov/27760868/). In parallel with our increasing experience of off-label use of rituximab, we were also national coordinators for industry sponsored (Roche) development of the next generation of rituximab, the humanized form, ocrelizumab, and thus gained a systematic experience in B-cell depletion for MS. At the time when ocrelizumab (https://pubmed.ncbi.nlm.nih.gov/28002679/) was approved for MS treatment by the Food and Drug Administration (FDA), USA (2017), and by the European Medicines Agency (EMA), Europe (2018), we had already establish rituximab as an off-label routine therapy at Haukeland University Hospital.

We had also by then established a quality control system for the off-label rituximab therapy through the Norwegian MS-Registry. We were able to confirm the surprisingly high efficacy of the treatment, reported by Swedish colleagues, at least at the level that were reported from

the ocrelizumab trials. Thus, based on this experience, we had established a routine treatment strategy of rituximab as a first-line therapy at an annual cost of about 7 500 NOK, and realized we would not be able to continue this practice with newly approved ocrelizumab at price of about 230 000 NOK, thus more than 30 times the price of rituximab.

Realizing this challenge, we made a strategic plan aiming at continuation for high-efficacy therapy, by off-label rituximab, at a sustainable cost for the society, which included several initiatives:

1. We submitted an initiative to perform an Norwegian Health Technology Assessment of MS-therapy, including rituximab.
2. We submitted a proposal to perform a non-inferiority, double-blinded randomized clinical trial comparing rituximab to ocrelizumab – The «OVERLORD-MS trial».
3. We submitted an initiative to update Norwegian MS-Treatment Guidelines to include rituximab as a treatment option.
4. We designed several studies for evaluation efficacy and safety of rituximab in clinical practice – thus generating real would evidence data.
5. We established international collaboration to promote rituximab at a sustainable cost for the society world-wide – through the Multiple Sclerosis International Federation

Key researchers and what positions they held at the administrative unit.

Dr Kjell-Morten Myhr (https://www.uib.no/en/persons/Kjell-Morten.Myhr), Professor in Neurology and Senior Consultant in Neurology at University of Bergen (UiB) and Haukeland University Hospital (HUH) is the chair of the Bergen MS-Research group (https://www.uib.no/en/rg/ms). **Dr Øivind Torkildsen** (https://www.uib.no/personer/%C3%98ivind.F..Grytten.Torkildsen), Professor in Neurology and Senior Consultant in Neurology at UiB and HUH is principal investigator (PI) of the «OVERLORD-MS trial**». Dr Lars Bø** (https://www.uib.no/personer/Lars.B%C3%B8) Professor in Neurology and Senior Consultant in Neurology at UiB and HUH, is the chair of the Norwegian quality and competence network for MS at HUH. **Dr Stig Wergeland** (https://www.uib.no/personer/Stig.Wergeland_1) Associate Professor in Neurology and Senior Consultant in Neurology at UiB and HUH, is the chair of the Norwegian MS-Registry at HUH. **Dr Silje Skrede** (https://www.uib.no/personer/Silje.Skrede) Professor in Clinical Pharmacology and Senior Consultant in Pharmacology at UiB and HUH, is the chair of the Pharmacology Research Group at UiB and HUH.

Drs **Gro Owren Nygaard** and **Marton König**, Clinical Neurologists and researchers at Oslo University Hospital that are key collaborators on several of the rituximab projects.

3. References to the research

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2. Hauser SL, Bar-Or A, Comi G, Giovannoni G, Hartung HP, Hemmer B, et al. ; OPERA I and OPERA II Clinical Investigators. Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis. N Engl J Med 2017;376:221-234. doi: 10.1056/NEJMoa1601277. PMID: 28002679 (https://pubmed.ncbi.nlm.nih.gov/28002679/).
3. Torgauten HM, Myhr KM, Wergeland S, Bø L, Aarseth JH, Torkildsen Ø. Safety and efficacy of rituximab as first- and second line treatment in multiple sclerosis - A cohort study. Mult Scler J Exp Transl Clin 2021;7:2055217320973049. doi: 10.1177/2055217320973049. PMID: 33796328 (https://pubmed.ncbi.nlm.nih.gov/33796328/)
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Lab 2022;25:53-60. doi: 10.1016/j.jmsacl.2022.07.004. PMID: 35910410 (https://pubmed.ncbi.nlm.nih.gov/35910410/)
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4. Details of the impact

1. Norwegian Health Technology Assessment (HTA) of MS-therapy, including rituximab:
The "Nye metoder" (New Methods) (https://www.nyemetoder.no/english/), the national system of managed introduction of new methods in the specialist health care services in Norway, approved our suggestion to perform an overall HTA of MS-therapy, and concluded in 2019 that rituximab had comparable efficacy and safety as other high-efficacy MS-therapies, but that more data should be available, preferable through randomized trials.

They concluded that:

- Rituximab is approved for treatment of relapsing remitting multiple sclerosis (RRMS) in Norway, given that the patients was informed of the off-label therapy.
- Treatment with rituximab should be registered in the Norwegian MS registry.

2. Suggestion of a non-inferiority, double-blinded randomized clinical trial comparing rituximab to ocrelizumab – The «OVERLORD-MS trial»:

By October 2019, The Regional Health Authorities of Norway (KlinBeForsk - https://kliniskforskning.rhf-forsk.org/) granted funding of 19.2 MNOK for the "Ocrelizumab VErsus Rituximab Off-Label at the Onset of Relapsing MS Disease (OVERLORD-MS) (https://classic.clinicaltrials.gov/ct2/show/NCT04578639). The clinical trial received all approvals during 2020 – and started recruitment November 2020, and was fully recruited by November 2022. This is a double blinded randomized non-inferiority study of newly diagnosed RRMS patients, with new MRI T2 lesions as endpoint. All patients are observed for 30 months and results are expected in Q2/Q3 2025. In addition, we have established collaboration with research groups in Copenhagen and Amsterdam, performing similar head-to-head trials, that are still recruiting (https://classic.clinicaltrials.gov/ct2/show/NCT04688788; https://classic.clinicaltrials.gov/ct2/show/NCT05834855)

3. **Initiative to update Norwegian MS-Treatment Guidelines to include rituximab as a treatment option:**
   The Norwegian Directorate of Health accepted the suggestion of updating the MS-Guidelines, and the revised version were launched in 2022. The Norwegian MS Guidelines are among the most offensive guidelines world-wide, recommending high-efficacy therapy at diagnosis, including the option to use rituximab (https://www.helsedirektoratet.no/retningslinjer/multippel-sklerose). The latest annual report from the Norwegian MS-registry shows that 96% of newly diagnosed patients are receiving high-efficacy therapy from the time of diagnosis (https://www.kvalitetsregistre.no/sites/default/files/2023-06/%C3%85rsrapport%202022%20Norsk%20MS-register%20og%20biobank_0.pdf)

4. **Research evaluating the efficacy and safety of clinical practice using rituximab:**
   The Bergen MS-Research Group has studied various aspects of safety and efficacy of off-label rituximab therapy in RRMS. Rituximab is the most frequent used MS-therapy in MS at our Department and in Norway. We have shown that rituximab is highly effective https://pubmed.ncbi.nlm.nih.gov/33796328/), but patients receiving therapy have a small but significant increased risk of hospitalisation due infections (https://pubmed.ncbi.nlm.nih.gov/36842313/). The treatment induces long-lasting effects – and is therefore an attractive option for use prior to planned pregnancy, and we have shown that rituximab is safe during breastfeeding (https://pubmed.ncbi.nlm.nih.gov/35879056/). We have also shown that rituximab effectively reduces the risk of rebound after termination of fingolimod therapy, another MS-therapy (https://pubmed.ncbi.nlm.nih.gov/35462167/). Although rituximab reduces the humoral vaccination response (https://pubmed.ncbi.nlm.nih.gov/35072702/ and (https://pubmed.ncbi.nlm.nih.gov/34670844/) – the treatment seems safe without any increased risk for severe covid infections (***manuscript in press***)

   In addition, we are performing studies in basic pharmacology, developing methods for quantification of serum concentration of rituximab and ocrelizumab (https://pubmed.ncbi.nlm.nih.gov/35910410/), and evaluate mode of action through complement activation (https://pubmed.ncbi.nlm.nih.gov/37816262/).

5. **Establish international collaboration to promote rituximab at a sustainable cost for the society.**
   Professor Myhr, the Norwegian MS Society representative in the Scientific Advisory Bord of the Multiple Sclerosis International Federation (https://www.msif.org/), has contributed with important rituximab real world experience for the application of including MS-therapies on the WHO's Essential Medicines List – that succeeded for the first time in 2023.

In summary, the Bergen MS-Research Group's initiative for highly effective MS therapy at sustainable costs for society, will facilitate access to such therapy throughout Norway. Our initiative has contributed to the MSIF initiative to include MS therapies on the WHO's list of essential medicines. Awaiting the results of our RCT ((https://classic.clinicaltrials.gov/ct2/show/NCT04578639) – which will hopefully confirm that rituximab is not inferior compared to ocrelizumab – we will contribute with results that could have an impact across Europe and the rest of the world.

5. Sources to corroborate the impact

- **Norwegian Health Technology Assessment (HTA) of MS-therapy, including rituximab:** https://www.nyemetoder.no/4a4f08/siteassets/documents/rapporter/disease-modifying-treatments-for-relapsing-remitting-multiple-sclerosis-including-rituximab-hta-rapport-2019.pdf

- **Norwegian decision on the approval of use of rituximab for multiple sclerosis:** (https://www.nyemetoder.no/metoder/legemidler-inkludert-off-label-behandlingen-rituksimab-ved-rrms-fullstendig-metodevurdering-/

- **Norwegian Guidelines for diagnosis and treatment of multiple sclerosis:** https://www.helsedirektoratet.no/retningslinjer/multippel-sklerose

- **The Regional Health Authorities of Norway (KlinBeForsk) decision for funding the "OVERLORD-MS Trial":** https://kliniskforskning.rhf-forsk.org/149-millioner-kroner-til-klinisk-behandlingsforskning/

- **Clinicaltrials.gov registration of the "OVERLORD-MS Trial":** https://classic.clinicaltrials.gov/ct2/show/NCT04578639).

- **Annual Report of the Norwegian MS-Registry 2022:** https://www.kvalitetsregistre.no/sites/default/files/2023-06/%C3%85rsrapport%202022%20Norsk%20MS-register%20og%20biobank_0.pdf

- **Multiple Sclerosis International Federation – press release WHO Model List of Essential Medicines:** https://www.msif.org/wp-content/uploads/2023/07/MSIF_WHO-EML-decision_press-release_FINAL.pdf

- WHO Model List of Essential Medicines - 23rd list, 2023: https://iris.who.int/bitstream/handle/10665/371090/WHO-MHP-HPS-EML-2023.02-eng.pdf?sequence=1

Institution: University of Bergen (UiB) and Haukeland University Hospital, Helse Bergen (HB)
Administrative unit: Section of Neurology, Department of Clinical Medicine (K1), UiB, and Neurology Clinic, Haukeland University Hospital, HB
Title of case study: NAD-replenishment therapy as a disease modifying strategy for neurodegeneration
Period when the underpinning research was undertaken: 2012-2017
Period when staff involved in the underpinning research were employed by the submitting institution: 2012-2022
Period when the impact occurred: 2021-2022

2. Summary of the impact (indicative maximum 100 words)

Building on their underpinning research, which highlighted the role of mitochondrial dysfunction and nicotinamide adenine dinucleotide (NAD) metabolism in Parkinson's disease (PD), the group proposed NAD-replenishment therapy as a potential disease-modifying strategy. By conducting clinical trials, they discovered that it is possible to increase NAD levels in the human brain using nicotinamide riboside (NR). Furthermore, they showed that NR-treatment augments NAD metabolism in PD, and this is associated with improved cerebral metabolism and clinical improvement. These findings have nominated NAD-therapy as a neuroprotective strategy for PD and have led to multiple ongoing trials, and significant intellectual property and commercialization endeavours.

2. Underpinning research (indicative maximum 500 words)

During 2012-2014, while conducting mechanistic research on mitochondrial disease, Prof. Tzoulis (the Director of the DECODE-PD group) discovered that aberrant mitochondrial DNA (mtDNA) maintenance led to severe respiratory complex I deficiency and degeneration of the dopaminergic *substantia nigra* neurons, a neuronal population that is severely affected in Parkinson's disease. These findings were published in seminal, highly cited papers, and prompted the group to investigate the role of mtDNA maintenance and mitochondrial respiratory dysfunction in Parkinson's disease (PD).

In 2016, Prof. Tzoulis and the DECODE-PD group published findings showing that mtDNA maintenance is indeed impaired in the dopaminergic *substantia nigra* neurons of individuals with PD. Specifically, they performed single-neuron studies in different brain regions and discovered that, while dopaminergic substantia nigra neurons of healthy individuals responded to an age-dependent accumulation of somatic deletions by upregulating their total mtDNA copy number, this compensation was blunted in PD, resulting in loss of wild-type mtDNA. Studying genomic data from their patients and other larger cohorts, they were able to show that this aberrant mtDNA homeostasis in PD is partly driven by polygenic inherited variation – a finding later confirmed by other groups. Furthermore, they showed that mitochondrial respiratory chain dysfunction, primarily in the form of complex I deficiency, is not limited to the substantia nigra, as previously thought, but affects neurons throughout the PD brain. These highly cited studies, published during 2016-2018, greatly strengthened the evidence for a pathogenic mitochondrial contribution in PD and provided new mechanistic insight in terms of the role of mtDNA maintenance and respiratory deficit.

During 2015-2017, while exploring the downstream impact of impaired mitochondrial respiration in PD, Prof. Tzoulis hypothesized that this may lead to aberrant NAD-metabolism. Directly showing NAD-deficiency in the patient brain was challenging at the time, due to the volatile nature of this metabolite after death. Instead, they studied the state of histone acetylation which is largely regulated by NAD-dependent enzymes (i.e., sirtuins). Intriguingly, they found that the PD brain is

characterized by genome-wide increased histone acetylation and dysregulation of gene expression, which are plausibly linked to decreased NAD-dependent deacetylation.
These findings provided for the first time a link between mitochondrial impairment, aberrant NAD-metabolism and epigenomic dysregulation in PD. Dysfunction in this pathway may be key to understanding and treating PD due to both its fundamental role in cell function and survival, but also its amenability to therapy via the administration of NAD-precursors.

- Names of the key researchers and what positions they held at the administrative unit at the time of the research (where researchers joined or left the administrative unit during this time, these dates must also be stated).
- Any relevant key contextual information about this area of research.

Prof. Charalampos Tzoulis, Professor of Neurology, Senior Consultant of Neurology, Director of the DECODE-PD group
Dr Christian Dölle, Senior Researcher, DECODE-PD group
Dr Irene Fløtnes, Postdoctoral Fellow, DECODE-PD group
Dr Johannes Gaare, Senior Researcher, DECODE-PD group
Dr Lilah Toker, Senior Researcher, DECODE-PD group

3. References to the research (indicative maximum of six references)

1. Tzoulis C*, Tran GT, Schwarzlmüller T, Specht K, Haugarvoll K, Balafkan N, Lilleng PK, Miletic H, Biermann M, Bindoff LA. *Severe nigrostriatal degeneration without clinical parkinsonism in patients with POLG mutations.* Brain. 2013 Aug;136(Pt 8):2393-404. doi: 10.1093/brain/awt103.
2. Tzoulis C*, Tran GT, Coxhead J, Bertelsen B, Lilleng PK, Balafkan N, Payne B, Miletic H, Chinnery PF, Bindoff LA. *Molecular pathogenesis of polymerase γ-related neurodegeneration.* Ann Neurol. 2014 Jul;76(1):66-81. doi: 10.1002/ana.24185
3. Dölle C, Fløtnes I, Nido G, Miletic H, Kristoffersen S, Lilleng KP, Larsen JP, Tysness OB, Haugarvoll K, Bindoff LA, and Tzoulis C*. *Defective mitochondrial DNA homeostasis in the dopaminergic substantia nigra of patients with Parkinson's disease.* Nat Commun. 2016 Nov 22;7:13548. doi: 10.1038/ncomms13548.
4. Brakedal B, Fløtnes I, Dölle C, Torkildsen Ø, Assmus J, Engeland A, Haugarvoll H and Tzoulis C*. *Glitazone use associated with reduced risk of Parkinson's disease.* Mov Disord. 2017 Sep 1. doi: 10.1002/mds.27128.
5. Fløtnes I, Fernandez-Vizarra E, Lykouri M, Brakedal B, Skeie GO, Miletic H, Lilleng PK, Alves G, Tysnes OB, Haugarvoll H, Dölle C, Zeviani M and Tzoulis C*. *Widespread neuronal complex I deficiency in Parkinson's disease.* Acta Neuropathol. 2018 Mar;135(3):409-425. doi: 10.1007/s00401-017-1794-7.
6. Toker L, Tran GT, Sundaresan J, Tysnes OB, Alves G, Haugarvoll K, Nido G, Dölle C, and Tzoulis C*. *Dysregulation of histone acetylation and decoupling from transcription in Parkinson's disease.* Mol. Neurodegeneration. 2021 May 5;16(1):31. doi: 10.1186/s13024-021-00450-7.

4. Details of the impact (indicative maximum 750 words)

Based on the findings of their underpinning research, the DECODE-PD group proposed that treatments increasing brain NAD levels may have neuroprotective, disease-modifying potential against PD and other neurodegenerative disorders.
To test their hypothesis, in 2018 they initiated randomized, double-blinded phase I-II clinical trials of NAD-replenishment in PD, using the NAD-precursor nicotinamide riboside (NR). These studies led to the **seminal discovery that it is possible to increase NAD levels in the human brain using oral NR**. Furthermore, they showed that NR: **1)** is safe in PD; **2)** increases NAD levels in the human brain and related metabolites in cerebrospinal fluid (CSF); **3)** improves brain metabolism; **4)** is associated

with clinical improvement; **5)** induces a potent systemic augmentation of the NAD metabolome and activates pathways critical to mitochondrial respiration and proteostasis; **6)** reduces neuroinflammation. Collectively, these findings **nominated NAD-replenishment with NR as a neuroprotective therapy for PD** and led to seminal publications [1–3], as well as extensive recognition by the field, as illustrated by independent commentaries published in scientific journals[4,5] and highlighted by major PD organizations[6].

Moving forward, during 2020-2022, these findings led to the initiation of national and multinational phase II/III trials of NAD-therapy for PD, led by Prof. Tzoulis and the DECODE-PD group. The largest of these trials, NOPARK[7], will include 400 patients from 12 Hospitals throughout Norway, thereby, offering hundreds of individuals with PD the opportunity to participate. Additionally, the findings of the DECODE-PD group have led to the initiation of a multinational clinical trial of NAD-replenishment therapy for atypical parkinsonian syndromes (APS), including progressive supranuclear palsy (PSP), multiple system atrophy (MSA) and corticobasal syndrome (CBS)[8]. APS are major and entirely unaddressed health challenges.

Furthermore, the discoveries of the DECODE-PD group have triggered multiple trials of NAD-replenishment therapy all over the world, for different neurological diseases, including ALS, and dementia.

The group's findings have also formed the basis for an innovation project which has secured IP for the use of NR as a treatment for PD and has now entered the commercialization phase. This project was also supported by a KOMMERSFORSK grant by the RCN.

Beneficiaries of these results include: 1) the patients with PD and atypical parkinsonisms; 2) their families and caretakers; 3) the Norwegian health services; 4) the Norwegian society; 5) the global society; 6) the global scientific field; 7) the pharmaceutical industry.

How these stakeholders benefit from this work is described below.

The specific impacts of this work include:

1. For the first time, large phase II and III treatment studies for PD and atypical parkinsonisms were initiated and conducted in Norway, providing hope and experimental treatment options for these patients (**more than 500 patients are currently enrolled in trials in Norway**). Moreover, this led to the establishment of a national network for clinical trials for these disorders, with readiness and infrastructure to conduct multiple future trials. This has enormous benefits for patients and their caretakers, the Norwegian health services, and society.

2. Improve care for these patients by systematic high-quality follow-up and establishment of new and improved clinical routines.

3. By bringing us closer to disease-modifying drug, contribute to decreased disability, care-giver burden, and need for institutionalization. This will be a major benefit to healthcare and society, including cuts of related direct and indirect socioeconomic costs.

4. Contribute to training Norwegian neurologists across the country in diagnosing and treating PD and related disorders. This directly improves the care of individuals with these rare diseases.

5. Raise awareness about PD and related disorders so that more research is carried out, using our study and data as a starting point, or in new directions.

6. Positive trial results will provide level 1b evidence (UK CEBM) for new treatments, resulting in grade A practice recommendation (i.e. treatment should be used to treat PD, unless a clear and compelling rationale for an alternative approach is present). Thus, positive results from the projects alter standard medical practice.

7. Research results lead to innovation and commercialization projects. For instance, their ongoing innovation work aims to develop NR into a regulated drug for PD, and other neurodegenerative disorders. Four patents based on the group's previous and ongoing findings have been submitted, describing > 50 claims involving different indications and compositions of NR therapy in PD and other parkinsonisms. This innovation work has already picked up the interest of several major industries, some of which have already expressed explicit interest. The filings can be found here:

https://patents.google.com/patent/WO2022269064A1/en?oq=WO2022269064A1
https://patents.google.com/patent/WO2023209010A1/en?oq=WO2023209010A1

5. Sources to corroborate the impact (indicative maximum of ten references)

1. Brakedal, B. *et al.* The NADPARK study: A randomized phase I trial of nicotinamide riboside supplementation in Parkinson's disease. *Cell Metab* **34**, 396-407.e6 (2022).
2. Gaare, J. J. *et al.* Nicotinamide riboside supplementation is not associated with altered methylation homeostasis in Parkinson's disease. *iScience* **26**, 106278 (2023).
3. Berven, H. *et al.* NR-SAFE: a randomized, double-blind safety trial of high dose nicotinamide riboside in Parkinson's disease. *Nat Commun* **14**, 7793 (2023).
4. Kriebs, A. NAD supplementation in Parkinson's disease. *Nat Aging* **2**, 274–274 (2022).
5. Martínez-Villota, V. A., Rossi, M. & Castillo-Torres, S. A. Nicotinamide Adenine Dinucleotide Supplementation in Parkinson's Disease: A Potential Disease-Modifying Agent Targeting Multiple Pathways. *Movement Disorders Clinical Practice* **9**, 735–736 (2022).
6. Bailey, S. Nicotinamide riboside for Parkinson's: pilot results published. *Cure Parkinson's* https://cureparkinsons.org.uk/2022/03/nicotinamide-riboside-for-parkinsons/ (2022).
7. Haukeland University Hospital. *A Randomized Controlled Trial of Nicotinamide Supplementation in Early Parkinson's Disease: The NOPARK Study*. https://clinicaltrials.gov/ct2/show/NCT03568968 (2020).
8. Haukeland University Hospital. *The NADAPT Study: A Randomized Double-Blind Trial of NAD Replenishment Therapy for Atypical Parkinsonism*. https://clinicaltrials.gov/study/NCT06162013 (2023).

University of Bergen, Department of Clinical Science] Impact case 1

Institution: University of Bergen (UiB)
Administrative unit: Department of Clinical Science
Title of case study: Catching the rhythms
Period when the underpinning research was undertaken: 2015-2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2012-2022
Period when the impact occurred: 2020-22

1. Summary of the impact

Hormones are secreted in pulses and convey their message, not only by their concentrations, but by their rhythms. Disruption of hormone rhythms is an early sign of endocrine disease, which until now has been difficult to detect outside the research setting. Current clinical practice using conventional single–time point measurements of hormone levels in blood provide very limited information about rhythmicity and, crucially, do not provide information during sleep, a time when many hormones show huge fluctuations.

To overcome this problem and to measure free hormones within their target tissues, we used microdialysis, an ambulatory fraction collector, and ultra-sensitive liquid chromatography–tandem mass spectrometry to obtain high-resolution profiles of tissue adrenal steroids over 24 hours while the person being investigated did daily life activities.

We were able to define **"**dynamic markers**"** of normality in healthy individuals stratified by sex, age, and body mass index, and to identify how these biomarkers change in hormonal diseases. The technology represents a sea change in understanding hormone rhythms and provide a unique tool to develop new and more sensitive diagnostic procedures for endocrine diseases. It is a way to investigate the patient during sleep – a period when hormones display great dynamic variability but when the person is usually unavailable for testing. The technology can be adapted to other settings where dynamic changes in tissue metabolites is of interest, such as drug metabolism, and in situations where blood volume is an issue as in neonatal intensive care.

2. Underpinning research

Essential for the impact was 25 years of translational research in endocrinology building on registries and biobanks of carefully phenotyped patients and world-leading expertise in steroid metabolomics using liquid chromatography tandem mass spectrometry.

A major hurdle has been the insensitive methods to diagnose endocrine diseases. Many hormones fluctuate with rhythms of varying frequencies. Some follow the light-dark cycle (circadian), some are shorter than 24-hours (ultradian rhythms), while others are monthly such as the menstrual cycle. In addition, many hormones are largely bound to proteins in the circulation, while the free biologically active fraction is minute. The levels of hormone binding proteins also show great variation among individuals and their levels are subject to change by common medications. For example, contraceptive pills increase total cortisol levels in serum by inducing the production of cortisol-binding protein. All these factors contribute to very wide reference ranges, making it difficult to know if an isolated hormone value is normal or not.

Our long-term goal has been to develop simple and cost-effective methods to monitor hormone rhythms in a clinical setting. Because of the complexity of such an endeavour we built an international consortium of clinicians, specialists in biochemistry and clinical chemistry,

mathematicians and engineers to solve this complex issue. We applied for EU-funding in Horizon-2020 on a call for patient-near devices and were funded as one of 9 out of 460 applications.

Two major hurdles were crossed in the project. In collaboration with UK-based Designworks Windsor our consortium developed the **U-rhythm sampling device** that made it possible to sample microdialysis fluid over 24 hours from a catheter located in the subcutaneous tissue on the abdomen. In parallel, we developed an ultrasensitive automated method to measure up to 20 different steroids in microdialysis fluid volumes down to 5 µl in 72 fractions covering 24 hours by liquid chromatography tandem mass spectrometry. Utilising these developments, we sampled healthy subjects (see Figure) and patients with overproduction of aldosterone (primary aldosteronism, PA), and cortisol (Cushing's syndrome), and lack of these hormones (adrenal insufficiency), and developed new diagnostic criteria based on dynamic biomarkers and criteria for monitoring replacement therapy, respectively.

So far, the adrenocortical hormone profiles of healthy subjects have been published in Science Translational Medicine (High-resolution daily profiles of tissue adrenal steroids by portable automated collection - PubMed (nih.gov)) and the results on the clinical trials in primary aldosteronism, Cushing's syndrome and adrenal insufficiency are forthcoming. These developments will enable us to detect early perturbation in hormone rhythms and make a diagnosis early before organ complications develop. The results have made big impact in the scientific community including an accompanying editorial (Closing the loop on adrenal health, dysfunction, and disease | Science Translational Medicine).

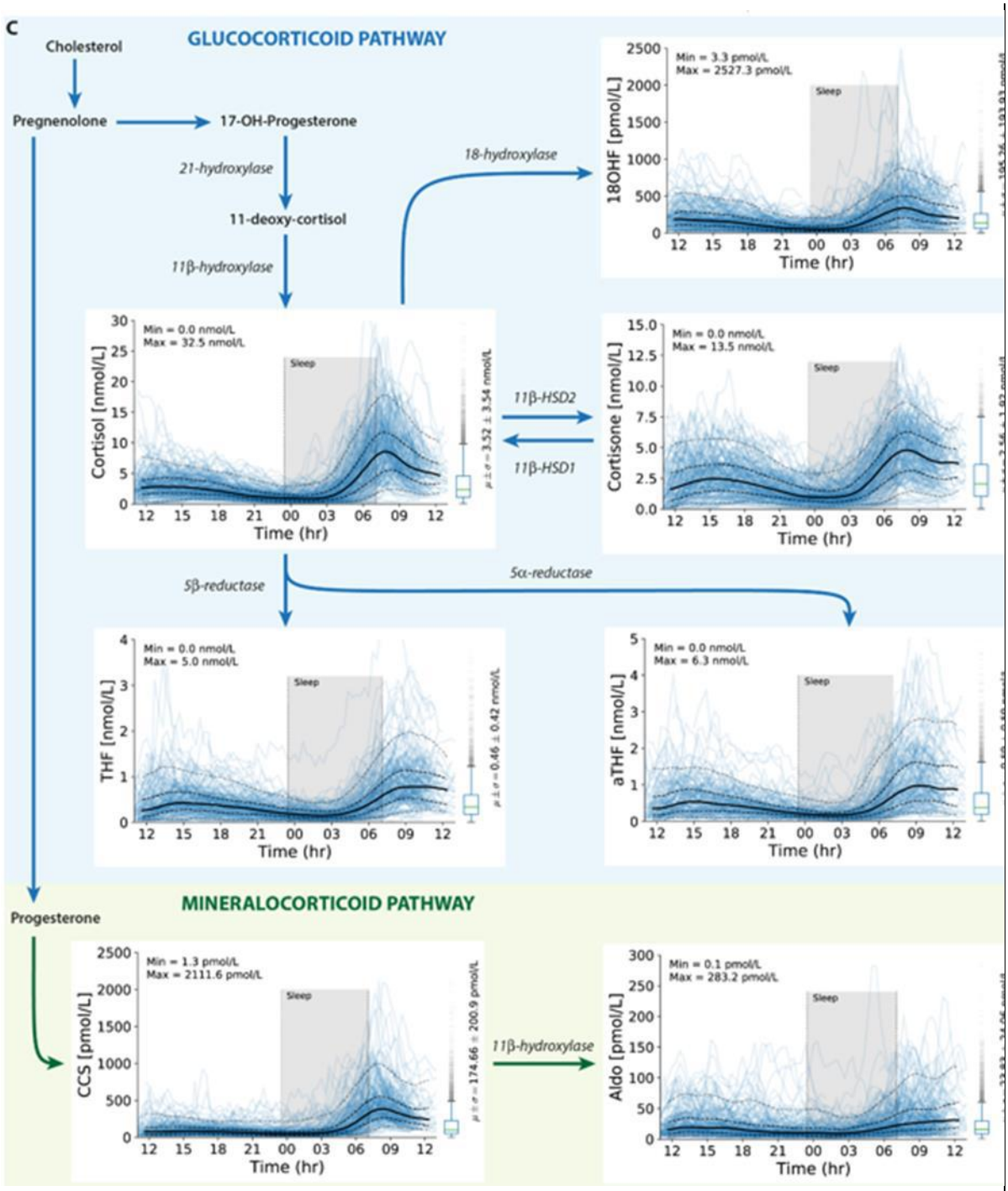
Names of the key researchers and what positions they held at the administrative unit
Professor **Eystein Husebye (PI)** is the **head of The Endocrine Medicine group** and The National Registry on adrenal insufficiency. Husebye coordinated H2020-Ultradian and FP7-Euradrenal and was the head of K.G. Jebsen Center for Autoimmune Diseases, and Focus Lead for adrenal and cardiovascular endocrinology in the European Society for Endocrinology.
Associate professor **Paal Methlie** is an endocrinologist and expert in metabolomics. He developed the mass spectrometry method for H2020-Ultradian and performed the steroid analyses. Associate professor **Marianne Øksnes**, MD PhD **Marianne Grytaas,** MD PhD **Grethe Ueland**, and MD PhD **Marianne Astor** are all consultant endocrinologist, and experts in clinical trials involving dynamic hormone measurements and have been involved in the Ultradian project. Professor **Helge Ræder** is professor and paediatric endocrinologist with clinical experience in adrenal insufficiency and the use of wearables.

3. References to the research

1) Upton et al. High-resolution daily profiles of tissue adrenal steroids by portable automated collection. Sci Transl Med. 2023. doi: 10.1126/scitranslmed.adg8464 (PMID: 37343084)
2) Husebye ES et al. Adrenal insufficiency. Lancet. 2021. doi: 10.1016/S0140-6736(21)00136-7. (PMID: 33484633)

4. Details of the impact

The Endocrine Medicine group has brought together reputable researchers, dynamic entrepreneurs, and well-established companies from different disciplines and countries to collectively push the boundaries of knowledge and technological development at the intersection between *endocrinology, mathematics* and *medical device technology*. With diseases of hormone excess and deficiency we have demonstrated for the first time that it is



From Upton et al, Science Translational Medicine, Free concentrations of adrenal hormones in 214 healthy subjects. The figure displays 24-hour profiles of seven different adrenal steroids over of both the glucocorticoid (cortisol, cortisone, 18OH-cortisol, tetra-hydro-cortisol (THF), allo-tetra-hydro-cortisol (aTHF) and mineralocorticoid (Aldo, aldosterone; CCS, corticosterone) pathways.

feasible to obtain interpretable 24-hour continuous dynamic hormone profiles that can be used to diagnose and monitor patients with endocrine diseases in the out-patient setting. Thus, we have demonstrated for the first time that hormone profiling is feasible in the outpatient setting (Ultradian Hormone Diagnostics | University of Bergen (uib.no)).

Scientific impact
Our dynamic profiling method provide the scientific community with a versatile research tool to address a number of scientific questions regarding hormone rhythms; how they vary during stress and different physiological conditions such as illness, exercise and sleep.

This ultradian dynamic profiling provides clinicians with a tool that can make more complicated testing of the endocrine system superfluous, thereby making diagnostic evaluation faster and more cost-effective. Furthermore, dynamic hormone profiling will enable clinicians to monitor replacement therapy in adrenal insufficiency, a condition where the adrenal is unable to secrete adequate amounts of steroids, and in monitoring hormone levels in critically ill patients.

The technology also opens up for measurement of other analytes that show dynamic variation such as metabolites of intermediary metabolism and drugs.

Economic/technological impact
The dynamic hormone profiling can be combined with other wearable devices that can register physiological and environmental factors thereby providing additional input to aid interpretation of hormone rhythms. Examples of such input are tissue glucose and lactate, blood pressure, pulse, movement, and sleep. Data sets can be trained into models providing a basis for a digital twin development in the future.

The global market for wearables offers an immense business opportunity a marked that is forecasted to reach US$1.1Trn by the end of 2031. The size of this market reflects the increasing prevalence of chronic diseases and the advances in healthcare IT infrastructure. With the existing trend to increase investments in the global digital health industry (towards the development of effective wearable devices and eHealth platforms), one of the critical barriers limiting market expansion is the lack of technological tools and experts. The dynamic hormone profiling method we have developed addresses these needs. The U-rhythm device developed by our consortium has already been spun out to a company and further development will equip researchers and clinicians with a easy and reliable way to measure dynamic hormone profiles from patients.

Societal impact

Our sampling method contributes to the shift from hospital to home-based data collection, which increases quantity and quality, patient comfort and cost-effectiveness, which will ultimately change the way diagnosis and treatment decisions are made. This shift is expected to happen naturally and gradually as the various tools and devices are introduced, but will be supported by communication to policymakers, health payers and broader audiences.

The path to societal impact goes through providing scientific evidence through clinical trials and building trust in the solutions thorough transparent engagement with patients and healthcare systems. It also involves validating and building trust in tools for self-management of chronic disease which requires significant user involvement. Close collaboration with patient organizations will be an important step to secure this.

5. Sources to corroborate the impact (indicative maximum of ten references)

- Editorial in Science Translational Medicine: Closing the loop on adrenal health, dysfunction, and disease | Science Translational Medicine
- Commentary in Nature Reviews Endocrinology: Non-invasive daily profiles of tissue adrenal steroids | Nature Reviews Endocrinology
- The U-rhythm device spinout company: Pioneering Portable Biosampling — U-RHYTHM
- BBC: Device developed in Bristol offers 'revolution' in hormone understanding - BBC News
- Presentation of Ultradian in "Indremedisineren": Ultradian Hormone Diagnostics – Fremtidens måte å diagnostisere hormonsykdommer? | Indremedisineren
- News, University of Bergen: New U-Rhythm prototype | Ultradian Hormone Diagnostics | UiB
- News and features, University of Bristol: June: U-RHYTHM device | News and features | University of Bristol

University of Bergen, Department of Clinical Science] Impact case 2

Institution: University of Bergen
Administrative unit: Department of Clinical Science (K2)
Title of case study: Changing clinical practise in childhood diabetes by precision medicine
Period when the underpinning research was undertaken: 2012 - 2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2012 - 2022
Period when the impact occurred: 2012 - 2022

1. Summary of the impact

Diabetes affects 0.5% of the Norwegian child population. The prevalence is increasing, and the disease is a great burden due to acute and long-term complications. Our research has uncovered novel disease mechanisms in childhood diabetes, established tools for differentiating specific subgroups of patients, and developed new and personalized care. The findings allow preventive strategies and precision diagnostics contributing to new classification protocols supporting precision treatment strategies. Change in treatment in patient subgroups can improve quality of life and metabolic control, reduce future life-threatening common complications of diabetes, avoid unnecessary treatments, reduce costs and excessive mortality rates associated with complications.

2. Underpinning research

Diabetes is a heterogenous disease.

Diabetes is a major cause of morbidity and mortality around the world. No treatment has been able to cure or prevent this disease which prevalence increases epidemically. Diabetes represents multiple phenotypes with different etiologies and mechanisms, which makes it challenging to classify diabetes and to personalize treatment. Present research and health care focus primarily on type 1 diabetes (T1D) and type 2 diabetes (T2D). The former entails an autoimmune destruction of insulin-producing β-cells. Fifty per cent of T1D patients are children. T2D is multifactorial and heterogeneous, often associated with obesity. Most cases of diabetes fall within these two entities (10% T1D, 85% T2D). The remaining cases are diabetes arising secondary to other diseases, or monogenic diabetes including neonatal diabetes with disease onset before six months of age, and Maturity-Onset Diabetes of the Young, MODY, with onset of diabetes between six months and 25-35 years of age. There are several subtypes of MODY. The most frequent is MODY2, which is caused by mutations in the glucokinase (*GCK*) gene, and MODY3, caused by mutations in the hepatocyte nuclear factor-1alpha (*HNF1A*) gene.

Childhood diabetes is more than type 1 diabetes

Whereas heterozygous *GCK* mutations cause MODY2, we had previously discovered that homozygous *GCK* mutations can cause neonatal diabetes (3.1). A new cause of diabetes was identified establishing also that diabetes in neonates is a genetic disease. That was important for the later discovery done by colleagues at the University of Exeter. They found a mutation in the potassium channel gene *KCNJ11* in a patient with neonatal diabetes and reached out to us. We screened our collection of neonatal diabetes and confirmed the finding in 50% of our cases resulting in a joint publication (3.2). An aspect of *KCNJ11* neonatal diabetes was that many patients had neurological challenges. We were the first to perform IQ tests and discovered in 2020 that one mutation was highly associated with severe intellectual disability (3.3).

Encouraged by the important findings that *GCK* and *KCNJ11* can cause pediatric diabetes, using exome sequencing, we screened the Norwegian Childhood Diabetes Registry in collaboration with researchers at Oslo University Hospital and discovered that up to 6.5% of children that did not harbour autoimmune antibodies carried pathogenic or suspected pathogenic variants in several MODY genes (3.4). We repeated the screening by exome sequencing five years later and focused

on the most common gene, *HNF1A* (3.5) Adding functional studies in β-cell models, we could estimate that 0.3% of the pediatric diabetes population carry pathogenic genes variants in *HNF1A*.

Genetics can inform change of treatment in childhood diabetes

KCNJ11-neonatal diabetes was believed to be insulin-dependent for life. However, since it was known that the anti-diabetes drug sulfonylurea binds to the potassium channel, which was affected in children with *KCNJ11* neonatal diabetes, we tested and discovered in three children that sulfonylurea could restore the channel function and replace insulin. We were the first to publish this result, which was ground-breaking since sulfonylurea can be taken orally while insulin must be taken by injections (3.6). The news spread rapidly through the International Society for Pediatric and Adolescent Diabetes (ISPAD) and various meetings, and several studies followed. We then joined with researchers at the University of Exeter and Hôpital Necker Enfants Malades in Paris and characterized 50 children that had successfully been switched to sulfonylurea, establishing the principle (3.7). It was still an open question whether this effect could remain in the long term. After ten years, we took the initiative to do an international, multicenter follow-up study involving 90 patients from all over the world. Indeed, we found that sulfonylurea is safe, even with high doses, and excellent glycemic control was maintained during the follow-up period of mean ten years (3.8). It had been speculated that early introduction of sulfonylurea could improve neurological delay since the sulfonylurea receptor gene is expressed in the brain. Unfortunately, we could not observe improvement with early introduction of sulfonylurea (3.3).

We had previously observed that patients with MODY3 were very sensitive to sulfonylurea (3.9). Thus, we included children identified with variants in *HNF1A*, pathogenic and with unclear significance, to a treatment trial with sulfonylurea. All children carrying pathogenic variants and two of three carrying variants of unknown significance could be transferred to sulfonylurea (3.5).

PRECISE-DIA: a large center and clinical unit with 67 researchers

We have access to large, Norwegian population-based clinical and genetic data from three diabetes registries and three health surveys in addition to many international cohorts and biobanks through collaboration. The team has competence in clinical medicine, genomics, epigenetics, statistical genetics, bioinformatics, proteomics, biochemistry, structural biology, stem cell biology and animal models. PRECISE-DIA is located at the Children's Hospital at K2 and Haukeland Medical Campus.

Key researchers involved in the impact case

Ingvild Aukrust, Ph.D.: post doc, associate professor (2013-present).
Lise Bjørkhaug, Ph.D.: Ph.D. student, postdoc, professor (1998-2013).
Alba Kaci, Ph.D.: Ph.D. student (2016-2010).
Henrik Irgens, M.D., Ph.D.: Ph.D. student, consultant physician (2017-present).
Bente B. Johansson, Ph.D.: post doc, senior engineer (2010-present).
Stefan Erik Johansson, Ph.D.: post doc, professor (2004-present).
Janne Molnes, Ph.D.: Ph.D. student, senior engineer (2001-present).
Anders Molven, Ph.D.: professor (2004-present)
Pål Rasmus Njølstad, M.D., Ph.D.: professor (2000-present) (**leader**).
Helge Ræder, M.D., Ph.D.: Ph.D. student, postdoc, professor (2003-present).
Jørn Vegard Sagen, M.D, Ph.D.: PhD student, post doc, professor (2000-2022).
Marie Holm Solheim, Ph.D.: Ph.D. student, post doc (2014-2020).
Åsta Sulen, M.D.: student (2016-2020).
Pernille Svalastoga, M.D.: Ph.D. student (2019-2023).
Oddmund Søvik, M.D., Ph.D.: professor, professor emeritus (1992-2019).
Erling Tjora, M.D., Ph.D.: Ph.D. student, consultant physician (2010-present).

3. References to the research

3.1: Njølstad PR, Søvik O, Cuesta-Muñoz A, Bjørkhaug L, Massa O, Barbetti F, Undlien DE, Shiota C, Magnuson MA, Molven A, Matschinsky FM, Bell GI. Neonatal diabetes mellitus due to complete glucokinase deficiency. *N Engl J Med.* 2001 May 24;344(21):1588-92. doi: 10.1056/NEJM200105243442104. PMID: 11372010.

3.2: Gloyn AL, Pearson ER, Antcliff JF, Proks P, Bruining GJ, Slingerland AS, Howard N, Srinivasan S, Silva JM, Molnes J, Edghill EL, Frayling TM, Temple IK, Mackay D, Shield JP, Sumnik Z, van Rhijn A, Wales JK, Clark P, Gorman S, Aisenberg J, Ellard S, Njølstad PR, Ashcroft FM, Hattersley AT. Activating mutations in the gene encoding the ATP-sensitive potassium-channel subunit Kir6.2 and permanent neonatal diabetes. *N Engl J Med.* 2004 Apr 29;350(18):1838-49. doi: 10.1056/NEJMoa032922. PMID: 15115830.

3.3: Svalastoga P, Sulen Å, Fehn JR, Aukland SM, Irgens H, Sirnes E, Fevang SKE, Valen E, Elgen IB, Njølstad PR. Intellectual Disability in K(ATP) Channel Neonatal Diabetes. *Diabetes Care.* 2020 Mar;43(3):526-533. doi: 10.2337/dc19-1013. PMID: 31932458.

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*This article is from 2023, but the data was presented at several international and national meetings, eg Nordic Society for Human Genetics and Precision Medicine (Copenhagen, 2022), International Society of Pediatric and Adolescent Diabetes (Abu Dhabi, 2022 and Lisboa/virtual, 2021), and Norwegian Diabetes Meeting (Sundvolden, 2021). The results were henceforth disseminated widely already in 2021 why we included the paper in the impact case.

4. Details of the impact

From discoveries to clinical practise

Our findings have provided new diagnostic and prognostic strategies for patient care.

For 20 years ago, it was commonly believed that diabetes in children was equal with type 1 diabetes and insulin requirement for life. We proved that this was not the case. The five seminal articles published in the *New England Journal of Medicine, Lancet Diabetes and Endocrinology* (3.1, 3.2, 3.7, 3.8) and *Diabetes* (3.6) made a large impact for the health systems and changed the clinical practise. This is illustrated by editorial comments to our discoveries (5.1-5.4). New procedures for diagnostics and treatment emerged in guidelines of childhood diabetes around the world (5.5).

Precision diagnosis: Our findings showed that there was a subgroup of children with apparent type 1 diabetes and life-long insulin requirement that had other subtypes of diabetes. Before our discovery (3.1), it was believed that children with diabetes diagnosed early in life had an autoimmune type 1 diabetes. Our findings changed this notion and neonatal diabetes was now recognized as a genetic disease. Diagnosing the new subtypes, GCK-neonatal diabetes, and KCNJ11-neonatal diabetes as well as MODY subtypes in childhood diabetes, made a large impact as it provided a correct and a precise diagnosis and could inform choice of treatment (see below) and genetic counselling. As for the latter, many of the new subtypes of neonatal diabetes and all MODY subtypes are dominantly inherited. Hence, there is a 50% disease recurrence risk for the mother`s future pregnancies as well for the affected children`s future pregnancies.

Precision treatment: The immediate impact for the patients is that they can avoid painful insulin injections and frequent capillary blood sugar measurements. In addition, the metabolic control improved over ten years with a reduction in average HbA1c for individual patients from mean 65 to 46 mmol/mol, which is a remarkable change. Since the risk for diabetes-associated late complications are related to HbA1c values, children being transferred to sulfonylurea have a significantly reduced risk for complications in the future. Most patients (and their caretakers) who had *HNF1A* mutations and were transferred to sulfonylurea, experienced improved metabolic control in addition to no injections and improvement of quality of life (3.5). This change in clinical practice is also implemented in international guidelines of childhood diabetes (5.5).

Dissemination and communication of our discoveries

Our dissemination had a broad reach in the academic community because our research generated ground-breaking findings that were **published in high-profile medical journals, such as** *New Engl J Med*, *Lancet Diabetes Endocrinol*, and top special journals like *Diabetes Care*, *Diabetes*, and *Diabetologia*.

Our open access strategy ensured that a wide academic community benefitted from our research. We provided **free access to summary and raw data** in accordance with FAIR principles. Our group is member of national and international **scientific societies and consortia** (eg. ISPAD, European Association for the Study of Diabetes, American Diabetes Association, American Society of Human Genetics, Early Growth Genetics, Nordic Society of Human Genetics and Precision Medicine) and we frequently presented our results at their conferences.

To bring our research findings beyond academia, we **collaborated with clinicians, hospitals and patient organisations.** Our findings were of immediate relevance (precise diagnosis, new treatment, genetic counselling) to patients and caring clinicians. Connected to our PRECISE-DIA research center, we developed a clinical unit at Haukeland University Hospital where we could be consulted digitally. This service gained wide interest. We now receive referrals from the whole country every week. Our Center and activities were highlighted in the Norwegian Minister of Health and Care Services` "National Strategy for Personalized Medicine 2023-2030" (5.6).

We organise an annual Open Day on the World Diabetes Day 14 November. Here, we bring together clinicians, researchers, parents, children, and the **patient organization Norwegian Diabetes Association**, and inform about the findings and discuss the implications of the research.

Our findings have attracted Norwegian media, eg. local newspaper Bergens Tidende (5.7), national newspaper Dagens Medisin (5.8), and national television NRK (5.9) and TV2 (5.10).

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[University of Bergen, Department of Clinical Science Impact case 3

Institution: University of Bergen
Administrative unit: Department of Clinical Science
Title of case study: Heart Disease in Women
Period when the underpinning research was undertaken: 2002-22
Period when staff involved in the underpinning research were employed by the submitting institution: 2002-2022
Period when the impact occurred: 2018-20

1. Summary of the impact

The impacts of 2 decades of research on heart disease in women was 1) that the European Society of Cardiology included sex-specific thresholds for identification of hypertensive heart disease in the updated guidelines on management of hypertension that was published in 2018, and 2) that Centre for Research on Cardiac Disease in Women was established in 2020 at the University of Bergen (UiB) funded by private industries and non-governmental ideal organizations.

2. Underpinning research

Eva Gerdts was granted a scholarship from the Norwegian Medical Association in 2001 to focus on clinical studies of **sex differences in hypertension**. She was granted additional funding from the UiB through a postdoctoral fellowship from 2002. The project was performed within an international research collaboration with professor Richard B. Devereux and several research periods at Cornell Medical Centre in New York during 2001-2006, and represented a novel and original research focus at that time. Key research findings included that 1) women have better systolic function than men with hypertension, 2) women were more prone to develop cardiac organ damage like left atrial enlargement or left ventricular hypertrophy in hypertension, and 3) women had less regression of this cardiac organ damage during systematic antihypertensive drug treatment than men. Taken together, it seemed that hypertension was more damaging to the female heart. Eva Gerdts was employed as full professor at UiB in 2006, and a focused research group and a digital laboratory for advanced analyses of ultrasound images was established. This enabled performance of several clinical studies with focus on **heart disease in women.** Several PhD fellows and medical research students joined the group which grew like a tree with several branches. 1) PhD fellow Dana Cramariuc (now associate professor at UiB) focused on **sex differences in valvular heart disease (aortic valve stenosis)** and has developed a collaboration with Harvard University. 2) Research student Åshild E. Rieck went on to perform a PhD project on **the effect on hypertension on the aorta, aortic valve and the heart muscle** in aortic valve stenosis demonstrating the combined effects of sex and hypertension. She is now consultant PhD at Bærum Hospital. 3) PhD fellow Mai Tone Lønnebakken (now professor at UiB) focused on **non-obstructive coronary artery disease in women** using advanced ultrasound method initially and later cardiac computed tomography angiography. 4) PhD fellow Helga Midtbø (now senior researcher at UiB and consultant at Haukeland University Hospital [HUH]) demonstrated the **importance of hypertension for heart disease in women with rheumatoid arthritis.** She has continued her research on the **role of inflammation for heart disease in women** as postdoctoral fellow and now as senior researcher at the Centre and has developed a research collaboration with Karolinska Institute, Stockholm. 5) Eva Gerdts developed a new international research collaboration with professor Giovanni de Simone, Federico II University, Napoli, Italy who was an expert on obese heart disease. The collaboration from 2011-21 was initially funded by NRC, and later by Helse Vest and UiB and included exploration in the large Campania Salute Project database on how obesity contributed to the observed **sex differences in hypertensive and obese heart disease**. The key finding was that the risk of major cardiovascular events (myocardial

infarction, atrial fibrillation or heart failure) increased relatively more in women compared to men with hypertension when women developed left ventricular hypertrophy, independently of presence of obesity. 5) During 2018-21 the group collaborated with professor Grethe Tell (Department of Global and Public Health) to perform a new survey (the 3rd) in the Hordaland Health Study, collecting cardiovascular health information on 2200 women and men to further study **cross-sectional and longitudinal sex specific effects of hypertension, obesity and inflammation on incident organ damage and cardiovascular disease**. PhD fellow Ester Kringeland (now consultant at HUH) discovered in her studies 2018-21 that the **risk for heart disease increases at a lower blood pressure level in women** than in men. This challenges the current standard that the same blood pressure threshold is used in both sexes. Her findings were broadcasted in 100 countries. She will return as postdoctoral fellow at the Centre from March 2024 to continue her work.

Name, positions and employment at Department of Clinical Science of key researchers:
Eva Gerdts, PhD fellow 1993-6, postdoctoral fellow 2002-6, professor 2006-dd
Dana Cramariuc, PhD fellow 2007-9, postdoctoral fellow 2010-5, associate professor 2021-dd
Åshild E. Rieck, PhD fellow 2009-12
Mai Tone Lønnebakken PhD fellow 2008-10, postdoctoral fellow 2010-14, associate professor 2015, full professor 2019-dd.
Helga Midtbø, PhD fellow 2012-16, postdoctoral fellow 2016-21, senior researcher 2021-dd
Ester Kringeland, PhD fellow 2018-22

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4. Details of the impact

Impact 1. Inclusion of sex-specific thresholds for identification of hypertensive heart disease in the European Society of Cardiology guidelines on management of hypertension in 2018

The collaboration with world masters on documenting the difference between women and men in hypertensive heart disease in several different patient cohorts and both in USA and in Europe helped calling attention to our results. Abstracts were presented annually on the most important scientific meeting organized by the American Heart Association, the European Society of Cardiology (ESC) and the European Society of Hypertension. Our publications targeted high-end journals in the field of hypertension and cardiology and inspired several important research groups

in the USA and in Italy to enter our research field. The academic professor title gave further weight and recognition, as did several awards of research prizes. The research group got involved in European networks targeting sex and gender differences in cardiology and co-authored several important position and review papers. When we published the sex difference in prognostic impact of hypertensive heart disease, this was picked up by the ESC guideline committee and sex specific threshold values for identification of hypertensive heart disease was incorporated in the ESC 2018 Guidelines on management of hypertension as the new standard for clinical practice in cardiology. This document influenced management of hypertension in Europe and many other parts of the world. Eva Gerdts was invited by the ESC to chair a scientific publication on sex differences in hypertension in 2020. She was also elected as board member of the ESC Council on Hypertension in 2018, which gave the possibility to organize a number of webinars focusing on heart disease in women using their platform focusing on genetic mechanisms that underpin the cardiac differences that we described, and how biological sex plays a substantial role in disease etiology, onset, and progression, and sociocultural gender on disease risk, symptom recognition, disease manifestations, access to care, quality of care, and adherence
to treatment recommendations.

Impact 2. Establishment of Centre for Research on Cardiac Disease in Women at UiB in 2020

The initiative to fund the Centre was taken by representative from private industry non-governmental ideal organizations that served on the advisory board of Hjertefondet (the heart fund) at UiB. This made it possible to scale up the research and to organize a national conference (the Female Heart Workshop) to create interaction between national researchers and PhD fellows in the field and network opportunities with international masters. Around 200 national researchers and PhD fellows have so far participated. National attention was achieved because of several research prizes, including the Faculty of Medicine prize for best innovation and research 2020, the research prize from Helse-vest in 2021, and the heart research prize from the Norwegian Public Health Association in 2021. The government established a working group focusing on women's health, and the Centre contributed with research information and description of the importance of knowledge gaps on heart disease in women to the Norwegian official report 2023(5) in Women's health and sex disparities in health. Our contribution is reflected in several of the action points listed in the report. The report has the potential to reform current health professional education programs, health care services and our society at large if followed up politically.

5. Sources to corroborate the impact

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University of Bergen, Department of Clinical Science Impact case 4

Institution: University of Bergen (UiB)
Administrative unit: Department of Clinical Science
Title of case study: Pandemic preparedness: the COVID-19 case
Period when the underpinning research was undertaken: 2020-22
Period when staff involved in the underpinning research were employed by the submitting institution: 2020-22
Period when the impact occurred: 2020-22

1. Summary of the impact

Our early epidemiological, clinical and immunological findings during the COVID pandemic have shaped policy decisions at national and international levels. We identified key factors that reduce transmission (infections in diverse settings) and discovered an association between persisting long COVID symptoms, even after mild cases, and high immune responses. Our contributions have extended to the World Health Organisation (WHO) Solidarity antiviral study and four vaccine clinical trials, providing relevant guidance for treatment and vaccine utilisation. We played an important role in offering scientific counsel to national and international advisory bodies and have actively engaged in public outreach, including innovative science education approaches. Our research has been recognised for its substantial contributions to effective infection control measures, and a deeper understanding of the long-term consequences of COVID-19 which will aid future pandemic preparedness.

2. Underpinning research

Essential for our success was our 30 years of experience in bench to bedside research of collaboration between clinicians and laboratory-based scientists and our extensive experience in clinical trials (phase I to IV), placebo controlled randomized clinical trials and prospective longitudinal cohort studies. Building on this experience we expanded to a multidisciplinary research collaboration in February 2020. Our research focused on key clinical, epidemiological, and immunological aspects of SARS-CoV-2 in the general population, risk groups, and frontline healthcare workers across Western Norway. Our total team of 30 members was led by Rebecca Cox and Nina Langeland. Our impactful research was recognised with the prize for Best Research Group in 2022 at the Faculty of Medicine, UiB.

Our work in 2020-22 successfully identified critical factors that contributed to SARS-Cov-2 transmission in households, along with insights into healthcare service and nursing home vulnerabilities. These early findings played a pivotal role in shaping local, national, and international policy decisions and will be integral for control measures against future emerging pathogens.

We explored risk factors and the prevalence of short and long-term sequalae after SARS-CoV-2 infection identifying fatigue, dyspnoea and cognitive impairment as key long COVID symptoms. We discovered that persisting symptoms, even in mild cases, were closely related to high levels of SARS-CoV-2 immune responses. Our findings have also illuminated the plight of those suffering from long COVID, emphasising the need for comprehensive healthcare support and planning, extending beyond severe cases to encompass those with mild infections, adolescents, and young adults. We are continuing our research mission by coordinating antiviral clinical trials and rehabilitation long COVID intervention studies in Norway in randomized controlled clinical trials.

A significant part of the Infection and Microbiology group´s work spearheaded by The Influenza Centre involved the development of a wide array of immunological assays. We evaluated the magnitude, breadth, and longevity of immune responses post-infection and after vaccination in all age ranges from one to 103 years old. Our research revealed surviving hospitalized patients exhibited higher magnitude and breadth of convalescent immune responses than community-isolated patients, although immune responses post-vaccination were similar. We found that both

the humoral and cellular immune responses are higher in individuals with post viral sequelae. In 2021, our research showed the elderly needed two vaccine doses at a three-week interval and ideally a first booster dose already after 5 months.
As the virus evolved with novel variants of concern emerging, our research adapted accordingly. Our centralized SARS-CoV-2 testing in Bergen municipality allowed us to identify the risk of reinfection with different variants among previously infected or vaccinated individuals. We determined that the period of vaccine protection diminished, particularly with the emergence of variants like Delta and Omicron. This information was crucial for defining revaccination strategies for various age and risk groups.
Our work has been widely recognized, with 27 high-impact publications in 2020-22 on SARS-CoV-2 in prestigious medical journals such as Nature Medicine, Lancet Infectious Diseases, and Clinical Infectious Diseases. Our contributions have substantially advanced the fields of post infection sequelae, infection control and pandemic preparedness.
We have actively engaged in national and international advisory roles, providing scientific counsel to various national and international bodies and organizations. Our public outreach efforts, including innovative science education approaches, have played a vital role in disseminating knowledge and fostering understanding in the general public. Furthermore, our online presence, featuring our dedicated website and extensive participation in media discussions, has allowed us to reach diverse audiences both within Norway and internationally providing trustworthy information in a period of information disinformation.

Names of the key researchers and what positions they held at the administrative unit

Rebecca Cox (Professor in Medical Virology UiB and Haukeland University Hospital (HUH leads the Research group in Infection and Microbiology and head the Influenza Centre. Her co-lead on COVID-19 research is Nina Langeland (Professor and Senior Consultant in Infectious Diseases). Key members during the COVID-19 pandemic working at UiB and HUH are Professor and Senior Consultant Infectious Diseases Bjørn Blomberg, Assoc. Professor and Senior Consultant in Infectious Diseases and Acute Medicine Kristin Mohn, Senior Consultant in paediatrics and leader of clinical trials unit Professor Camilla Tøndel, as well as Professor in Immunology Karl Brokstad (UiB and Western Norway University of Applied Science) and Senior consultant and Professor Bård Kittang (UiB, Haraldsplass Deaconess Hospital, Bergen Municipality).

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3. Details of the impact

In early 2020, the Infection and Microbiology group embarked on a collective mission to understand clinical, epidemiological, and immunological aspects of SARS-CoV-2 in Western Norway meeting UiBs strategical goal "*knowledge that shapes society*". Our multidisciplinary consortium, comprising outbreak scientists, virologists, infectious disease clinicians and immunologists, representing collaboration between the Universities, Bergen municipality, and major hospitals in the Western Norway region.
The following section highlights how our work was important in shaping the pandemic responses.

Shedding light on the long-term effects of COVID-19

We identified factors to reduce infection in households, healthcare settings, and nursing homes, shaping future infection control protocols and informing local, national, and international policies. Our research defined risk factors and the prevalence of short and long term sequalae after SARS CoV-2 infection from the first cases in Bergen contributing to UiBs strategy "*of a sustainable development by top-quality scientific research*". We found long-term complications even after mild disease, and in adolescents and young adults including shortness of breath, fatigue, and cognitive problems (memory loss and concentration difficulties). We further showed that persisting symptoms are related to high levels of SARS-CoV-2 humoral and cellular immune responses. Our research emphasized the need for preparedness efforts that encompass patients with long-term sequelae, advocating for a holistic approach to managing the aftermath of COVID-19. Our Nature Medicine paper on long COVID in mild cases was recognized in 2021 for the best scientific paper at the Faculty of Medicine, UiB, and by the Norwegian Infectious Diseases Society. This paper has been cited over 500 times is ranked 1st of the 123 tracked articles of a similar age in Nature Medicine and 30th of 436 219 similarly aged tracked articles in all journals.

Advancing treatment and vaccination measures

The Infection and Microbiology group´s work spearheaded by The Influenza Centre developed a portfolio of SARS-CoV-2 immunological assays and observed differences in immune responses between hospitalized and community-isolated patients. Vaccination reduced these differences, but emerging variants rapidly reduced vaccine protection. The rapid development and deployment of COVID-19 vaccines has been important in protecting high-risk groups and health care workers from severe disease and death. However, there was limited participation in licensing trials for understudied groups such as children and the elderly. We therefore ran investigator initiated clinical studies identifying the need for early booster vaccination in healthcare workers and the elderly over 80 years. Rebecca Cox, Camilla Tøndel and Kristin Mohn conducted a phase I trial of a Norwegian COVID vaccine from Nykode and three phase II EU funded Vaccelerate clinical trials of COVID vaccines to evaluate optimal timing and need for booster doses in the elderly and adults, as well as whether previously infected children require one or two vaccinations.
Bjørn Blomberg, Bård Kittang, Kristin Mohn and Nina Langeland participated in the World Health Organization's Solidarity trials through the NOR-Solidarity trials. These trials rapidly identified the most promising antiviral drugs for treatment of COVID-19 in hospitalized patients. Five publications have so far resulted from these trials. Nina Langeland, Bjørn Blomberg and Rebecca Cox are involved the Precious initiative which has combined over 1700 datasets from >64000 long COVID cases to understand the impact of COVID-19 by measuring the long-term effects, predicting recovery, and identifying support needs for those living with debilitating long COVID.

Sharing knowledge during the pandemic

We were highly productive, publishing 27 scientific papers up to 2022 in prestigious medical journals. We contributed widely to education of students, scientists and health care workers at UiB and internationally through webinars, and a school of respiratory viruses in India in 2022. Four Ph.D. students defended their PhDs in 2022 which included COVID-19 research. Anders Madsen received the Medical Faculty's best Ph.D. prize for his research on influenza and COVID-19 which was conducted concurrently with his medical education. Four new PhD students were enrolled in the group. During this period, we regularly presented our research in lectures, webinars and online conferences to meet "*to educate candidates to take on the challenges of a changing world*". Since 2019, Rebecca Cox has been deputy chair of the international society for influenza and other respiratory viruses (isirv). She organised several international conferences including Options for the Control of Influenza XI, with over 1200 delegates Northern Ireland in 2022 including a mini school for young scientists to meet the experts. Overall, our body of work significantly influenced policy changes at various levels, guiding Norwegian vaccination strategies and shaping pandemic responses worldwide.

Our efforts played a pivotal role in connecting our research with the wider community through trustworthy public dissemination. Our researchers were interviewed >1000 times in over 20 media channels including television, radio, newspapers and in magazines about COVID-19 contributing to UiBs vision of "*sharing knowledge for a sustainable* society". Our online presence through the Influenza Centre website effectively disseminated research updates and information to a global audience. Our COVID-19 science education and public dissemination initiatives extended to participatory theatre, podcasts, short videos and a board game "The Pandemic is over". Rebecca Cox received the Meltzer prize for excellent scientific dissemination in 2022, recognising our efforts and underscoring the importance of our research.

Impact upon pandemic response

We assumed roles as scientific advisors to influential organizations, which further solidified our impact. Rebecca Cox was appointed in 2017 the WHO Strategic Advisory Group of Experts (SAGE) on Immunization for influenza vaccination which compiled interim guidelines in 2020 for Seasonal Influenza Vaccination Recommendations during the COVID-19 Pandemic.

The Influenza Centre's work on COVID vaccines led to Rebecca Cox being appointed the national coordinator for the EU H2020 funded Vaccelerate project to advance COVID vaccine development and evaluation in Europe, with five publications so far. Rebecca Cox was appointed as a Member European Medicines Agency Scientific Advisory Group on Vaccines in 2022.

In 2020, Rebecca Cox served as a scientific advisor to the European Commission's Group of Chief Scientific Advisors with the development of the policy-based Scientific Opinion on Pandemics. She also served as a scientific advisor to the UK on human challenge from 2020-2021. Rebecca Cox and Nina Langeland have been members of the European Commission's expert group on SARS-CoV-2 variants from 2021.

Rebecca Cox was a member of the study group National Academy of Science, Engineering and Medicine (NASEM) in the USA, which looked at lessons learned from the COVID-19 pandemic to develop recommendations to optimize vaccine research and development for future seasonal and pandemic influenza. In 2022 Rebecca Cox was appointed to the WHO Technical Advisory Group on the full value of influenza vaccines assessment, became a Member European Medicines Agency Scientific Advisory Group Vaccines and joined Nina Langeland as a member of The Norwegian Academy of Science and Letters.

Rebecca Cox, Kristin Mohn and Nina Langeland were members of two expert groups: the Norwegian National Knowledge programme on COVID-19 and the expert group on COVID-19 vaccines providing scientific advice to the Norwegian government. Nina Langeland sat in the two independent Coronavirus Commissions which comprehensively reviewed and evaluated the Norwegian authorities handling of the pandemic from 2020 to 2022. She was appointed as leader of the regional ethical committee for Western Norway in 2021 for a 4-year period. She leads the Reference group for National competence for CFS/ME at Oslo University Hospitals.

Shaping future pandemic response strategies

Through our earlier pandemic/epidemic preparedness work and permanent funding from the Department of Health and Care Services for the Influenza Centre, UiB and HUH， we were ideally situated to rapidly respond to the COVID-19 pandemic. In 2020-22, we joined national and international consortia and received over 40 million NOK in grant funding for 9 projects supported by the EU H2020, EU Innovative Health Initiative, Norwegian Research Council in partnership with Trond Mohn Foundation and Western Norway Regional Health authority research fund. The latter recognized Kristin Mohn with a clinical fellowship from 2022 to 2027, a post-doctoral position for young talented medical doctor Anders Madsen and provided funding for a PhD student. From 2023, Norway will lead the EU initiatives for alignment and coordination of European clinical and public health research on infectious disease with epidemic potential. Nina Langeland will co-lead this Coordination Mechanism for Cohorts and Trials (CoMeCT) was recently funded by the EU Horizon Health Program placing Norway at the heart of European efforts to align preparedness plans.

For the future, The Infection and Microbiology group has built a multidisciplinary team in Western Norway covering the municipalities, nursing homes, and city hospitals which will allow broad scientific collaboration on future outbreaks, epidemics, and pandemics. We have established a national network for research on prevention of post sequelae complications after viral infections. Our research work continues with ongoing financed projects and an unwavering commitment to future pandemic preparedness and the challenges that lie ahead.

Sources to corroborate the impact.

1. **EU H2020 *Vaccelerate* project.** European Corona Vaccine Trial Accelerator Platform. Cox is National coordinator and WP leader. https://vaccelerate.eu
2. **Commentary on SARS-CoV-2 specific immune responses.** Cox RJ, Brokstad KA. Not just antibodies: B cells and T cells mediate immunity to COVID-19. Nat Rev Immunol. 2020;20(10):581-582. IF 108.6, https://pubmed.ncbi.nlm.nih.gov/32839569/
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4. **Corona commission mandate assessing management of the pandemic by the Norwegian authorities. https://www.koronakommisjonen.no/mandate-in-english/**
5. European SARS-CoV-2 expert group to advise Union and the EEA

https://ec.europa.eu/transparency/expert-groups-register/screen/expert-groups/consult?lang=en&groupId=3791&fromMeetings=true&meetingId=27935

6. **National Academies of Sciences, Engineering and Medicine on lessons learned from the COVID-19 pandemic to optimize vaccine research and development for future seasonal and pandemic influenza events. https://nap.nationalacademies.org/catalog/26282/vaccine-research-and-development-to-advance-pandemic-and-seasonal-influenza-preparedness-and-response**
7. **Press release for Coordination of European Union coordination of preparedness responses (CoMeCT) https://www.fhi.no/en/projects/comect/#:~:text=CoMeCT%20(Coordination%20Mechanism%20for%20Cohorts,nationally%20and%20at%20EU%20level.**
8. **Precious initiatives for measuring the long COVID https://www.preciouscovidoutcomes.org**
9. **First international in person conference in 2022 https://www.optionsxi2022.org.uk**
10. **WHO interim recommendations for influenza vaccination during COVID-19** https://www.who.int/publications/m/item/who-sage-seasonal-influenza-vaccination-recommendations-during-the-covid-19-pandemic

UiO_DentFac_1

Institution: University of Oslo
Administrative unit: Faculty of Dentistry
Title of case study: Dental anxiety in individuals exposed to sexual abuse and/or torture
Period when the underpinning research was undertaken: 2003- 2020
Period when staff involved in the underpinning research were employed by the submitting institution: 1998-2024
Period when the impact occurred: 2000-2024

1. Summary of the impact (indicative maximum 100 words)

From 2003 Willumsen´s research group has explored dental anxiety and sexual abuse experiences. In 2011, the Norwegian authorities decided to establish a treatment service for people subjected to sexual abuse, torture or odontophobia (TOO). Based on her research, Willumsen led the work to develop the treatment programs in TOO. It soon emerged that knowledge of torture experiences and dental treatment was very sparse. The research group´s studies from 2013-20 have raised awareness of the impact of oral health challenges in torture victims and laid the foundation for better clinical treatment. TOO treatment is now offered all over Norway by the public dental health.

2. Underpinning research (indicative maximum 500 words)

The research group has worked with cooperation between researchers in dentistry and psychology. Initially in an RCT study dental anxiety was treated by using three contrasting treatment principles. Dental anxiety decreased substantially in all three treatment groups also in a 5- year follow up (2003). During this trial it emerged that several of the participants had experiences of sexual assault and/or torture that complicated the anxiety treatment. Thus, in a questionnaire study (2004) we found that women with sexual abuse experiences often have dental anxiety and that they often are unaware of a connection between the sexual assaults and problems receiving dental treatment. This aspects were further explored in a quantitative study where we found that dental anxiety in sexual abuse victims often were trauma- driven, giving flashbacks of the traumatic event (2019, 2020). In the study it was indicated that these reactions were in contrast to a more phobia driven anxiety were fear of painful treatment and other concrete situations were more prominent. In this study the informants also expressed that dentists often have very limited knowledge and seldom seemed to be aware of this problem. Consequently, as people often are unaware or reluctant to speak about traumatic experiences like sexual abuse or torture many dentists treat traumatized patients without attention to their special needs.

Oral health challenges in torture victims had to our knowledge never previously been explored systematically. The research group, now involving a medical specialist, dr med Birgit Lie, proceeded with a quantitative study comparing oral health challenges in refugees with or without torture experiences (2013-2015). A high proportion of current refugees in Norway reported having been subjected to torture and/or sexual abuse, and these traumatized individuals demonstrated significantly more oral health problems, dental anxiety, and difficulties with seeking dental care compared to other refugees. Dental anxiety was also closely related to symptoms of posttraumatic stress (PTSD).

In 2018-2020 the research group further explored torture victims' challenges with seeking and undergoing dental treatment in a qualitative study. The results indicated that the predicaments with subjecting to dental treatment was closely related to the objectification experienced when having to hand over control to others. The analyses resulted in concrete clinical advice to dental personnel treating torture victims – advice which all has the end goal of enhancing the patients' sense of control and safety. These findings show the importance of a trauma sensitive approach to all dental patients is important as part of professional dental care.
Names of the key researchers: - Olav Vassend Cand psycol, dr. philos, employed at The Faculty of dentistry as professor 1988- 2005 - Tiril Willumsen Cand odont, dr. odont employed at UiO as phd student 1995- 1999, post doc 1999- 2003, Associate Professor from 2003 to 2012, and as Professor from 2012 to the present date. - Ann Catrin Høyvik cand odont, PhD, employed at UiO as PhD fellow from 2013 to 2021 (50%), and as Assistant Professor from 2021 to the present date.

3. References to the research

1. Willumsen T, Vassend O. Effects of Cognitive Therapy, Applied Relaxation and Nitrous Oxide Sedation. A Five-years Follow-up Study of Patients Treated for Dental Fear. Acta Odontol Scand. 2003; Apr;61(2):93-9.
2. Willumsen T. The impact of sexual abuse on dental fear. Community Dent Oral Epidemiol. 2004; Feb;32(1):73-9.
3. Halvorsen B, Willumsen T. Willingness to pay for dental fear treatment: Is such treatment profitable? Eur J Health Econ. 2004; Dec;5(4):299-308..
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6. Høyvik, A. C., Willumsen, T., Lie, B., & Hilden, P. K. (2021). The torture victim and the dentist: The social and material dynamics of trauma re-experiencing triggered by dental visits. *Torture Journal*, *31*(3), 70–83. https://doi.org/10.7146/torture.v32i3.125290

4. Details of the impact (indicative maximum 750 words)

Educational impact

Graduate education

The underpinning research performed by the research group has been essential in development of the curriculum for dental students. The impact from the research and focus on victims of sexual- and eventually torture experiences have introduced trauma- sensitive care as part of dental behavioral sciences.

Today, all dental personnel educated in Norway should have this knowledge.

Continuous education

Dental anxiety and sexual abuse

Members of the research group have presented research and clinical implications from the research nationally as well as internationally.

Examples: Both Høyvik and Willumsen have given a substantial number of lectures throughout Norway as well as in Denmark and Sweden (2012- 22).

Wíllumsen has been giving systematic continuing education courses arranged in cooperation with the Norwegian Dental Association. This course has been given locally in all Norwegian counties as part of a program with 2 x 2 days lectures and group-based home assignments (2016- 2022).

Torture experiences and dental treatment

Høyvik has given lectures in interdisciplinary forums, thereby increasing the awareness and knowledge of the impact of oral health in the identification and rehabilitation of torture victims.

Examples: TADA – seminars for dental personnel and psychologists (2012-23), Norwegian Directory of Health, (2017) International Organization for Migration (2018), Norwegian Institute of Public Health (2018), Red Cross symposium (2020) International congress participation (CED-IADR) 2017 and 2019, Danish Institute Against Torture, 2016 and 2020

Text books

Willumsen has initiated and edited:

- Odontologisk psykologi (Gyldendal, 2018)
- Oral Heath Psychology (Springer, 2022)

Høyvik is portrayed in "Our Voices – Torture Survivors" (2022)

Award
Willumsen was awarded with "Akademikerprisen" for "excelled contributions to academic freedom and communication of knowledge"

Clinical impact
The TADA project
The earliest publications on dental anxiety in victims of sexual abuse were important references in a report from the Norwegian Helsedirektoratet from 2009. IS 1844 (Dental health services adapted for people who have been victims from torture, abuse or odontophobia) where it was encouraged to establish interdisciplinary treatment (dentists and psychologists) in all the counties in Norway to offer this type of treatment (the TADA project).
In 2012, a national working group was established. The working group was given responsibility for building competence and developing a national competence enhancement programme. Based on her research, Willumsen was elected leader of the group.
From 2012, the working group explored and tested specific competence necessary for providing quality care, and established guidelines for inclusion criteria and treatment methods. The first national guide was developed by the working group and was published in 2014.
In 2016, the service was expanded to include interdisciplinary teams in all counties in Norway. Now in 2024 treatment is being offered to people across the country. The need for TADA treatment is far greater than the authorities expected and at the moment there are long waiting lists at all treatment sites. From 2016- 2020, 5300 individuals have been included and treated in the TADA project.

The TADA-focus on torture survivors, as well as the research group's collaboration with UDI in the planning and implementation of the quantitative refugee project resulted in the inclusion of a question regarding oral health in the form "Health Examination of Asylum Seekers at 3 months".

Primary dental care

Throughout their lives, Torture victims and victims of sexual abuse will have most of their encounters with dental health personnel in primary dental care clinics.
The research group has provided concrete practical advice to dental health personnel on how to meet and provide dental treatment to traumatized individuals that are communicated to, and utilized in both specialized clinics (TADA), and in other public and private dental clinics. Emphasis has also been laid on teaching general dental practitioners to recognize signs that a patients may be a trauma victim, and how trauma sensitive care is possible to practice with all patients, traumatized or not.

Impact on research
The research group at det Dental Faculty in Oslo is small, but through focus upon cooperation with other institutions members of the research group have as senior researchers in the field of dentistry for people exposed to sexual abuse/ torture experience, planned and supervised projects in University of Tromsø and a number of regional Oral Health Centres of Expertise: Rogaland (Stavanger), Northern Norway (Tromsø), Middle Norway (Trondheim) and Southern Norway (Arendal, closed in 2019). These research projects have increased knowledge and have been and still are essential in the ongoing work to develop more evidence-based, efficient and less burdensome clinical approach and methods for sexual abuse- and torture victims in dental settings.

5. Sources to corroborate the impact (indicative maximum of ten references)

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5. Søftestad S, Fredriksen T, Kranstad T, Willumsen T. Invading Deeply into Self and Everyday Life: How Oral Health-related Problems Affect the Lives of Child Sexual Abuse Survivors J Child Sex Abus. 2019 Nov 6:1-17. doi: 10.1080/10538712.2019.1682096.
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9. Myran, L., Sen, A., Willumsen, T., Havnen, A., Kvist, T., Rønneberg, A., Dahllöf, G., & Høvik, H. (2023). Associations of adverse childhood experiences with caries and toothbrushing in adolescents. The Young-HUNT4 Survey. *BMC oral health*, *23*(1), 760. https://doi.org/10.1186/s12903-023-03492-z
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UiO_DentFac_2

Institution: University of Oslo
Administrative unit: Faculty of Dentistry
Title of case study: Development of Synthetic bone graft materials, from lab bench to clinical use
Period when the underpinning research was undertaken: 2012-2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2010-2024
Period when the impact occurred: 2012-2024

1. Summary of the impact (indicative maximum 100 words)

Our department has successfully developed, patented, and commercialised a groundbreaking synthetic bone graft material, transitioning from laboratory research to clinical application. This innovation significantly advances the field of bone graft materials, traditionally categorised into autografts, allografts, xenografts, and alloplasts. Our novel material addresses key challenges in bone grafting, such as the risk of disease transmission, ethical concerns, and limitations of natural graft materials. It demonstrates optimal properties like osteoconductivity and customisable physical characteristics, suitable for various clinical applications. This achievement represents a significant technological advancement and aligns with the increasing preference for synthetic materials in medical applications, anticipating a substantial impact on future bone grafting practices.

2. Underpinning research (indicative maximum 500 words)

The impactful development of a new synthetic bone graft material from our department was grounded in a series of key research insights and findings produced over several years. This body of work collectively underpinned the innovative approach to creating a material that effectively addresses both the biological and practical challenges in bone grafting.

Nature of Research Insights or Findings:

The research primarily focused on overcoming the limitations of traditional bone graft materials like autografts, allografts, and xenografts, which are plagued by issues such as limited availability, potential disease transmission, and variable resorption rates. Our research aimed to develop a synthetic alternative that exhibits osteogenic, osteoinductive, and osteoconductive properties akin to autografts while offering greater versatility in customisation and availability.

Outline of Underpinning Research:

The project began with exploring various synthetic materials for their potential in bone graft applications. This exploration led to the development of a novel ceramic-based composite, which showed promising results in terms of biocompatibility, osteoconductivity, and mechanical strength. Extensive in vitro testing was conducted to ascertain the material's properties, including porosity, pore size, and interconnectivity – all crucial for supporting bone ingrowth.

A significant part of our research involved optimising the composition and manufacturing process of the material to achieve the desired characteristics. We investigated different formulations and processing techniques to enhance the material's physical and biological properties. This included the development of a unique foam replication process to create porous structures suitable for bone ingrowth. Followed by intensive in vitro and in vivo experiments.

Timeline of Research Activities:

The research journey spanned several years, commencing in the early 2010s. The initial phase focused on material selection and property analysis. By mid-decade, we had moved towards

refining the manufacturing process and conducting in vivo studies to evaluate the material's performance in animal models. The latter half of the decade saw further optimisation and the beginning of clinical application studies. The clinical study was initiated in 2022 and finalised in 2023.

Research Outputs and Evidence of Quality:
This extensive research effort led to significant outputs and evidence of the material's efficacy and potential:

- Generated significant EU and national funding (NewBone and NanoScaff projects)
- Generation of 4 patents, protecting the innovative aspects of the synthetic bone graft material and its manufacturing process.
- Publication of 36 scientific papers in peer-reviewed journals, demonstrating the depth and breadth of the research conducted.
- Completion of 5 PhD theses, each contributing critical insights into different aspects of the material's development and application. 3 of these received Kings Medal for their thesis.
- Guidance of 20 Master's theses facilitated the exploration of various sub-areas within the larger research framework.

The quality and significance of this research are further underscored by the recognition it received within the academic and medical communities and the interest from commercial entities in the patented technology. The transition from laboratory research to clinical application marks a pivotal milestone in the field of bone graft materials, setting a new standard for future developments.

- Names of the key researchers: Anders Verket (2010-), Hanna Tiainen (2008-), Håvard J Haugen (2013-), S Petter Lyngstadaas (2001-), JE Ellingsen (1993-), David Wiedmer (2015-2019), Benjamin Müller (2012-2015), Minh Thieu (2019-2022), Maria Schröder (2017-2021)

3. References to the research (indicative maximum of six references)

1. Thieu, M.K.L.; Stoetzel, S.; Rahmati, M.; El Khassawna, T.; Verket, A.; Sanz-Esporrin, J.; Sanz, M.; Ellingsen, J.E.; Haugen, H.J. Immunohistochemical comparison of lateral bone augmentation using a synthetic TiO(2) block or a xenogeneic graft in chronic alveolar defects. Clin Implant Dent Relat Res 2023, 25, 57-67, doi:10.1111/cid.13143.
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4. Details of the impact (indicative maximum 750 words)

The impact of our department's research in developing a new synthetic bone graft material has been profound and wide-reaching. The journey from laboratory bench to clinical use has been

marked by a distinct and material contribution to the field of bone grafting, influencing both medical practice and patient care.

Research Underpinning the Impact:
The research underpinning this impact involved a comprehensive study of ceramic-based composites, leading to the development of a synthetic bone graft material with optimal biocompatibility, osteoconductivity, and mechanical strength. We have used a Norwegian mineral mined at Dalane, Rogaland, for this new biomedical device. The research was crucial in identifying and overcoming the limitations of existing bone graft materials. The patents and publications generated from this work provided the foundational knowledge and proof of concept necessary for the material's development and eventual clinical application. The results support not only Norwegian academic institutions but also its mining industry and medical device SMEs.

Process Leading to Impact:
Disseminating our research findings through scientific publications and conferences played a key role in raising awareness and generating interest in synthetic bone graft material. The patented technology attracted commercial interest, leading to collaboration with a medical device company (Corticalis AS) for further development and commercialisation. Our engagement with the medical and dental community also facilitated translating this research into clinical practice, in line with the research and innovation goals of UiO.

Collaborative Contributions:
While our department spearheaded the research, the project benefited from collaborative efforts with other institutions and researchers. These collaborations enriched the research, bringing in diverse expertise and perspectives. The specific contribution of our department was in the initial conceptualisation, material development, and the majority of in vitro and in vivo testing, which formed the project's core. Major partners in this project have been University of Giessen, Complutense University Madrid, University of Balearic Island, AGH Krakow and Technische Universität München. Around 30 Erasmus exchange students from these universities have researched this topic at our department.

Beneficiaries of the Impact:
The primary beneficiaries of this impact are patients requiring bone grafts for various medical procedures, including dental implants and orthopaedic surgeries. Healthcare professionals, particularly surgeons and dentists, have also benefited from having a more reliable and versatile option for bone grafting. The medical device industry has also been impacted by the introduction of a new synthetic bone graft material into the market.

Nature of the Impact:
Patients have benefited from a reduced risk of disease transmission, less morbidity associated with autograft procedures, and more predictable outcomes. Healthcare professionals have gained a reliable and versatile tool for bone reconstruction, enhancing the success rates of various surgical procedures. The medical device industry has seen the introduction of a novel product with significant market potential and raised the competitiveness for Norwegian SMEs.

Evidence of Impact:
The extent of the impact is evidenced by:
The adoption of the synthetic bone graft material in multiple clinical settings, both nationally and internationally.
Positive clinical outcomes were reported in surgeries using this material.
Commercial success, as evidenced by the technology adoption by leading medical device companies and its integration into their product lines.

Increased demand for the material, as reflected in sales and usage statistics from medical device companies.
Recognition within the medical community, with numerous citations in clinical guidelines and reviews.

Timeline of Impact:
The impacts began to materialise after initial in vivo studies were completed and continued to grow as the product underwent clinical trials and received regulatory approvals. The most significant impacts have been observed in the years following the product's commercial launch, with a steady increase in its adoption in clinical practice.

In conclusion, the research conducted by our department has not only contributed to advancing the field of bone grafting but has also had a tangible and positive impact on patient care and medical practice. The development of this synthetic bone graft material is a testament to the power of academic research in driving innovation and improving lives.

5. Sources to corroborate the impact (indicative maximum of ten references)

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9. Rubert, M.; Pullisaar, H.; Gomez-Florit, M.; Ramis, J.M.; Tiainen, H.; Haugen, H.J.; Lyngstadaas, S.P.; Monjo, M. Effect of TiO2 scaffolds coated with alginate hydrogel containing a proline-rich peptide on osteoblast growth and differentiation in vitro. J Biomed Mater Res A 2013, 101, 1768-1777, doi:10.1002/jbm.a.34458.
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peri-implant cortical defect model. Acta Biomater 2013, 9, 5390-5399, doi:10.1016/j.actbio.2012.09.009.

UiO_DentFac_3

Institution: University of Oslo
Administrative unit: Faculty of Dentistry
Title of case study: Antimicrobial resistance: Unifying research, education and stakeholders
Period when the underpinning research was undertaken: 2018-2022
Period when staff involved in the underpinning research were employed by the submitting institution: Fernanda Petersen, employed at UiO as Associate Professor from 2007 to 2012, and as Professor from 2012 to the present date. Roger Junges, employed at UiO as Associate Professor since 2020
Period when the impact occurred: 2018-2022

1. Summary of the impact (indicative maximum 100 words)

The research conducted by Prof. Petersen's group at the Institute of Oral Biology in the field of antimicrobial resistance, aided by substantial external funding over the past nine years, has led to significant advancements. The impactful outcomes of their research have been amplified through a synergistic approach, bringing together research, education, and active participation of stakeholders. Their efforts have fostered interdisciplinarity and facilitated a closer connection between the basic research conducted by the group and its users. By engaging stakeholders from various disciplines and sectors, including healthcare providers, public health organizations, and private businesses, they bridge the gap between research and practical application, ensuring that the benefits of their work reach the intended users. This connection enhances the relevance and impact of their research in addressing the global challenge of antimicrobial resistance.

2. Underpinning research (indicative maximum 500 words)

Prof. Petersen's group actively invests in studying the microbiome, an evolving field that provides detailed insights into resistance genes in the environment and factors influencing their spread. Their research has yielded impactful findings that inform decision-making processes, such as the MODIC study conducted in collaboration with Oslo University Hospital. Led by Prof. Petersen, the study demonstrated a persistent increase in antimicrobial resistance (AMR) abundance and diversity following prolonged antibiotic use termination.

The MODIC study involved several researchers and collaborators, including Dhariwal and Sturød (PhD candidates), Dr. Salvadori (postdoc), Ahmed Bargheet (visitor; master student), Åmdal (senior engineer), and Dr. Junges (associate professor) from the University of Oslo. The main collaborators from Oslo University Hospital were Dr. Bråten (medical doctor), Dr Berild (professor and former head of the Department of Infectious Diseases), Dr. Zwart, and Dr. Storheim (researchers and medical doctors). Initially published in 2022, the study provides valuable insights for addressing antimicrobial resistance.

Another front with significant findings relates to the "Born in the Twilight of Antibiotics" project. Led by Prof. Petersen and funded by the Research Council of Norway's INDNOR program, the project commenced in 2018 and concluded in 2023; ongoing analyses are currently underway. The primary objective was to gain insights into the development of the respiratory microbiome and resistome, aiming to acquire knowledge that would improve antibiotic use recommendations for preterm infants.

While the cohort results are not included here as they were still being analyzed by the end of 2022, it's worth noting the impact of other technological and translational achievements up until that point. Collaborating with partners from various sectors, including Oslo University Hospital, LHMC New Delhi, the Norwegian Public Health Institute, and additional partners from Copenhagen University Hospital, the project has achieved notable milestones.

One notable accomplishment was the joint publication of a systematic review in Neonatology (2020) that analyzed antibiotic stewardship programs for premature infants. The review found that tailored, multifactorial programs focusing on reducing antibiotic initiation or shortening therapy duration can be effective for premature newborns. Importantly, this study has been referenced in the "European Consensus Guidelines on the Management of Respiratory Distress Syndrome: 2022 Update."

Furthermore, the project led to the development of a methodology, published in 2022, for studying the resistomes of the upper respiratory tract. Overcoming challenges such as high human DNA content and low microbial load, this methodology is significant as respiratory pathogens commonly colonize this site and contribute to death from antimicrobial resistance.

Moreover, the group has made noteworthy contributions in developing novel tools for antimicrobial resistance research. One notable achievement is the creation of the user-friendly web-based platform "Resistoxplorer." Led by Prof. Petersen and a team of researchers including Dr. Dhariwal, Dr. Junges from IOB, UiO, and Dr. Chen from the Forsyth Institute. ResistoXplorer enables researchers, educators, students, and healthcare professionals to perform comprehensive analyses on antibiotic resistance genes in microbiomes without the need for programming expertise. Published in 2021, ResistoXplorer has become a valuable resource for downstream analysis of resistome data since its development began in 2019.

3. References to the research (indicative maximum of six references)

Author	Title	Year	Type of output	Details
Petersen, FC, Dhariwal, Junges R, Salvdori R, and RESISPART group (NFR project 244867)	Exploring the Landscape of Antibiotic Resistance in Microbiomes	Launched in 2021	Educational/ Research Massive Open Online Course	https://www.futurelearn.com/courses/exploring-the-landscape-of-antibiotic-resistance-in-microbiomes;
Dhariwal A, Haugli Braten LC, Sturod K, Salvadori G, Bargheet A, Amdal H, Junges R, Berild D, Zwart JA, Storheim K, Petersen FC	Differential response to prolonged amoxicillin treatment: long-term resilience of the microbiome versus long-lasting perturbations in the gut resistome	2022 (online) and 2023 (printed)	Article (Gut Microbes. 2023 Jan-Dec;15(1):2157200)	doi: 10.1080/19490976.2022.2157200
Dhariwal A, Junges R, Chen T, Petersen FC	ResistoXplorer: a web-based tool for visual, statistical and exploratory data analysis of resistome data. NAR Genom Bioinform.	2021	Article (NAR Genom Bioinform.)	doi: 10.1093/nargab/lqab018
Rajar P, Dhariwal A, Salvadori G, Junges R, Åmdal HA, Berild D, Fugelseth D, Saugstad OD, Lausten-Thomsen U, Greisen G, Haaland K, Petersen FC.	Microbial DNA extraction of high-host content and low biomass samples: Optimized protocol for nasopharynx metagenomic studies	2022	Article (Front Microbiol. 2022 Dec 21;13:1038120)	doi: 10.3389/fmicb.2022.1038120
Rajar P, Saugstad OD, Berild D, Dutta A, Greisen G, Lausten-Thomsen	Antibiotic Stewardship in Premature Infants: A	2020	Article (Neonatology.	doi: 10.1159/000511710

U, Mande SS, Nangia S, Petersen FC, Dahle UR, Haaland K.	Systematic Review.		2020;117(6): 673-686)	

4. Details of the impact (indicative maximum 750 words)

1. ResistoXplorer was officially launched in 2020, and it has since been actively updated, incorporating feedback from users and advancements in the field. Over the past two years, the web server has processed over 13,000 data analysis jobs submitted by more than 3,000 users worldwide. The tool is referenced within the Bio.Tools Elixir.
2. Learning of the tool was incorporated into a 3-week massive open online course "Exploring the Landscape of Antimicrobial Resistance in Microbiomes", launched in 2021 using the Future Learn platform. To date, 974 participants from all over the world have enrolled on the course.
3. The collaboration between Norway and India in the "Born in the twilight of antibiotics " led by Dr Petersen (IOB, UiO) helped to bring together perspectives from two countries experiencing low and high AMR burden, respectively. The systematic review described above has recently been used as a reference in the "European Consensus Guidelines on the Management of Respiratory Distress Syndrome: 2022 Update" (Neonatology. 2023;120(1):3-23), bringing to attention the importance to have policies in place to narrow the spectrum and minimize duration of antibiotic therapies.
4. Prolonged use of antibiotics in MODIC patients with chronic low back pain: the results shed light on the risks associated with prolonged antibiotic exposure, highlighting the importance of considering these risks in relation to conditions with no significant benefits from prolonged antibiotic therapy, The study was published online in 2022 and in print in 2023 in Gut Microbes (IF 12.2 (2022)).
5. Open events arranged by the RESISPART and RESISFORCE groups led by Prof Petersen and with international partners in Brazil, India, Canada and the USA, which included presentations by institutional leaders and representatives of funding sectors, public health, cultural sectors and embassies from collaborator countries in the Norwegian Panorama Strategy. The projects are funded by the Research Council of Norway under the INTPART program (RESISPART project 2016 to 2022; and RESISFORCE 2021 to 2026)
    a. Antimicrobial resistance: A challenge that crosses borders; resisforce-norse-program-db-english.pdf (uio.no); 2023 Oslo, Norway
    b. Antimicrobial resistance: challenges and prospects; RESISPART Symposium, 2022 Sao Paulo, Brazil
    c. PER-IADR Oral Health Research Congress, September 2022, Symposium "Antimicrobial resistance: off-target effects of antibiotics, new approaches and educational challenges" https://www.odont.uio.no/om/aktuelt/aktuelle-saker/2022/-antibiotikaresistens-pa-agenda-pa-per--idar-kongr.html
    d. IADR congress, September 2021; Symposium "IADR - Let´s talk about microbiomes". https://www.odont.uio.no/english/about/news/2021/--iadr---let%C2%B4s-talk-about-microbiomes.html
    e. RESISPART symposium and workshop (2/12 to 7/12): Sao Paulo, Brazil; https://www.odont.uio.no/iob/english/research/groups/antibiotic-resistance/news/international-collaboration-at-piracicaba-dental-s.html
    f. Research and education in biofilm and antimicrobial resistance, University of Illinois at Chicago, USA; https://www.odont.uio.no/iob/english/research/groups/antibiotic-resistance/news/kicked-off-international-collaboration

5. Sources to corroborate the impact (indicative maximum of ten references)

1. Sweet DG, Carnielli VP, Greisen G, Hallman M, Klebermass-Schrehof K, Ozek E, Te Pas A, Plavka R, Roehr CC, Saugstad OD, Simeoni U, Speer CP, Vento M, Visser GHA, Halliday HL. **European Consensus Guidelines on the Management of Respiratory Distress Syndrome: 2022 Update**. Neonatology. 2023;120(1):3-23. doi: 10.1159/000528914. Epub 2023 Feb 15. PMID: 36863329; PMCID: PMC10064400.
2. O'Connor L, Heyderman R. The challenges of defining the human nasopharyngeal resistome. Trends Microbiol. 2023 Aug;31(8):816-831. doi: 10.1016/j.tim.2023.02.008. Epub 2023 Mar 24. PMID: 36967247.
3. Elixir biotools: (*bio.tools* is anchored within ELIXIR, the European Infrastructure for Biological Information. ResistoXplorer · bio.tools
4. https://www.resistoxplorer.no/
5. https://www.futurelearn.com/courses/exploring-the-landscape-of-antibiotic-resistance-in-microbiomes. Overview of enrolled participants.
6. Google Analytics Audience Overview - 8/20/23, 11:34 AM <https://lookerstudio.google.com/reporting/5c50aa66-3080-4ed0-843d-442328900650/page/tWDGB?utm_source=google-datastudio&utm_medium=email&utm_campaign=scheduled-report&s=sU4MxlaT-F4>

UiO_DentFac_4

Institution: University of Oslo
Administrative unit: Faculty of Dentistry
Title of case study: The Covid pandemic - smell and taste.
Period when the underpinning research was undertaken: 2017-2024
Period when staff involved in the underpinning research were employed by the submitting institution: 2002-2024
Period when the impact occurred: 2020-2024

1. Summary of the impact (indicative maximum 100 words)

The COVID-19 pandemic is one of the most dramatic global health crises in recent history, presenting unparalleled challenges for societies all over the world. This infectious disease, caused by the novel coronavirus SARS-CoV-2, has spread rapidly affecting millions of individuals and causing substantial morbidity and mortality. As of August 2023, there have been almost 1.5 million confirmed cases of COVID-19 in Norway and over 768 million worldwide. COVID-19 seems to manifest in mild to severe forms, while some individuals remain asymptomatic. Sudden loss of smell and taste is known to be the most discriminative symptom of COVID-19 infection.

The overarching goal of Bano Singh's research is:

- to explore the prevalence of smell, taste and trigeminal disturbances in different patient groups as well as in the general population.
- to determine the neural and behavioral function of the olfactory, gustatory and trigeminal system and to differentiate between health and disease.
- to evaluate, diagnose and treat patients with smell, taste and trigeminal dysfunction.

To answer these issues, Bano Singh's group has conducted several different research studies using a wide range of methods, including psychophysical and behavioral tests, functional brain imaging (fMRI), structural brain imaging, and clinical studies.

2. Underpinning research (indicative maximum 500 words)

In period 2010-2015, Singh's research work (molecular biological, neurophysiological and clinical studies) focused on understanding how taste, smell and trigeminal senses are mediated from the oral cavity to the central areas in the brain. Singh's research work identified areas in the brain responsible for processing of sense of smell, taste and trigeminal pain. After understanding molecular mechanisms in the healthy state, research focus (during 2015-2022) was shifted to identifying pathological reasons in the different groups of patients.

- Preet Bano Singh (2006-), Janicke L Jensen (2011-), Alix Vik (2010-), Lene Hystad Hove (2013-), Morten Rykke (2002-2022)

3. References to the research (indicative maximum of six references)

1. **Singh, Preet Bano;** Hummel, Thomas; Gerber, Johannes; Landis, Basile & Iannilli, Emilia (2015). Cerebral processing of umami: A pilot study on the effects of familiarity. Brain Research. ISSN 0006-8993. 1614, p. 67–74. doi: 10.1016/j.brainres.2015.04.019.

2. Sinding, Charlotte; Gransjøen, Ann Mari; Schlumberger, Gina; Grushka, Miriam; Frasnelli, Johannes & **Singh, Preet Bano** (2016). Grey matter changes of the pain matrix in patients with burning mouth syndrome. European Journal of Neuroscience. ISSN 0953-816X. 43(8), p. 997–1005. doi: 10.1111/ejn.13156.
3. Rusthen, Shermin; Young, Alix; Herlofson, Bente Brokstad; Aqrawi, Lara Adnan; Rykke, Morten; Hove, Lene Hystad; Palm, Øyvind; Jensen, Janicke Liaaen & **Singh, Preet Bano** (2017). Oral disorders and oral health-related quality of life in patients with primary Sjögren's Syndrome. European Journal of Oral Sciences. ISSN 0909-8836. 125(4), p. 265–271. doi: 10.1111/eos.12358.
4. **Singh, Preet Bano**; Young, Alix; Lind, Synnøve; Leegard, Marie Cathinka; Capuozzo, Alessandra & Parma, Valentina (2018). Smelling anxiety chemosignals impairs clinical performance of dental students. Chemical Senses. ISSN 0379-864X. 43(6), p. 411–417. doi: 10.1093/chemse/bjy028.
5. **Singh, Preet Bano**; Young, Alix; Homayouni, Amin; Hove, Lene Hystad; Petrovski, Beata; Herlofson, Bente Brokstad; Palm, Øyvind; Rykke, Morten & Jensen, Janicke Liaaen (2019). Distorted Taste and Impaired Oral Health May Affect Nutritional Status in Patients with Sicca Complaints. Nutrients. ISSN 2072-6643. 11(2). doi: 10.3390/nu11020264.

Parma, Valentina; Ohla, Kathrin; Veldhuizen, MK; Niv, Masha Y.; Kelly, Christine E.; Bakke, Alyssa J.; Cooper, Keiland W.; Bouysset, Cedric; Pirastu, Nicola; Dibattista, Michele; Kaur, Rishemjit; Liuzza, Marco Tullio; Pepino, Marta Y.; Schöpf, Veronika; Pereda-Loth, Veronica; Olsson, Shannon B.; Gerkin, Richard C.; Dominguez, Paloma Rohlfs; Albayay, Javier; Farruggia, Michael C.; Bhutani, Surabhi; Fjaeldstad, Alexander W.; Kumar, Ritesh; Menini, Anna; Bensafi, Moustafa; Sandell, Mari; Konstantinidis, Iordanis; Di Pizio, Antonella; Genovese, Federica; Ôztürk, Lina; Thomas-Danguin, Thierry; Frasnelli, Johannes; Boesveldt, Sanne; Saatci, Ôzlem; Saraiva, Luis R.; Lin, Cailu; Golebiowski, Jerome; Hwang, Liang-Dar; Ozdener, Mehmet Hakan; Guàrdia, Maria Dolors; Laudamiel, Christophe; Ritchie, Marina; Havlicek, Jan; Pierron, Denis; Roura, Eugeni; Navarro, Marta; Nolden, Alissa A.; Lim, Juyun; Whitcroft, Katherine L.; Colquitt, Lauren R.; **Singh, Preet Bano** & Hayes, John E. (2020). More than smell- Covid-19 is associated with severe impairment of smell, taste, and chemethesis. Chemical Senses. ISSN 0379-864X. 45(7), p. 609–622. doi: 10.1093/chemse/bjaa041.

4. Details of the impact (indicative maximum 750 words)

A. Research performed in period 2012-2022 has resulted into establishment of one of a kind, novel clinical facility for this patient group. In 2021, Clinic for smell, taste and oral pain was founded by Singh at the faculty of dentistry, University of Oslo. Patients with chemosensory (smell and taste), trigeminal (burning mouth) and salivary (dry mouth) dysfunctions are referred here for evaluation and treatment from all around the country.
B. Singh was invited as a speaker to "Long term consequences of the Covid-19 Pandemic" Conference held by the Pandemic Centre, University of Bergen, Norway.
C. Singh was part of P1H (Center for pandemic and one-health research, University of Oslo) workshop held in 2022 and 2023. The vision of the workshops was to contribute to that the society gets more robust to threat of future pandemics by effectively using existing expertise.

5. Sources to corroborate the impact (indicative maximum of ten references)

1. Gerkin, Richard C; Ohla, Kathrin; Veldhuizen, Marie G; Joseph, Paule V; Kelly, Christine E; Bakke, Alyssa J; Steele, Kimberley E.; Farruggia, Michael C.; Pellegrino, Robert; Pepino, Marta Y.; Bouysset, Cedric; Soler, Graciela M.; Pereda-Loth, Veronica; Dibattista, Michele; Cooper, Keiland W.; Crojmans, Ilja; Di Pizio, Antonella; Ozdener, Mehmet Hakan; Fjaeldstad, Alexander W.; Lin, Cailu; Sandell, Mari A.; **Singh, Preet Bano**; Brindha, V. Evelyn; Olsson, Shannon B.; Saraiva, Luis R.; Ahuja, Gaurav; Alwashali, Mohammed K.; Bhutani, Surabhi; D'Errico, Anna; Fornazieri, Marco A.; Golebiowski, Jerome; Hwang, Liang Dar; Ôztürk, Lina; Roura, Eugeni; Spinelli, Sara; Whitcroft, Katherine L.; Faraji, Farhoud; Fischmeister, Florian Ph.S.; Heinbockel, Thomas; Hsieh, Julien W.; Huart, Caroline; Konstantinidis, Iordanis; Menini, Anna; Morini, Gabriella; Olofsson, Jonas K.; Philpott, Carl M.; Pierron, Denis; Shields, Vonnie D.C.; Voznessenskaya, Vera V.; Albayay, Javier; Altundag, Aytug; Bensafi, Moustafa; Bock, Maria Adelaida; Calcioni, Orietta; Fredborg, William; Laudamiel, Christophe; Lim, Juyun; Lundström, Johan N.; Macchi, Alberto; Meyer, Pablo; Moein, Shima T.; Santamaria, Enrique; Sengupta, Debarka; Dominguez, Paloma Rohlfs; Yanik, Hüseyin; Hummel, Thomas; Hayes, John E.; Reed, Danielle R; Niv, Masha Y; Munger, Steven D; Parma, Valentina (2021). Recent smell loss is the best predictor of COVID-19 among individuals with recent respiratory symptoms. Chemical Senses. ISSN 0379-864X. Volume 46. doi: https://doi.org/10.1093/chemse/bjaa081
2. Valentina Parma, Kathrin Ohla, Maria G Veldhuizen, Masha Y Niv, Christine E Kelly, Alyssa J Bakke, Keiland W Cooper, Cédric Bouysset, Nicola Pirastu, Michele Dibattista, Rishemjit Kaur, Marco Tullio Liuzza, Marta Y Pepino, Veronika Schöpf, Veronica Pereda-Loth, Shannon B Olsson, Richard C Gerkin, Paloma Rohlfs Domínguez, Javier Albayay, Michael C Farruggia, Surabhi Bhutani, Alexander W Fjaeldstad, Ritesh Kumar, Anna Menini, Moustafa Bensafi, Mari Sandell, Iordanis Konstantinidis, Antonella Di Pizio, Federica Genovese, Lina Öztürk, Thierry Thomas-Danguin, Johannes Frasnelli, Sanne Boesveldt, Özlem Saatci, Luis R Saraiva, Cailu Lin, Jérôme Golebiowski, Liang-Dar Hwang, Mehmet Hakan Ozdener, Maria Dolors Guàrdia, Christophe Laudamiel, Marina Ritchie, Jan Havlícek, Denis Pierron, Eugeni Roura, Marta Navarro, Alissa A Nolden, Juyun Lim, Katherine L Whitcroft, Lauren R Colquitt, Camille Ferdenzi, Evelyn V Brindha, Aytug Altundag, Alberto Macchi, Alexia Nunez-Parra, Zara M Patel, Sébastien Fiorucci, Carl M Philpott, Barry C Smith, Johan N Lundström, Carla Mucignat, Jane K Parker, Mirjam van den Brink, Michael Schmuker, Florian Ph S Fischmeister, Thomas Heinbockel, Vonnie D C Shields, Farhoud Faraji, Enrique Santamaría, William E A Fredborg, Gabriella Morini, Jonas K Olofsson, Maryam Jalessi, Noam Karni, Anna D'Errico, Rafieh Alizadeh, Robert Pellegrino, Pablo Meyer, Caroline Huart, Ben Chen, Graciela M Soler, Mohammed K Alwashahi, Antje Welge-Lüssen, Jessica Freiherr, Jasper H B de Groot, Hadar Klein, Masako Okamoto, **Preet Bano Singh**, Julien W Hsieh, GCCR Group Author, Danielle R Reed, Thomas Hummel, Steven D Munger, John E Hayes (2020). More Than Smell—COVID-19 Is Associated With Severe Impairment of Smell, Taste, and Chemesthesis. Chemical Senses, Volume 45, Issue 7, Pages 609–622, https://doi.org/10.1093/chemse/bjaa041

Impact cases – Department of Pharmacy, University of Oslo

Institution: The University of Oslo
Administrative unit: Department of Pharmacy
Title of case study: APC301 – a novel adjuvant in the fight against antimicrobial resistance (AMR)
Period when the underpinning research was undertaken: 2012-2022
Period when staff involved in the underpinning research were employed by the submitting institution: Research group Medicinal Chemistry 2009-2018
Period when the impact occurred: 2014-2022

1. Summary of the impact

This project, denoted ZinChel, meets several of the UN sustainability goals, and directly addresses sustainability goal number no. 3, Securing good Health and Quality-of-life for all. This has priority for the Norwegian government in our foreign aid and foreign policy in general. Antimicrobial resistance (AMR) is an emerging threat to the global healthcare system, particularly in low- and middle-income countries. This project identified a novel class of antibiotic adjuvants, which in combination with last resort antibiotics restores the activity against WHO prioritized resistant bacteria. Clinical phase I is planned in 2Q 2023 with the lead candidate APC301. This is the first time a drug candidate from research at the Pharmaceutical Department goes into clinical development. Market access to APC148 will reduce the number of patient deaths in outbreaks and epidemics and have a significant effect on patient healthcare when available on the global market. It will be an important treatment alternative for the hospital clinician to safely treat patients facing multidrug resistant infections. For UiO this project is important to build a Norwegian center of excellence in this prioritized area of research. A project ambition is also establishing Norwegian manufacturing of APC148 active drug substance and APC30R drug product.

2. Underpinning research

Antimicrobial resistance (AMR) is an emerging and devastating global health problem. Carbapenem-resistant gram-negative (GN) bacteria harboring β-lactamases (BL) are, according to the WHO 2017 list http://www.who.int/mediacentre/news/releases/2017/bacteria-antibiotics-needed/en/, the top-three most critical strains for which new antibiotics are urgently needed. The carbapenems, last resort antibiotics with restricted use because of resistance development, had no effect alone on the most problematic strains.

In 2013, the project group SYNFAS (on average 12-14 researchers and students), at the faculty of Natural Sciences at The University of Oslo (UiO), headed by professor Pål Rongved, discovered a new class of inhibitors of MBL (metallo-β-lactamases). SYNFAS was the first organic/medicinal chemistry research group that included chemists from both the Chemistry Department and the Pharmacy department at UiO.

When combined with carbapenems, their identified lead candidates reinstalled the effect of the antibiotic drug against the top bacteria on the WHO list. This resulted in two broad patent applications that today are granted in major markets. In 2013, SYNFAS initiated an aggressive strategy for application for funding, and during the years they received multiple grants from private (NOVO Pre Seed 2x) and public sources (NRC/EU: BIOTEK2021, FORNY, IPN x 2, Eurostars), including innovation funding from UiO.

The project met a huge medical need since no inhibitor adjuvants of clinically isolated bacterial strains harboring MBLs was clinically available.

After synthesis of more than 300 screening candidates, SAR studies in SYNFAS identified a highly water-soluble lead candidate adjuvant (ZN148) that had no intrinsic antibacterial activity, had an excellent *in vitro* MIC efficacy against a number of WHO prioritized strains harboring MBL. It also showed a good *in vivo* safety profile and was efficient in infection animal models with clinically isolated GN bacteria. SYNFAS showed that APC148 can potentiate the efficacy of the carbapenems up to 500 times (SSI, Copenhagen), simultaneously reducing the dose of the antibiotic significantly.

The target protein for ZN148 is the MBL, and the main mechanism of action (MoA) is that the adjuvant eliminates carbapenem resistance *in vitro* by disturbing the zinc functionality in the MBLs, without disturbing host eucaryotic zinc-dependent enzymes.

In 2019, the startup company Adjutec Pharma AS was established in collaboration with the Oslo Cancer Cluster Incubator (OCCI). The Norwegian Cancer Society communicated that about 20 % of cancer patients died from infectious diseases. In the following three years Adjutec attracted more than 70 mNOK in private funding. In 2022 AdjuTec successfully conducted a preclinical GLP package in collaboration with the European CRO Evotec (subsidiary Aptuit) and started the planning of a first time in man (phase 1) safety/dose finding study in Uppsala and started writing a CTA application in Sweden. Clinical phase I is planned in 2Q 2023 with the lead candidate APC301 (earlier ZN148). This is the first time a drug candidate from research at the Pharmaceutical Department initiates clinical development. The product is intended for intravenous treatment of hospitalized patients suffering from infections caused by resistant GN bacteria.

Adjuec has conducted meetings with regulatory authorities in major markets (FDA, EMA), and has been granted QUIDP (qualified infectious disease product) by the FDA, and has planned to file a marketing authorization application (MAA) in 2027.

3. References to the research

1. ZN148 is a Modular Synthetic Metallo-β-Lactamase Inhibitor That Reverses Carbapenem Resistance in Gram-Negative Pathogens In Vivo. Samuelsen Orjan; Frohlich Christopher; Lauksund Silje; Samuelsen Orjan; Lauksund Silje; Åstrand Ove Alexander Hogmoen; Schnaars Christian; Kildahl-Andersen Geir; Rongved Pal; Frohlich Christopher; et al, Antimicrobial agents and chemotherapy (2020), 64(6), 1- 14.

2. Synthesis and biological evaluation of new dipicolylamine zinc chelators as metallo-β-lactamase inhibitors. Prandina, Anthony; Radix, Sylvie; Le Borgne, Marc; Jordheim, Lars Petter; Bousfiha, Zineb; Frohlich, Christopher; Leiros, Hanna-Kirsti S.; Samuelsen, Oerjan; Froevold, Espen; Rongved, Paal, Tetrahedron (2019), 75(11), 1525-1540.6.

3. Synthesis and biological evaluation of zinc chelating compounds as metallo-β-lactamase inhibitors. Kildahl-Andersen, Geir; Schnaars, Christian; Prandina, Anthony; Radix, Sylvie; Le Borgne, Marc; Jordheim, Lars Petter; Gjoeen, Tor; Andresen, Adriana Magalhaes Santos; Lauksund, Silje; Frohlich, Christopher, MedChemComm (2019), 10(4), 528-537.

4. Synthesis and Preclinical Evaluation of TPA-Based Zinc Chelators as Metallo-β-lactamase Inhibitors. Schnaars, Christian; Kildahl-Andersen, Geir; Prandina, Anthony; Popal, Roya; Radix, Sylvie; Le Borgne, Marc; Gjoeen, Tor; Andresen, Adriana Magalhaes Santos; Heikal, Adam; Oekstad, Ole Andreas; Frohlich, Christopher; Samuelsen, Oerjan; Lauksund, Silje; Jordheim, Lars Petter; Rongcved, Paal; Aastrand, Ove Alexander Hoegmoen, Journal of Enzyme Inhibition and Medicinal ACS Infectious Diseases (2018), 4(9), 1407-1422.

5. Inhibitors of metallo-β-lactamase comprising a zinc chelating moiety. Rongved, Paal; Aastrand, Ove Alexander Hoegmoen; Bayer, Annette; Leiros, Hanna-Kirsti Schroeder; Samuelsen, Ørjan; Edvardsen, Kine Susann Waade. WO2015049546 A1 2015-04-09. The invention discloses metallo-β-lactamase comprising a zinc chelating moiety and methods of treating and/or preventing a bacterial infection in a human or non-human mammal.

6. Preparation of pyridinyl-nicotinamide sugars as antibacterial agents
Rongved, Paal; Aastrand, Ove Alexander Hoegmoen; Samuelsen, Oerjan; Schnaars, Christian; Kildahl-Andersen, Geir. WO2018033719 A1 2018-02-22.The invention provides compounds for use in a method of treating and/or preventing a bacterial infection in a human or non-human mammal, said method comprising administration of said compound in combination with (either simultaneously, sep., or sequentially) a β-lactam antibiotic, wherein said compound has the general formula Q-[-L-W]x (wherein: Q is a lipophilic, zinc chelating moiety which is selective for Zn2+ ions and which comprises at least one, preferably two or more (e.g 2, 3 or 4), optionally substituted, unsaturated heterocyclic rings, e.g. 5 or 6-membered heterocyclic rings preferably include at least one heteroatom selected from N, S and O, preferably N; wherein any optional substituents may be selected from alkyl, alkoxy, halogen, nitro, cyano, amine, and substituted amine; each L, which may be the same or different, is a covalent bond or a linker; each W, which may be the same or different, is a non-peptidic hydrophilic group which comprises one or more hydroxy groups; and x is an integer from 1 to 3) or a stereoisomer, pharmaceutically acceptable salt or prodrug thereof. Thus, pyridinyl-nicotinamide sugar I was prepared and tested in vitro and in mice as antibacterial agent against Klebsiella pneumoniae.

4. Details of the impact

a) Benefits to patients, healthcare and the R&D community:

APC301 will have a significant effect on patient healthcare when available on the global market. It will be an important treatment alternative for the hospital clinician to safely treat patients facing multidrug resistant infections. Today these patients are often treated with older, abandoned, toxic antibiotics with the risk of prolonged hospitalizations and fatal outcomes. The introduction of APC301 will allow for treatment in combination with a modern and safe antibiotic (meropenem) that avoid expensive and prolonged hospitalization including morbidity and mortality.

In this project Adjutec has collaborated with R&D (The University of Tromsø, SSI Copenhagen, others) and commercial providers (Evotec, Aptuit, Cyprotex) that will benefit from increased competence in BL/BLi development that will make them more attractive for business and secure jobs. For UiO, this project is important to build a Norwegian center of excellence in antibiotics. Antibiotic resistance is a prioritized area of research at the UiO Life Science Campus and is important in the strategy of building Oslo Science City. This project may also result in establishing Norwegian manufacturing of APC301 active drug substance and drug product. The use of Norwegian subcontractors including LINK Medical and Bonega will secure jobs in the companies.

b) Broader benefits to society:

AMR is a growing global health threat provoking grave societal and economic challenges. A continued rise in resistance would result in an estimated 10 million deaths globally each year, in a reduction of 2% to 3.5% in global gross domestic product and would cost the world economy up to USD 100 trillion by 2050(5). In countries with poor antibiotic stewardship, bacteria are increasingly becoming resistant to last-resort antibiotics. The south-east of Europe regularly experiences AMR

outbreaks. In the sub-Indian continent, as well as in the Middle East, the majority of patients are presenting with infections that are multi-drug resistant. Globalization and increasing migration due to climate change and wars are spreading AMR around the globe. Development of new antibiotic products is crucial to face this "silent pandemic".

The ZinChel project, leading to Adjutec Pharma, is important in the fight of AMR by developing new antibiotic products and is endorsed by the EU Council in their call for Member states to step up actions to combat AMR. The EU parliament forwarded a request to each member state in June 2023, to establish national AMR action plans and support R&D programs. The Norwegian government has recently announced that healthcare will have priority in becoming an important export industry. This project will enable Adjutec and Norway to be a part of these ambitions.

c) Dissemination of results:

All results from this project have been disseminated at meetings as oral presentations, posters and publications. Key results have been published in medical journals and have been presented on media platforms including the Adjutec web, Medwatch, HealthTalk, Radforsk podcasts and others. Working closely with academic institutions including UiO, results from academic researchers have also been communicated through their media platforms. Results have also been presented at life-science meetings (e.g. ECCMID and AMR world congress), investor meetings (e.g. BioEurope, BioUS).

5. Sources to corroborate the impact

The above sections already comprise multiple sources underpinning and corroborating the impact.

The company Adjutec Pharma AS is starting clinical phase 1 in 2Q24. Therefore, the project has not yet launched a product on the market, which is expected to generate significant benefits to patients, healthcare and the R&D community.

Examples of impacts already established:

1. The project received repeated and multiple grants from different funding sources, e.g. during the years received multiple grants from private (NOVO Pre Seed 2x) and public sources (NRC: BIOTEK2021, FORNY, IPN x 2, Eurostars), including innovation funding from UiO. These grants have led to multiple master and PhD degrees, publications, patents and educational dissemination of aspects and challenges related to AMR.

2. As stated, key results have been repeatedly presented on media platforms including the Adjutec web, Medwatch, HealthTalk, Radforsk podcasts etc. Working closely with academic institutions including UiO, results from academic researchers have also been communicated through their media platforms. Results have also been presented at life-science meetings (e.g. ECCMID and AMR world congress), investor meetings (e.g. BioEurope, BioUS).

3. The project filed 5 patent applications with inventors from UiO and UiO licensed IP ownership. The first two were granted in major markets, the last three are in the priority year. To achieve granted patents, a challenging examination process in the national patent offices takes place before the application leads to a granted patent. This has led to a solid IPR (intellectual property rights) platform. Because of the tri-partition model ("tredelingsmodellen") at UiO, the institution, the administrative unit and the inventors will benefit economically if Adjutec is successful in launching a product meeting a huge medical need.

Institution: University of Oslo
Administrative unit: Department of Pharmacy
Title of case study: Capitalizing on Norwegian birth cohort and registry data to generate real-world evidence about medications in pregnancy
Period when the underpinning research was undertaken: 2015–
Period when staff involved in the underpinning research were employed by the submitting institution: 2015–
Period when the impact occurred: 2015–

2. Summary of the impact

Capitalizing on Norway's imperative advantage to a unique birth cohort and health registries, researchers in the Pharmacoepidemiology and Drugs Safety (PharmaSafe) research group at the Department of Pharmacy have united researchers within epidemiology, biostatistics, teratology, genetics, and neurodevelopmental to generate cutting-edge, real-world evidence on the safety of pharmaceuticals during pregnancy, particularly on potential long-term effects for the offspring.

This impact case highlights PharmaSafe's key achievements and the broader societal impact of their research within *perinatal pharmacoepidemiology and real-world registry-based research*. Through commitment to excellence, multidisciplinary collaboration, and international engagement, PharmaSafe has played a pivotal role in advancing perinatal pharmacovigilance knowledge and clinical and regulatory practice. These efforts have contributed to the safety and well-being of pregnant women in need of pharmaceuticals and their children, not only in Norway, but in the European Union (EU) and beyond.

3. Underpinning research

As learned from the thalidomide catastrophe, results from animal studies cannot be directly extrapolated to humans and the structure or activity of the drug is generally not predictive of teratogenesis. Due to ethical concerns, pregnant women are generally excluded from randomized controlled trials, leaving a critical gap in knowledge about the use and safety of pharmaceuticals during pregnancy. Therefore, prospective, real-world pharmaco-epidemiological studies among pregnant women offer the only real solution to fill the gap of knowledge concerning safety of pharmaceuticals in pregnancy.

Since its inception in 2015, the overall objective of PharmaSafe's researchers has been to generate novel and robust evidence about the use and safety of pharmaceuticals in pregnancy. The work is driven by the dedication and passion of two professors (Prof. Nordeng and Prof. Lupattelli) in collaboration with partners and many PhD students and post docs over the past decade.

Research Excellence and Impact: PharmaSafe's commitment to research excellence is evidenced by a series of prestigious research projects, like Prof. Nordeng's ERC StG DrugsInPregnancy (2012–2015), Prof. Lupattelli's and Dr. Wood's Young Research Talent Grants Healthx2 (2019–2023) and Safe2Treat (2020–2025). Together, these projects provide novel and invaluable insights into drug safety in pregnancy, especially related to the neurodevelopmental toxicity of drugs and pharmacoepigenetic effects in the offspring.

Notable ground-breaking publications include studies of how prenatal exposure to analgesics (i.e., paracetamol) and antidepressants (i.e., (es)citalopram) impacts DNA methylation in offspring (Gervin et al, Clin Epigenetics 2017, Olstad et al, Front Genet 2023, Olstad et al, Transl Psychiatry 2023). These cutting-edge studies paved the way for a new field of *perinatal pharmaco-epigenetics* and provided recommendations for how to perform state-of-the-art studies within this field (Olstad et al, Epigenetics 2022).

PharmaSafe researcher have played a key role for how to perform modern real-world studies of medication safety in pregnancy by demonstrating that the reproductive safety of pharmaceuticals cannot be assures without evidence about the long-term safety. Influential examples of this include studies on prenatal exposure to antidepressants and the risk of attention-deficit/hyperactivity disorder (Lupattelli et al, BJOG 2021), opioids and scholastic skills (Trønnes et al, JAMA Netw Open 2022), as well as investigations into maternal medication use and childhood cancer (Hjorth et al, Am J Epidemiol 2021). Moreover, the insight the HEALTHx2 has identified actionable treatment and knowledge gaps among perinatal women with mental disorders (Trinh et al, JAMA Psych 2023). By both informing clinical treatment guidelines for pregnant women and regulatory requirements for post authorization safety studies (PASS) in pregnant populations, the PharmaSafe's research output has translated into concrete societal impact.

PharmaSafe's expertise, interdisciplinarity and responsiveness, together with rapid access to high-quality health registry data, has been critical during the pandemic. Notably, the group has represented Norway in COVID-19 studies commissioned by the European Medicines Agency (EMA) (e.g., CONSIGN) and by pharmaceutical industry (e.g., Pfizer, Moderna), and have leading roles in large EU and Nordic funded consortia (e.g., VERDI, COHERENCE). PharmaSafe's involvement in these projects has for example demonstrated the impact of COVID-19 on medication use in vulnerable patient groups and that vaccines are safe in pregnancy and childhood. Moreover, though this work, the research group has established an efficient and sustainable data analytical pipeline at the University of Oslo for real-world studies.

Key impact would not be impossible without a strong engagement in fundamental methodological work, as exemplified through PharmaSafe's contribution to multinational federated data analyses using Big Data approaches. The most renown examples are data harmonization via the ConcePTION common data model (CDM) (Thurin et al, Clin Pharmacol Ther 2022) and the perinatal extension of the OMOP CDM (Abellan et al, 2024). These CDMs have enabled a next generation of studies on pharmaceuticals and vaccines in pregnancy and pediatrics, in terms of speed, study power, and interdisciplinarity.

Most recently, the impact on EU health authorities has been demonstrated by positioning the Department of Pharmacy/UiO as Norway's representative in the EMA's DARWIN program. DARWIN has the scope to generate evidence on the use, safety, and effectiveness of medicines, including vaccines, from real-world healthcare databases across the EU for regulatory purpose.

4. Details of the impact

Uniquely placed for real-world pharmacoepidemiological studies: Norway is home to some of the world's most comprehensive and well-maintained health care registries and birth cohorts. These contain invaluable data on patient demographics, diagnoses, treatments, and outcomes for the entire Norwegian population, as well as genetic and epigenetic data from the MoBa biobank. Over the past decade, PharmaSafe researchers have built expertise in harnessing and analyzing these data sources to perform real-world, methodologically sound observational studies on the use and safety of pharmaceuticals, especially among vulnerable patients (Research projects - Department of Pharmacy (uio.no)).

The research has been driven by two professors (Prof. Nordeng & Prof. Lupattelli), their partners and the numerous PhD and post doc students under their supervision. This is demonstrated by the number of prestigious research grants and scientific publications (>200), the PharmaSafe group's roles in leading academic societies and networks, and the translation of research into clinical and regulatory actionable guidelines. They have hosted and trained over 40 international visiting researchers since 2015 and led research schools (NFIF) and networks (iAPOGEE, PharmaTox QLS), demonstrating their impact and dedication to scientific advancement.

Scientific excellence and expertise have significantly enhanced the Department of Pharmacy, attracted major research grants, and positioned the department as Norway's representative in the EMA's DARWIN program for evidence on medication use, safety, and effectiveness across the EU.

Scientific Achievements and Impact:

- Providing novel insight into the long-term safety of *in utero* exposure to pharmaceuticals on the offspring for drugs such as antidepressants, opioids, benzodiazepines, triptans, NSAIDs, and antibiotics (>20 publications, including Lupattelli et al, BJOG 2021, Trønnes et al, JAMA Netw Open 2022, Harris et al, JAMA Netw Open. 2022, Gervin et al, Clin Epigenetics 2017, Olstad et al, Front Genet 2023, Olstad et al, Transl Psychiatry 2023).
- Identifying the impact of medication use in pregnancy on *maternal* health outcomes such as gestational diabetes, preeclampsia, postpartum depression and relapse of mental illness in the perinatal period (Trinh et al, JAMA Psychiatry 2023, Lupattelli et al, PDS 2022, Lupattelli et al, PDS 2017).
- Revealing teratogenic perceptions, medications non-adherence, and pregnant womens' beliefs about medications (> 20 publications, including Roldan Munoz et al, BMJ Open 2020, Ceulemans et al, Curr Pharm Des.2019, Amundsen et al, BMJ Open 2019, Juch et al, Patient Educ Couns 2016, Nordeng et al, Eur J Clin Pharmacol 2010).
- Driving uptake of advanced biostatistical and causal inference methods in real-world perinatal pharmacoepidemiological studies and thereby strengthen the causal interpretation. This includes use of propensity scores, marginal structural models, trajectory modelling, multiple imputation, probabilistic bias analysis and emulated trial designs (e.g., Wood et al, Epidemiol Rev 2022, Harris et al, PDS 2020, Lupattelli et al, Clin Therapy 2019, Wood et al, PDS 2018).
- Establishing a comprehensive data analytical pipeline for real-world health registry-based research at the University of Oslo. A notable demonstration is the CONSIGN EHR study, led by Prof. Nordeng, including almost 9,000 pregnant women with COVID-19 in Europe. Shortly after the pandemic outbreak, the multinational ConcePTION network was mobilized and demonstrated for example the marked increase in antithrombotics prescribed to pregnant women with COVID-19 (e.g., 61.9% in the Valencia region; Hurley et al, Eur J Clin Pharmacol 2024). We recently used this pipeline for studies where computational and machine learning (ML) techniques were applied to give deeper insights into health outcomes of COVID-19 and COVID-19 vaccines (Shakibfar et al, Front Public Health 2023).

PharmaSafe has also contributed to the vibrant interdisciplinary research ecosystem at the University of Oslo. The group's involvement in innovative projects such as UiO:RealArt* showcases our dedication to cross-disciplinary collaboration and the convergence of life science research.

**a UiOLifeSceince convergence environment aiming to improve causal inference in perinatal pharmaco-epidemiology using machine learning approaches on real-world and artificial data.*

Societal impact: Improved Regulatory Guidance and Expert Consensus:

Findings related to neurodevelopmental outcomes and knowledge gaps have contributed to an international debate among researchers (e.g., paracetamol safety – see Bauer et al, Nat Rev Endocrinol 2021, Nordeng et al, BMJ 2017). These debates led authorities to revise GVP guidelines on pregnancy studies (GVP III, 2022 – Prof. Nordeng part of drafting group), and motivated PharmaSafe to push for international expert consensus in how to assess neurodevelopment in pregnancy studies (Bromley et al, Front Pharmacol 2023).

One example of international recognition, is the appointment by the EU commission of Prof. Nordeng as independent scientific expert member to PRAC (EMA's pharmacovigilance committee) in 2018. In the monthly plenary meetings including all 27 EU member states, patient and health care professional representatives, and six experts, she uses her expertise to ensure surveillance of medication safety during pregnancy and breastfeeding in Europe.

Societal impact: Informed Prescribing Practices:

Significant improvements to clinical practice have been made by providing evidence, disseminating findings, and contributing to the education of health care personnel, such as pharmacists and physicians. Examples of revised national clinical guidelines include guidelines on perinatal mental health, epilepsy, general pharmacotherapeutic principles of medication use in pregnancy, and vaccines in pregnancy. Moreover, the responsibility for the recommendations on medications in pregnancy and breast feeding in the Norwegian National Therapeutic Formulary lies with the PharmaSafe group (G8 Amming og legemidler | Legemiddelhåndboka (legemiddelhandboka.no)). By dissemination of national and international guidelines, we have empowered prescribers leading to more well-informed and cognizant prescribing practices.

PharmaSafe's research is in line with the **sustainability goals (SDGs)**, in particular SDG 3, focusing on improving medication use during pregnancy to reduce maternal mortality (SDG 3.1). Additionally, the research supports SDG 5 by addressing knowledge inequalities between men and women regarding the use and safety of medicines. By developing transparent and reproducible health data analysis methods, we contribute to SDG 9 (sustainable innovation).

Jointly, our research activities have an impact on the health of the millions of pregnant women and their unborn children in Norway and beyond in need of vaccines and medications for chronic and acute illnesses in pregnancy.

5. Sources to corroborate the impact

Scientific leadership and excellence in research:

1. International Partnerships for Excellent Education, Research and Innovation on genetic pharmacoepidemiology (iAPOGEE)
2. UiOLifeScience convergence environment UiO:RealArt: Real world – artificial worlds: Improving causal inference in perinatal pharmaco-epidemiology using machine learning approaches on real-world and artificial data.

Obtaining international expert consensus (PharmaSafe members in **bold**):

3. Bromley RL, Bickle Graz M, Bluett-Duncan M, Chambers C, Damkier P, Dietrich K, Dolk H, Grant K, Mattson S, Meador KJ, **Nordeng H,** Oberlander TF, Ornoy A, Revet A, Richardson J, Rovet J, Schuler-Faccini L, Smearman E, Simms V, Vorhees C, Wide K, **Wood A**, Yates L, **Ystrom E**, Supraja TA, Adams J. Expert consensus on neuro-developmental outcomes in pregnancy pharmacovigilance studies. Front Pharmacol. 2023;14:1094698.
4. Motrico E, Moreno-Peral P, Uriko K, Hancheva C, Brekalo M, Ajaz E, Apter G, Bramante A, Conejo-Cerón S, Christoforou A, Dikmen-Yildiz P, Evagorou O, Fonseca A, **Lupattelli A,** Radoš SN, Al Maach N, Rodriguez-Muñoz MF, Žutić M, Lambregtse-van den Berg MP. Clinical practice guidelines with recommendations for peripartum depression: A European systematic review. Acta Psychiatr Scand. 2022; 146(4):325-339.

Representing Norway with Norwegian health data in European pharmacovigilance:

5. DARWIN: https://www.darwin-eu.org/

Impact on regulatory guidance and medication labels:

6. Guideline on good pharmacovigilance practices (GVP). Product- or Population-Specific Considerations III: Pregnant and breastfeeding women
   Paracetamol Summary of Product information (SmPC): section 4.6 Fertility, pregnancy, lactation: describing neurodevelopmental conflicting results.

Translating research into national Clinical guidelines and Text books:

7. National obstetric guidelines: Veileder i fødselshjelp (legeforeningen.no)
8. Drugs in pregnancy and breast feeding in the Norwegian National Therapeutic Formulary lies with this research group (G8 Amming og legemidler | Legemiddelhåndboka (legemiddelhandboka.no)).
9. Nordeng H. Chapter 3.3.1 Drug utilization in pregnant women. In Drug Utilization Research: Methods and Applications Wiley. 2023.
10. Obstetrics and Gynecology - online textbook for medical students - sundhed.dk

Institution: University of Oslo
Administrative unit: Department of Pharmacy
Title of case study: Improving patient health and wellbeing – the impact of individualized drug therapy
Period when the underpinning research was undertaken: 2012-
Period when staff involved in the underpinning research were employed by the submitting institution: 1992-
Period when the impact occurred: 2014-

6. Summary of the impact (indicative maximum 100 words)

Our research on individualized and optimized drug therapy has significantly impacted patient health and healthcare services by improving prescribing practices and patient-centered decision making. Specifically, our research has focused on the correct dosing of immunosuppressive drugs, which plays a crucial role in reducing complications and improving patient outcomes in renal transplant recipients. We have contributed to the development of international guidelines and participated in the implementation of patient-friendly home-based sampling for drug monitoring. Furthermore, we have investigated methods to improve the drug treatment for patients with multiple long-term conditions, through medication reconciliation, reviews and information to the patients. These services have proven to improve the health and wellbeing of these vulnerable patients.

2. Underpinning research (indicative maximum 500 words)

Drugs are crucial for treating symptoms, slowing down disease progression and preventing the development of future illnesses. The ultimate goal of pharmacotherapy is to develop therapeutic strategies that is better tailored to individual patients' needs rather than fitting them all into a "one size fits all" approach. Over the past decade, our research has focused on genetics, age, gender, disease status, and drug interactions as sources of individual variation in drug response (treatment failure and side effects), as well as strategies for managing this variation in clinical practice to personalize the drug treatment. Furthermore, to fully optimize the treatment the patients' values and resources need to be considered as well as strategies for improved patient empowerment. All of these approaches will ultimately impact the health and overall well-being of patients. Although several patient populations have been included in our research over the years, the largest impact on patients' health and wellbeing has been in renal transplant recipients and patients with multiple long-term conditions. All our research is performed in close collaboration with the clinic (Oslo University Hospital, the Hospital Pharmacies Enterprises, South-Eastern Norway and Diakonhjemmet Hospital Pharmacy).

In renal transplant recipients, individualized drug treatment and precise dosing are key factors to improving graft- and patient survival, while also reducing adverse effects. Following a kidney transplantation, the recipient needs life-long immunosuppressive therapy which must be carefully balanced to avoid under-immunosuppression (risk of allograft rejection) and over-immunosuppression (risk of infection or cancer development). Correct dosing of immunosuppressive drugs is challenging due to a large inter- and intra-individual variability in pharmacokinetics. Improved personalized and tailored immunosuppression monitoring strategies have been stated as the current most important, modifiable factor to improve long-term patient and graft outcomes following renal transplantation. Over the last decade, our research has contributed to optimize the immunosuppressive therapy in renal transplant recipients through development of computerized dosing tools and volumetric finger-prick sampling (Ref 1), monitoring intracellular and tissue drug concentration, and investigations of adherence, bioequivalence (Ref 2), pharmacokinetic variability, accurate determination of renal function (GFR), drug-drug interactions, pharmacogenetics, and post transplantation diabetes (Ref 3).

Meeting the complex care needs of patients with multiple long-term conditions is one of the main challenges faced by healthcare services. Multimorbidity is associated with polypharmacy, increased use of health care services, reduced life expectancy and high risk of drug related problems. We have performed the first randomised controlled trial (RCT) on the efficacy of Integrated Medicines Management (IMM) in patients with multiple long-term conditions (Ref 4). IMM comprises three steps, medication reconciliation at admission, repeated medication reviews and medication reconciliation and patient information at discharge from hospital. The intervention group received IMM throughout the hospital stay, delivered by clinical pharmacists and the control group received standard care. IMM reduced mortality by 34%, but there was no statistically significant effect on time to readmission. Furthermore, we have previously revealed that 80% of patients admitted to medical wards in Norway have at least one medication discrepancy (Ref 5) and we have mapped the medication information at hospital discharge (Ref 6). This last work will contribute to the innovation of an improved service to strengthen the patients' self-management of medication and improve health literacy.

Professor Hege Christensen (1992-present)
Professor Anders Åsberg (full time professor from 2002-2013, professor 2 from 2013-present)
Associate professor Ida Robertsen (2017-present)
Associate professor Liv Mathiesen (2017-present)
Post doctor Marianne Lea (2019 – present)
Professor Espen Molden (professor 2 from 2013 -present)
Associate professor II Kirsten K. Viktil (2009 – present)
Professor II Hege Salvesen Blix (2009 – present)

3. References to the research (indicative maximum of six references)

1. **Gustavsen MT**, Midtvedt K, Vethe NT, **Robertsen I**, Bergan S, **Åsberg A**. Tacrolimus Area Under the Concentration Versus Time Curve Monitoring, Using Home-Based Volumetric Absorptive Capillary Microsampling. Ther Drug Monit. 2020;42(3):407-14.

2. **Robertsen I**, **Åsberg A, Ingerø AO**, Vethe NT, Bremer S, Bergan S, Midtvedt, K. Use of generic tacrolimus in elderly renal transplant recipients: precaution is needed. Transplantation. 2015;99(3):528-32.

3. Halden TAS, **Kvitne KE**, Midtvedt K, Rajakumar L, **Robertsen I**, Brox J, Bollerslev J, Hartmann A, **Åsberg A**, Jensen T. Efficacy and Safety of Empagliflozin in Renal Transplant Recipients With Posttransplant Diabetes Mellitus. Diabetes Care. 2019;42(6):1067-74.

4. **Lea M**, Mowe M, **Molden E**, Kvernrød K, Skovlund E, and **Mathiesen L**. Effect of medicines management versus standard care on readmissions in multimorbid patients: a randomised controlled trial. BMJ Open 2020;10:e041558

5. Nilsson N, **Lea M**, Lao Y, Wendelbo K, Gloersen G, Mowe M, **Blix HS** and **Viktil KK**. Medication discrepancies revealed by medication reconciliation and their potential short-term and long-term effects: a Norwegian multicentre study carried out on internal medicine wards. European Journal of Hospital Pharmacy. 2015;22:298-303.

6. **Rognan SE**, Sporrong SK, Bengtsson K, Lie HB, Andersson Y, Mowé M, and **Mathiesen L**. Discharge processes and medicines communication from the patient perspective: A qualitative study at an internal medicines ward in Norway. Health Expectations. 2021; 24:892–904

4. Details of the impact (indicative maximum 750 words)

Our research impacts the health and wellbeing of the targeted patient groups through improving prescribing practices and facilitating patient centred decision making. Patient injuries occur for approximately 13% of hospital stays in Norway and are estimated to contribute 15% of the total hospital cost. In 2021, drug related injuries were the most frequent category, occurring in 2.3% of hospital stays. Thus, optimization of drug therapy will impact both patients' health as well as the economy of health services.

Incorrect dosing of immunosuppressive drugs contributes significantly to increased morbidity, reduced graft survival and increased mortality. Our research has focused on an overall improvement in patient health and wellbeing by focusing on the right drug in the right doses. Immunosuppressive therapy has serious adverse effects such as nephrotoxicity, post-transplant diabetes mellitus (PTDM), infection and cancer. PTDM is a common and serious complication and require drug treatment. In our study, we show the treatment with SGLT2 inhibitors is a safe and effective treatment in renal transplant recipients with PTDM. Close monitoring of drug dosing is necessary to avoid under immunosuppression. Current international guidelines emphasize using advanced computer tools and AUC-targeted drug monitoring. The outcome from our research has been central in the development of these guidelines both concerning the implementation of advanced dosing tools as well as the use of generic formulations. As stated in the international guidelines, part of the transplant community has been concerned with the use of generic drugs, especially given the fact that tacrolimus is a narrow therapeutic index drug and that the bioequivalence studies are performed in healthy volunteers. Following the results from our bioequivalence study, showing a significant difference between the generic and the original tacrolimus formulation in elderly renal transplant recipients, Oslo University Hospital discontinued the use of the generic tacrolimus formulation and also removed the substitution list. Also, the Norwegian Medicine Agency showed great interest in the results and raised a concern regarding this matter in the European Medicine Agency. We have also been central in the development of microsampling of capillary blood (finger-prick) to determine tacrolimus concentrations. This patient friendly home-based sampling can be performed by the patients themselves and save both resources at the hospital and limit the number of visits to the hospital as the microsamples are sent to laboratory by standard mail service. This has been implemented into clinical practice (from 2021). Further, this sampling methods also align with the general focus on increased use of home hospital as stated in the national plan for health and the hospital sector 2020-2023.

Multimorbidity is associated with increased use of medications and health care services and a high risk of drug related problems. Notably, drug related problems are responsible for 10-30% of all hospitalizations. Performing medication reviews is a tool to optimise the drug treatment for the individual patient, taking age, body weight, sex, genetics, diseases, and patient preferences into account. Inadequate information exchange during care transitions, exemplified with 80 % of patients having at least one medication discrepancy at hospital admission, emphasize the importance medication reconciliations in these situations. Our research demonstrates that in patients with multiple long-term conditions an intervention (IMM) comprising medication reconciliation ciliation at admission, repeated medication reviews and medication reconciliation and information at discharge from hospital reduced mortality by 34%. However, there was no statistically significant effect on time to readmission (median 116 vs 184 days, p=0.106). A recent systematic review on interventions on transition of care which included our RCT (*Taylor N et al JAMA Netw Open.* 2023;6(11):e2344825. doi: 10.1001/jamanetworkopen.2023.44825) concluded that interventions such as IMM significantly reduced the odds of readmission at 180 days compared to usual care (OR 0.45; 95% CI 0.30 to 0.66). However, in this review no significant effect on mortality was seen. Although the results from our RCT might be a chance finding, there should be little doubt that IMM positively impact patients' the health and wellbeing. Our research has had several impacts on the quality of Norwegian health care services. Firstly, it has contributed to an increased emphasis on medication reconciliation and reviews during the past decade,

including through the national program for patient safety (Pasientsikkerhetsprogrammet). The research was also referred to in the national plan for health and the hospital sector, published in 2019. Furthermore, our research has impacted the recently launched national guidelines on medication reconciliations and reviews. Additionally, our research has contributed to the development of hospital procedures on medication reconciliation at the largest university hospital in Norway.

5. Sources to corroborate the impact (indicative maximum of ten references)

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Opptak av legemiddelanamnese og samstemming av legemiddellister, E-håndboken OUS HF. eHåndbok - Opptak av legemiddelanamnese og samstemming av legemiddellister (ous-hf.no)

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PSI 1

Institution: University of Oslo
Administrative unit: Department of Psychology
Title of case study: Bridging Body and Mind through effective interventions, tools, and health literacy
Period when the underpinning research was undertaken: 2010-2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2015-2022
Period when the impact occurred: 2012-2022

1. Summary of the impact

The Mind Body Lab investigates the intricate interplay of stress physiology and expectancies within the nexus of the brain and body, resulting in societal impact across various domains, including but limited to: 1) Changing national policy through innovative interventions in the field of work and health; 2) Guiding health literacy through widespread communication on stress, pain and fatigue; 3) Contributing to health services by developing and widely disseminating concrete tools for health care personnel.

2. Underpinning research

New policy of innovative interventions in the field of work and health

Individually and collaboratively, Reme & Jacobsen have spearheaded multiple projects dedicated to mitigating work disability and enhancing workers' health, each leaving a considerable imprint on society: 2012-2014, Reme and Jacobsen contributed through their research to the development of a work-place intervention for nurses in several large hospitals in the Boston area (1,2,3).

2017-2020, as the first of its kind, Jacobsen was pivotal in developing and testing an Acceptance and Commitment Therapy (ACT) version of the "Norwegian model" of in-patient work rehabilitation in a randomized controlled trial (RCT) (5,6). Norway is dependent on in-patient work-related rehabilitation, and the program stood out by substantially increasing work participation in those on long-term sick leave for chronic pain and/or fatigue (4).

Reme has served as the Principal Investigator for several multicenter RCTs exploring the innovative job support model, Individual Placement and Support (IPS). Initially developed for individuals with severe mental illness, Reme spearheaded the first study testing this model in Norway (8). Another multicenter trial led by Reme investigated the integration of IPS with cognitive-behavioral therapy for individuals with common mental disorders (7). Long-term results from both trials (9,10) not only demonstrated effectiveness in terms of improved work participation and health, but also showcased cost-effectiveness.

Recent collaborative efforts by Reme and Jacobsen have focused on adapting the IPS model for chronic pain populations. Piloting and rigorously testing the model through a RCT yielded promising outcomes (11).

Guiding health literacy through widespread communication on stress, pain, and fatigue

The Mind Body Lab organized a seminar at the University of Oslo in October 2022, uniting key researchers and clinicians from across Europe in the realm of chronic fatigue. During this meeting, they established the Oslo Chronic Fatigue Consortium, which promptly led to the publication of a consensus statement (12). Remarkably, the article has set an unprecedented record for the journal in which it was published, accumulating over 16,000 views.

In 2019, Professor Steven J. Linton retired, distinguished for his pioneering contributions to pain psychology. Colleagues alongside Reme and Jacobsen reviewed the latest advancements in pain psychology, discussing topics ranging from the fear avoidance model to emotion-focused treatments for chronic pain. This resulted in an impactful paper on pain psychology in the 21st century (14).

In 2021 the Mind Body Lab launched the SURGE model for chronic post-surgical pain (CPSP). CPSP is prevalent after surgeries like breast cancer surgery, with psychological factors playing a significant role in its development. This review and model propose that patients' expectations, influenced by stress and inflammation, can lead to sustained CPSP. It suggests that interventions like presurgical hypnosis could potentially modify these expectations and help prevent CPSP.

Contributing to health services by developing and disseminating tools for health care personnel
Jacobsen co-developed a communication model for health personnel dealing with complex pain patients in a tertiary health setting. This model was implemented in all four university pain clinics in Norway and was described in a high impact scientific paper (19).

Reme supervised the doctoral candidate who developed a communication tool for general practitioners. The communication tool proved to be highly successful in terms of alleviating symptoms, sick leave, and improving quality of life in patients with medically unexplained physical symptoms. Reme served as the corresponding author of the publication which was published in eClinicalMedicine by Lancet (18).

Reme and Jacobsen have also contributed to enhance clinical practice by spearheading the development, translation, and validation of a diverse array of screening tools and questionnaires (e.g., 16,17).

Silje Endresen Reme:

- 2015: Associate professor
- 2017: Professor

Henrik Børsting Jacobsen:

- 2019: Senior Researcher
- 2023: Associate professor

3. References to the research

New policy of innovative interventions in the field of work and health

1. **Reme SE et al** (2012) Musculoskeletal pain and psychological distress in hospital patient care workers. Journal of Occupational Rehabilitation, 22(4):503-10.
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Guiding health literacy through widespread communication on stress, pain, and fatigue

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Contributing to health services by developing and disseminating tools for health care personnel.

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4. Details of the impact

New policy of innovative interventions in the field of work and health

Work disability and exclusion from the workforce entail substantial societal costs and pose a significant health burden on affected individuals. The major reasons for long-term sick leave and disability pension in Norway are chronic pain conditions and mental health problems. The Mind Body Lab has consistently emphasized the health-promoting and therapeutic impacts of work on both mental and physical well-being since its inception in 2011 when Reme and Jacobsen first joined forces. Their collaborative efforts have not only contributed to the development of innovative interventions but have also spearheaded research initiatives on these interventions. The consequential outcomes have triggered substantial shifts in policy and practice:

In their early collaboration, Reme and Jacobsen contributed through their research to the development of a work-place intervention for nurses in several large hospitals in the Boston area. Their publications on sleep, work to family conflict and cardiometabolic risk also led to widespread dissemination and literacy interventions for nurses in both the US and later in Norway.

Under the leadership of Reme, the innovative job support model (IPS) was evaluated in a multicenter RCT, which resulted in a markable policy shift. The proven efficacy of IPS has led to its nationwide implementation, ensuring that individuals with severe mental illness in every municipality of Norway have access to this effective program. Every year, between 6000-7000 individuals receive this intervention, with more than half of them obtaining sustainable employment. This is unique in an international perspective and has attracted significant attention from all over the world, resulting in Reme giving keynote lectures in 7 different countries so far.

Another of these national multicenter trials, headed by Reme, investigated the IPS intervention integrated with cognitive behavioral therapy for people with common mental disorders. The favorable results from this trial led to the widespread adoption of this specific intervention nationwide, ensuring its accessibility to all patients within the target group.

As the first of its kind, Jacobsen was pivotal in developing and testing an Acceptance and Commitment Therapy (ACT) based in-patient work rehabilitation in a RCT. Norway is dependent on in-patient work-related rehabilitation, and the program stood out by substantially increasing work participation in those on long-term sick leave for chronic pain and/or fatigue. This program has been adapted into national guidelines and has led to the widespread implementation of ACT as part of in-patient work rehabilitation in Norway.

Guiding health literacy through widespread communication on stress, pain, and fatigue
This part of the Mind Body Lab's impact plays an essential role in addressing pain, fatigue, and stress-related disorders in Norway. This is underlined by our country's health literacy figures, showing a significant proportion of the population at the lowest level in health promotion (28%), healthcare (22%), and overall health literacy (33%). Such numbers underscore the urgency and relevance of the Lab's commitment to simplifying complex medical science and disseminating practical health insights. Our widespread communication crucially bridges the gap for all of those who are facing difficulties grasping health-related information, ultimately fostering a more enlightened and healthier society.

As examples of this, The Mind Body Lab has significantly shaped the public opinion on stress and fatigue. Our Oslo statement synthesizes the most recent evidence on persistent fatigue conditions and underscores the potential for recovery. With the involvement of 50 co-authors, this collaborative effort stemmed from our initiated meeting at the University of Oslo, where Reme assumed the roles of corresponding author and primary press contact. The ensuing press releases garnered attention in multiple countries, resulting in widespread dissemination across Europe and the US.
The same can be said for stress and pain, both in scientific publications such as (14,15) and public discourse. Through diverse media involvement, including widely read, viewed, and listened to features advocating scientific stress relief methods, Oslo Chronic Fatigue Consortium, and prominent discussions, the Lab influences national dialogue. Reme and Jacobsen's consistent public engagements, such as op-eds and TV appearances, have propelled scientific stress regulation to the forefront of public consciousness. Our collective efforts to clarify and communicate scientific findings not only challenge prevailing myths but also equip citizens with the knowledge to confront stress, pain, and fatigue with evidence-based strategies.

Contributing to health services by developing and disseminating tools for health care personnel.
Reme & Jacobsen are not only researchers, but also clinicians. During the last decade, they have developed and delivered several practical tools and interventions that are being used by other clinicians both nationally and internationally. This involves development, translation and validation of several patient questionnaires used in clinical practice (e.g., 16-17), but it also extends to communication tools. Through the Mind Body Lab, Reme and Jacobsen have developed and disseminated practical communication tools for general physicians and other health professionals. The communication tool co-developed by Jacobsen is currently being taught to medical students and psychology students as well as medical professionals seeking specialisation in pain management, while Reme's invaluable contributions to the communication tool for GPs has resulted in the tool being disseminated extensively. The tool has garnered substantial traction among General Practitioners (GPs), with a notable 20% of GPs projected to have received comprehensive training in this tool by the conclusion of 2024.

Reme and Jacobsen were instrumental in developing and implementing the Oslo Pain Registry, a Digital Health Registry for Chronic Pain at Oslo University Hospital which is the largest of its kind in the world. They both serve on the board of this registry (Repeated measures in > 5000 patients). The registry serves as a model for other pain clinics in the region of South-Eastern Norway and has so far been implemented in one other clinic. In their clinical roles Reme and Jacobsen co-founded, developed, and implemented a multi-disciplinary masters´ program in transdisciplinary pain treatment at the University of South-Eastern Norway. To date, 168 students (physicians, psychologists, nurses, and physical therapists) have completed this program. Finally, through their engagement in the pain clinic, they were involved in developing a regional guideline for multidisciplinary pain management, which is open access for all students and clinicians.

5. Sources to corroborate the impact (indicative maximum of ten references)

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2. National guidelines for work-related rehabilitation in Norway
3. Press release about the Oslo Chronic Fatigue Consortium
4. One of several news articles covering the Oslo Statement about fatigue conditions
5. Annual Report of the Norwegian Medical Association confirming the dissemination of the communication tool for GPs.
6. Reme SE (2023) News article: how to prevent chronic pain/fatigue after breast cancer
7. Reme & Jacobsen (2023) Live stream and video disseminating the main results of our research on prevention of pain and fatigue after breast cancer.
8. Jacobsen H. B. (2022.31.12) How to relieve stress in 30 days? (>600.000 unique reads. VG is Norway's most popular newspaper)
9. Jacobsen H. B. (2023.6.3) Podcast: Is stress dangerous? (>50.000 downloads and top episode in 2023)
10. Jacobsen H. B. (2018.9.7) Op-ed: Pills that do not work. (Op-ed in Norways largest news outlet)
11. Jacobsen H. B. (2023.10.12) Op-ed: The stress watch (2023s most read Op-ed in Norways largest news channel, >220.000 unique reads)
12. Jacobsen H. B. (2023.19.12) TV performance: HRV and the measurement of stress (Dagsnytt18 is Norways 3rd most popular tv show in 2023)
13. Jacobsen H. B. (2024.4.1) TV performance: Health influencers (Debatten is Norways 9th most popular tv show in 2023)

PSI 2

Institution: University of Oslo
Administrative unit: Department of Psychology (PSI)
Title of case study: A human rights approach in psychology and the primary, secondary, and tertiary prevention of torture and other ill-treatment
Period when the underpinning research was undertaken: 2004-2017
Period when staff involved in the underpinning research were employed by the submitting institution: 2004-2019
Period when the impact occurred: 2012-2022

1. Summary of the impact

A significant global issue persists with numerous individuals facing torture and ill-treatment, leading to enduring physical and psychological consequences. Nora Sveaass and her colleagues have made substantial contributions through research and practical interventions, focusing on preventing torture, rehabilitating victims, prosecuting perpetrators, and providing effective psychological treatment. In recognition of her outstanding efforts in the field of human rights, Nora Sveaass has been honoured with the Order of St. Olav.

2. Underpinning research

The influential research initiative “Human rights research group” highlights the significance of incorporating a human rights perspective into psychology, specifically examining the psychosocial repercussions of torture and ill-treatment. It delves into primary, secondary, and tertiary prevention strategies for mitigating these adverse effects. Nora Sveaass, the driving force behind this program at PSI, served at PSI from 2008 until her retirement in 2019.

Nora Sveaass’ group has been actively publishing on this subject since 1989, starting with "Psychosocial problems among refugees in Norway," and continuing with significant contributions to this day, including the chapter "The politics of torture: legal, social and political dynamics" in the Research Handbook on the Politics of Human Rights Law in 2023. Through collaborations, teaching, and supervision at PSI, they have ensured the transmission of Sveaass’ human-rights approach and focus on impactful research to the next generation. An example is the paper "‘Discuss it with your legal guardian’: Challenges in practising care for young unaccompanied refugee minors," resulting from her co-supervision of G Omland, now an Associate Professor at PSI.

The group’s earlier work primarily explored possibilities for secondary and tertiary prevention, with a notable emphasis on the impacts of policies and societal interventions. This focus is exemplified by four key publications:

In 2004, they conducted one of the first studies on the effects of psychosocial support on traumatic symptoms in refugees [1]. Structured interviews with 966 refugees revealed a high prevalence of experience of torture and traumatic experiences, strongly linked to PTSD symptoms. The presence of family and work or school activities were found to lower symptom load, and to buffer from the effects of high exposure to trauma. The study emphasizes the importance of psychosocial measures in the integration of traumatized refugees in a host community. It recommended policy changes to facilitate family reunion and work participation.

In 2013, Sveaass authored an influential review paper outlining the practical implementation of new international legislation on the right to rehabilitation and reparation for victims of torture from a traumatological and victim-centered perspective [2]. This paper, reflecting her expertise in trauma therapy and international human rights law, serves as a culmination of her interdisciplinary approach. Emphasizing issues from the victims' standpoint, the paper underscores the essential role of trauma-informed health professionals in actively participating in implementing the right to redress and rehabilitation in national procedures.

The subsequent paper advocates for trauma rehabilitation as a crucial factor in facilitating the integration of refugees into their host society. Nora Sveaass, along with colleagues from NTNU Trondheim, conducted a survey study involving 200 refugees, revealing that a history of trauma had a detrimental effect on the motivation to learn Norwegian [3].

The fourth study examined the experiences of individuals affected by gross human rights violations in Argentina's dictatorship era regarding economic reparations [4]. Thirty-seven participants, primarily survivors or family members of those severely impacted by violence from 1976 to 1983, were interviewed. The findings indicate that economic reparations, constituting a transitional justice mechanism, were perceived as problematic and contradictory, especially in the absence of legal justice, highlighting the importance of a comprehensive transitional justice process encompassing truth and legal accountability.

In their recent publications, Sveaass and colleagues have shifted towards a greater emphasis on primary prevention, a transition mirrored in Sveaass' advocacy efforts. This evolution is exemplified through two research papers:

Since its adoption in December 2002, the United Nations Optional Protocol to the Convention against Torture establishes a framework for regular visits by independent international and national bodies to places of detention, aiming to prevent torture and other inhuman treatment. Sveaass and Madrigal-Borloz investigated the collaboration between these bodies, emphasizing their crucial role in protecting individuals with mental disabilities in detention, who are vulnerable to exploitation and severe human rights violations [5]. The exploration underscores the significance of these unannounced visits in addressing concerns outlined in Article 16 of the Convention on the Rights of Persons with Disabilities.

In the paper titled "Do No Harm? How Psychologists Have Supported Torture and What to Do About It," Nora Sveaass and her co-authors critically examine the professional ethics of psychologists and their organizations concerning torture [6]. Drawing on documents and personal experiences, they analyze the processes in two contexts: the post-9/11 United States and Apartheid-era South Africa. The study reveals various problematic responses from psychologists and psychological associations to violations of the absolute prohibition of torture, ranging from passive complacency to active involvement. This paper holds significant relevance for the ethical training of psychologists and the broader discourse on professional responses, extending to issues such as Israel and Palestine or Ukraine and Russia. The conclusion underscores the imperative of educating psychologists in human rights for fostering professional ethics and primary prevention.

3. References to the research

All articles cited have undergone rigorous peer review and are available for inspection by using the links provided. Where access is denied due to lack of institutional subscription, PSI will provide a full-text version upon request.

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4. **Sveaass, N**., & Sønneland, A. M. (2015). Dealing with the past: Survivors' perspectives on economic reparations in Argentina. *International Perspectives in Psychology: Research, Practice, Consultation*, *4*(4), 223. https://doi.org/10.1037/ipp0000041
5. **Sveaass, N**., & Madrigal-Borloz, V. (2017). The preventive approach: OPCAT and the prevention of violence and abuse of persons with mental disabilities by monitoring places of detention. *International journal of law and psychiatry*, *53*, 15-26. https://doi.org/10.1016/j.ijlp.2017.06.001
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4. Details of the impact

The research by Nora Sveaass' group has significantly influenced societal perspectives, shaped policies, and contributed to a more compassionate approach in addressing the psychological effects of torture, the needs of refugees, and broader human rights issues. Their scholarly endeavours have left an indelible mark on academic discourse and practical applications in the following ways:

A. Authoring the UN's Istanbul Protocol: Sveaass served on the Editorial Committee and as chapter editor for the "Istanbul Protocol: Manual on the Effective Investigation and Documentation of Torture and Other Cruel, Inhuman or Degrading Treatment or Punishment (2022 edition)". This is an extraordinary example of a researcher not only influencing policy but making policy based on a lifelong of experience.

B. Influencing Policy on Asylum Seekers' Mental Health: The research by Sveaass' group played a pivotal role in advocating for the psychological well-being of asylum seekers, leading to early interventions and support systems [see 1, 3]. Her report "Vulnerable asylum seekers in Norway and EU - Identification, organization and handling" (Brekke, Sveaass, & Vevstad, 2010) immediately resulted in several high-level decisions aiming at strengthening mental health of asylum-seekers and preventing deterioration of their condition. The Norwegian Directorate of Immigration, the Directorate of Health, and the Ministry of Children and Families established a systematic mechanism for early identification of vulnerable asylum seekers with special needs and revised the Norwegian reception system to ensure adequate follow-up.

C. Global Contribution through UN Committee Against Torture and UN Subcommittee for the Prevention of Torture: Serving on the UN Committee Against Torture, Sveaass has leveraged her research expertise [see 2, 4, 5] to contribute to the global work on torture prevention and accountability. Her insights have influenced international policies aimed at preventing torture and ensuring justice for victims.

In 2012, the UN adopted the *General Comment to Article 14 of the Convention against Torture* that she and three other members of this committee had authored. This highly influential document contains an in-depth description of what should be in place for rehabilitation to be possible, which she could deliver thanks to her many years of clinical work in the field. The work involved profound analysis of jurisprudence and practice in field, combined with insights into the needs of persons subjected to torture or ill-treatment.

As a member of the UN Subcommittee for the Prevention of Torture, she has investigated conditions for detained individuals in prisons, police custody, psychiatric institutions, and child welfare institutions in states that have signed the additional protocol to the UN Convention Against Torture.

D. Integration of Human Rights in Psychology: The Human rights research group at PSI has advocated for the integration of human rights perspectives into the field of psychology [see 6]. This impact extends beyond academic circles, influencing how psychologists approach their work, emphasizing the ethical dimensions and human rights considerations in psychological practice. In 1998, Nora Sveaass initiated the establishment of the Norwegian Psychological Association's Human Rights Committee (MRU), which she chaired until 2018. She believes that human rights thinking and professional ethics in social and health sciences are rooted in the same fundamental values. Therefore, she has been committed to stimulating interest in human rights among all those working with people, through teaching, writing, supervising, and advocacy. Her critical and principled voice was an important input to the "Independent Review Relating to APA Ethics guidelines, National Security Interrogations, and Torture" (Hoffman-report) prompting the APA Council of Representatives to enact a policy to prohibit APA member psychologists from practicing in certain interrogation-related settings.

E. Addressing the Needs of Torture Victims: PSI's work on the psycho-social needs of refugees, particularly those traumatized by torture, has influenced rehabilitation programs and support services. The group's research has contributed to the development of more comprehensive and tailored approaches to assist individuals in overcoming the psychological impact of torture. Their therapeutic approach to working with victims of torture has been widely adopted in Norway. Sveaass was among the first to do family therapy with refugees.

F. Mental Health and Human Rights Info (mHHRI): The establishment of Mental Health and Human Rights Info reflects Sveaass' commitment to disseminating information at the intersection of health and human rights. This organization has served as a valuable resource for policymakers, healthcare professionals, and advocacy groups, fostering a better understanding of the link between health and human rights. The website has evolved into a go-to resource for health-care professionals dealing with traumatized individuals for providing free, accurate, and actionable information, advice, and trainings. The site had 214 000 unique visitors in 2022, 16 300 followers on social media and 20.000 were reached through the newsletter. PSI has a long-standing collaboration with mHHRI through student internships, joint thesis supervision, and, lately, the Ukraine initiative, supporting colleagues in Ukraine through providing material, training, and supervision. The initiative has trained and supervised hundreds of students and therapists all over Ukraine via webinars and online training and supervision.

G. Advocacy for Vulnerable Populations: Through her involvement in various organizations and initiatives, Sveaass has advocated for vulnerable populations, ensuring that the group's research findings translate into concrete actions [see 2, 4, 5]. This work has influenced the formulation of policies that prioritize the rights and well-being of those who have faced human rights abuses.

In summary, the human rights research group at PSI, led by Nora Sveaass, has not only expanded our understanding of critical human rights issues but has also translated into tangible impacts on policies and practices. By addressing the psychological effects of torture, advocating for asylum seekers' well-being, and promoting a human rights perspective in psychology, their work has contributed to a more informed, compassionate, and rights-oriented approach within both academic and societal contexts.

5. Sources to corroborate the impact

Evidence of the group's societal impact are the awards Sveaass received for her work, among them The Academics' Award 2018 (Akademikerprisen); Amnesty Norway's Human Rights Award 2009 and UiO's Human Rights Award 2018. Below, we list some sources to verify each of the areas of impact named in the above section.

A. Istanbul protocol:

United Nations. Office of the High Commissioner for Human Rights (2022). *Istanbul protocol: Manual on the effective investigation and documentation of torture and other cruel, inhuman or degrading treatment or punishment*. United Nations Publications. https://www.ohchr.org/en/publications/policy-and-methodological-publications/istanbul-protocol-manual-effective-0

B. Policy on Asylum seekers' health checks:

Textbook chapter in the go-to resource for migrant psychiatry:

Sveaass, N., & Lie, B. (2021). Early assessment of mental health and options for documentation of torture in newly arrived asylum seekers. *Oxford textbook of migrant psychiatry*, 387-394. https://doi.org/10.1093/med/9780198833741.003.0046

Policy paper by the Norwegian Directorate of Immigration on the reorganization of reception:

Larsen, H. (2014). The Organisation of Reception Facilities for Asylum Seekers in Norway. UDI

C. UN Committee against Torture: Election papers 2005; 2009; 2014; Notice on reelection by Human Rights House Foundation (2009). **UN Subcommittee on Prevention of Torture:** Election 2014; 2018; Heading delegation to Bulgaria 2021; Report on Norway in Geneva 2017

General comment No. 3 (2012) on the implementation of article 14 by States parties: https://www.ohchr.org/en/documents/general-comments-and-recommendations/catcgc3-general-comment-no-3-2012-implementation

Research article detailing the work on and content of the General comment:

Grossman, C., **Sveaass, N.**, & Gaer, F. (2018). Rehabilitation in Article 14 of the Convention Against Torture and Other Cruel, Inhuman, or Degrading Treatment or Punishment. *International Lawyer, 1*. https://digitalcommons.wcl.american.edu/facsch_lawrev/576/.

D. Integration of Human Rights in Psychology:

Book for health practitioners on the Human Rights approach to health and social work.

Stang, E. G., & Sveaass, N. (2016). *Hva skal vi med menneskerettigheter?: Betydningen av menneskerettigheter i helse- og sosialfaglig arbeid [What Do We Need Human Rights For? On the Importance of Human Rights in Health and Social Work]*. Gyldendal akademisk.

Hoffman-report with interview with Nora Sveaass.

Hoffman, D. H., Carter, D. J., Viglucci Lopez, C. R., Benzmiller, H. L., Guo, A. X., Latifi, S. Y., & Craig, D. C. (2015). *Report to the special committee of the board of directors of the American Psychological Association: Independent review relating to APA ethics guidelines, national security interrogations, and torture*. http://www.apa.org/independent-review/revised-report.pdf

E. Addressing the Needs of Torture Victims:

UN Report citing the group's work:

Torture and other cruel, inhuman or degrading treatment or punishment: report of the Special Rapporteur (2020). UN. http://digitallibrary.un.org/record/3870734

The following policy paper by the Latin American Centre for Rural Development (RIMISP) cites Publication 4. It shows our impact on the discourse within Latin America on how to achieve reconciliation after violent conflict in Colombia:

Fergusson, L., Hiller, T., Ibáñez, A. M., & Moya, A. (2018). *Cómo nos reconciliamos? El papel de la violencia, la participación social y política, y el Estado en las actitudes frente a la reconciliación [Reconciliation once Conflict Ends in Colombia. The Role of Violence, Social and Political Participation, and the State on Attitudes towards Reconciliation]*. RIMISP. Centro Latinoamericano para el Desarrollo Rural. http://hdl.handle.net/10625/59390

Policy brief examining how political prosecution can enhance healing from trauma [based on 2]:

Skjelsbæk, I., **Sveaass, N**., & Gjerde Kvaale, R. M. (2015) Therapeutic Prosecutions? Assessing the therapeutic potential of criminal prosecution of international crimes at the International Criminal Court (ICC). *PRIO Policy Brief, 4*. Oslo: PRIO. https://www.prio.org/publications/8662

Policy briefs citing Publication 3:

Manzoni, C., & Rolfe, H. (2019). How schools are integrating new migrant pupils and their families. National Institute of Social and Economic Research, UK. NIESR.

Cerna, L. (2019), "Refugee education: Integration models and practices in OECD countries", *OECD Education Working Papers*, No. 203, OECD Publishing, Paris. https://doi.org/10.1787/a3251a00-en.

F. Mental Health and Human Rights Info (mHHRI):

See, in particular, the Ukraine Mental Health Resources, created in collaboration with many colleagues at PSI, in English and Ukrainian, and the Training Manual for Helping Survivors of Gender-Based Violence. The manual and tools are available in 14 languages, along with a video-based structured training. Numbers on reach stem from mHHRI's year report 2022.

G. Advocacy for Vulnerable Populations:

Policy paper by the German Federal Ministry of Labour and Social Affairs cites Publication 5 (p. 67):

Schröttle, M., Puchert, R., Arnis, M., Hafid, A., Sarkissian, A. H., Lehmann, C., ... & Thümmel, I. (2021). *Gewaltschutzstrukturen für Menschen mit Behinderungen-Bestandsaufnahme und Empfehlungen. [Violence Protection Structures for People with Disabilities - Stocktaking and Recommendations].* Bundesministerium für Arbeit und Soziales.

PSI 3

Institution: University of Oslo
Administrative unit: Department of Psychology
Title of case study: Examining and implementing trauma-focused treatment in child mental health clinics in Norway
Period when the underpinning research was undertaken: 2008 - 2024
Period when staff involved in the underpinning research were employed by the submitting institution: 2008-2024
Period when the impact occurred: 2012 - 2023

1. Summary of the impact (indicative maximum 100 words)

Many youths are exposed to trauma, leading to a range of mental health consequences that cause serious pain to families and children and substantial societal costs. There is an under-recognition of trauma and only a small portion of traumatized youth receive evidence-based treatment. Better screening and implementation of evidence-based treatment was needed. There was also a lack of knowledge on change processes which is essential for individualizing treatment. Filling in this gap Professor Jensen and colleagues at the Norwegian Centre for Violence and Traumatic Stress Studies have conducted a series of studies the have resulted in a government supported nation-wide implementation of Trauma Focused Cognitive Behavioural Therapy.

2. Underpinning research (indicative maximum 500 words)

Childhood trauma is one of the leading causes of mental health problems and impairment in children and adults. High rates of PTSD, depression, conduct disorder, alcohol dependence, self-harm, eating disorder and suicide have been found in trauma exposed persons. Studies show that elevated symptoms that are left untreated over 6 months may become chronic. In sum, the cost for the individual families and society are large. Improved screening and effective treatments are thus needed.

The prevalence rates for all types of childhood trauma are not well studied in Norway. However, rates for serious violence in the home and sexual abuse are estimated to be between 8 and 12%. Also, serious bullying in school has been found to have similar consequences as experiencing violence at home (**Birkeland, Skar & Jensen** 2022).

Only a small portion of traumatized youth receive treatment and even fewer evidence-based treatment (EBT). This is partly because the recognition of PTSD and trauma has been low and in Norway there has, until recently, not been any systematic screening policies in child and adolescent outpatient clinics (hereafter referred to as BUP). Also, before 2012 no EBT's were implemented and there were no implementation leadership programs available. There were also large knowledge gaps about predictors for trauma treatment outcomes and change processes which is needed for individualizing treatment.

Since 2008, Trauma-Focused Cognitive Behaviour Therapy (TF-CBT) has been considered first line treatment of choice for children and adolescents suffering with PTSD after trauma. Professor **Tine K. Jensen** at the Department of Psychology, University of Oslo, Norway (PSI) and the Centre for Violence and Traumatic Stress Studies (NKVTS) with colleagues, conducted a randomized controlled trial (RCT) in Norway (2008-20012) comparing TF-CBT to therapy as usual in BUP. This was the first RCT to be conducted outside of the USA, by independent researchers. Youth who

received TF-CBT had significantly fewer symptoms of PTSD, depression and general mental health problems and higher daily functioning than youth who received therapy as usual. Effects were maintained after 18 months (**Jensen, Holt, Ormhaug** et al. 2014; **Jensen, Holt, Ormhaug** 2017). Also, TF-CBT was a cost-effective alternative to standard treatment (Aas, Iversen, **Holt, Ormhaug**, **Jensen**, 2018).

Because of these promising results The Norwegian Ministry of Health and Care Services (HOD) have since 2012 funded a nationwide implementation of TF-CBT in BUP organized at NKVTS, where Jensen holds a part time position. A comprehensive implementation model was developed which included systematic trauma screening with a validated instrument (Sachser, Berliner, Risch, Rosner, **Birkeland**, Eilers, Hafstad, Pfeiffer, Plener**, Jensen**, 2022), implementing organizational changes and leadership training with the Leadership and Organizational Change for Implementation (LOCI) model (**Skar**, Braathu, **Jensen**, **Ormhaug** 2021). To facilitate implementation and personalized care a series of process and predictor studies for outcome and dropout were conducted by among others Tine K. **Jensen** (fulltime position at PSI), Marianne **Birkeland** (part-time position at PSI), post doc Ane-Marthe Solheim **Skar**, PhD candidates Tonje **Holt**, Marie Lindebø **Knutsen**, Silje Mørup **Ormhaug**, Kristianne Stigsdatter **Ovenstad** (all at engaged at PSI at the time).

2. References to the research (indicative maximum of six references)

1. **Jensen**, T. K., **Holt**, T., & **Ormhaug**, S. M. (2017). A Follow-up Study from a Multisite, Randomized Controlled Trial for Traumatized Children Receiving TF-CBT. Journal of Abnormal Child Psychology, 45(8), 1587-1597. doi:10.1007/s10802-017-0270-0
2. Aas, E., Iversen, T., **Holt**, T., **Ormhaug**, S. M., & **Jensen**, T. K. (2019). Cost-Effectiveness Analysis of Trauma-Focused Cognitive Behavioral Therapy: A Randomized Control Trial among Norwegian Youth. Journal of Clinical Child & Adolescent Psychology, 48(1), S298-S311. doi:10.1080/15374416.2018.1463535
3. **Skar**, A.-M. S., **Ormhaug**, S. M., & **Jensen**, T. K. (2019). Reported levels of upset in youth after routine trauma screening at mental health clinics. JAMA Network Open, 2(5), e194003-e194003.
4. Sachser, C., Berliner, L., Risch, E., Rosner, R., **Birkeland**, M. S., Eilers, R., Hafstad, G. S., Pfeiffer, E., Plener, P., & **Jensen**, T. K. (2022). The Child and Adolescent Trauma Screen 2 (CATS-2). Validation of an Instrument to measure DSM-5 and ICD-11 PTSD and complex PTSD in Children and Adolescents. European Journal of Psychotraumatology, 13(2).
5. **Jensen**, T. K., Braathu, N., **Birkeland**, M. S., **Ormhaug**, S. M., & **Skar**, A.-M. S. (2022). Complex PTSD and treatment outcomes in TF-CBT for youth: a naturalistic study. European Journal of Psychotraumatology, 13(2), 2114630.
6. Aminihajibashi, S., **Skar**, A. M. S., & **Jensen**, T.K. (2022). Professional wellbeing and turnover intention among child therapists: a comparison between therapists trained and untrained in Trauma-Focused Cognitive Behavioral Therapy. BMC Health Services Research, 22(1). doi:10.1186/s12913-022-08670- 3.

4. Details of the impact (indicative maximum 750 words)

I. Identifying trauma:

Before 2012 there was no systematic screening of childhood trauma at Norwegian BUPs, and few traumatized children were identified and assessed for PTSD. One early identified barrier to screening was clinicians fear of upsetting children. We therefore conducted a study to examine level of upset after screening with over 10,000 children that showed low upset levels (citing 3). Another barrier was the lack of updated, validated and easily accessible screening instruments. For this reason, we collaborated with international researchers to develop a screening instrument for

trauma exposure and PTSD with norm data that adhered to both the new ICD 11 og DSM-5 diagnostic criteria for PTSD (citing 4). This instrument is now used worldwide and is recommended in the Norwegian patient recommendations for screening and treatment (citing A) and is also being used in Norwegian municipalities for early detection. This has resulted in an increase in trauma identification (See Aktivitetsdata for psykisk helsevern for barn og unge- https://www.helsedirektoratet.no/rapporter/aktivitetsdata-for-psykisk-helsevern-for-barn-og-unge). The impact of the implemented trauma screen:

1. *Early identification:* By screening for trauma, professionals can identify children who have experienced trauma and provide them with appropriate interventions and support before the effects become deeply ingrained.
2. *Prevention of further harm*: Trauma can have a cumulative effect. By identifying traumatized children, professionals can work to prevent further harm by removing them from unsafe environments or ensuring they receive appropriate care and support.
3. *Tailored support and treatment*: Screening helps professionals understand the specific needs and challenges of each child, allowing them to provide tailored treatment.

II. Increased treatment effectiveness and outcomes

Understanding mechanisms of change is crucial for being able to provide individualized treatment and care. Our studies have greatly contributed to the understanding of predictors, moderators and mediators for outcomes and predictors for dropout and non-response (citing 1, E, F, I). Also, with the new diagnosis Complex PTSD, clinicians needed knowledge on whether new treatments were needed. Our studies were able to show that TF-CBT was efficient in reducing Complex PTSD (citing 5). In sum this research has had several impacts:

1. Improving patient outcomes and fewer dropping out of treatment (citing 1, I)
2. Informing policy (citing D, H)
3. Accommodating to changes in diagnostic criteria (citing 5)
4. Providing data made available to larger meta-analysis with the potential to increase treatment benefits (citing E).
5. Contributing to the development of better treatment models (intensive treatment is being tested) and use in new types of services (a Stepped-care model in the municipalities and TF-CBT in Norwegian Barnehus is being tested).

III. Nation-wide implementation of TF-CBT in BUP – Increased access to quality care and professional well-being

Through yearly national funding in the state budget, TF-CBT is being implemented in Norwegian BUPs since 2012. Today 78 % of the BUPs have implemented TF-CBT as routine service (citing I).

Training procedures for therapists and leaders have been implemented successfully (citing 6, G, I). Burnout and job turnover intention is a major challenge for trauma therapists. Therapists who are trained in TF-CBT have lower rates of burnout and job turnover intention than others (citing 6, G).

Overall, the implementation of TF-CBT in Norway has had a profound impact on the following:

1. **Improved access to evidence-based treatment:** The nation-wide implementation program has improved the availability of treatment, ensuring that more youth receive appropriate care.
2. **Enhanced Quality of Care:** By implementing TF-CBT, Norway has improved treatment outcomes for youth.

3. **Development of specialized expertise**: Implementing TF-CBT has led to the development of a skilled workforce enhancing the overall capacity of Norway's mental health care system to treat trauma.
4. **Increased Professional Confidence and development**: Working with an implementation team consisting of certified TF-CBT trainers (situated at NKVTS) and researchers (situated at PSI and NKVTS), encourages mental health professionals to continuously update their knowledge, increasing job satisfaction and reducing burnout.
5. **Ethical Responsibility:** By implementing TF-CBT, clinicians are following the Norwegian professional obligations according to the policy statement on Evidence-Based Practice in Psychology.

IV. **Reduced long-term costs**

Addressing trauma early in life through TF-CBT can prevent the development of chronic mental health conditions and decrease the likelihood of individuals requiring more intensive and costly interventions in the future. TF-CBT is more cost efficient than the therapy that is normally provided (citing 2). By minimizing the use of ineffective treatments and focusing on evidence-based approaches, clinics can allocate resources more effectively and reduce unnecessary costs.

V. TF-CBT in international and national guidelines

The Norwegian RCT study and subsequent research including the comprehensive implementation program being put in place has contributed to placing TF-CBT in the 2019 revision of the international guidelines (citing B) and the national guidelines in 2013 and 2020 (citing c).

5. Sources to corroborate the impact (indicative maximum of ten references)

A. **Routine screening** for trauma in children and reference to KATES (CATS) – Directorate of Health 2022b). Nasjonalt pasientforløp for utredning og behandling i psykisk helsevern, barn og unge. https://www.helsedirektoratet.no/nasjonale-forlop/psykiske-lidelser-barn-og-unge/ kartlegging-og-utredning-psykiske-lidelser-pakkeforlop-barn-og-unge#basis-utredning. Kartlegging og utredning - Helsedirektoratet

B. **TF-CBT in international guidelines as first recommendation**.
Jensen , T. K., Cohen, J. A., Joycox, L., & Rosner, R. (2020). Treatment of PTSD and complex PTSD. In D. Forbes, J. I. Bisson, C. Monson, & L. Berliner (Eds.), Effective treatments for PTSD. Practice guidelines from the international Society for Traumatic Stress Studies. (Third ed.). Guildford.

C. **TF-CBT in treatment guidelines in Norway with highest score**.
Traumefokusert kognitiv atferdsterapi (TF-CBT) (2. utg.) | Ungsinn

D. **TF-CBT in national strategic plans**.
Opptrappingsplan mot vold og overgrep (2017–2021).[Plan against escalation of violence and abuse (2017–2021)]
Prop. 12 S (2016–2017) (regjeringen.no)

E. **Contribution to understanding treatment effects.**
de Haan, A., Meiser-Stedman, R., Landolt, M. A., Kuhn, I., Black, M. J., Klaus, K., Patel, S. D., Fisher, D. J., Haag, C., Ukoumunne, O. C., Jones, B. G., Flaiyah, A. M., Catani, C., Dawson, K., Bryant, R. A., de Roos, C., Ertl, V., Foa, E. B., Ford, J. D., Gilboa-Schechtman, E., Tutus, D., Hermenau, K., Hecker, T., Hultmann, O., Axberg, U., Jaberghaderi, N., **Jensen**, T.K., **Ormhaug**, S. M., Kenardy, J., Lindauer, R.J.L,. Diehle, J., Murray, L., Kane, J.C., Peltonen, K., Kangaslampi, S., Robjant, K., Koebach, A., Rosner, R., Rossouw, J., Smith, P,. Tonge, B.J., Hitchcock, C., Dalgleish, T. (2023). Efficacy and moderators of efficacy of cognitive

behavioural therapies with a trauma focus in children and adolescents: an individual participant data meta-analysis of randomised trials. The Lancet Child & Adolescent Health. https://doi. org/10.1016/S2352-4642(23)00253-5

F. **Contribution to understanding treatment effects.**
Knutsen, M. L., **Jensen**, T. K., Sachser, C., **Holt**, T., & Goldbeck, L. (2019). Trajectories and Possible Predictors of Treatment Outcome for Youth Receiving Trauma-Focused Cognitive Behavioral Therapy. Psychological Trauma. doi:10.10 37/tra0000482

G. **Impact of leadership training for implementation**.
Skar, AM.S., Braathu, N., Peters, N. *et al.* A stepped-wedge randomized trial investigating the effect of the Leadership and Organizational Change for Implementation (LOCI) intervention on implementation and transformational leadership, and implementation climate. *BMC Health Serv Res* **22**, 298 (2022). https://doi.org/10.1186/s12913-022-07539-9

H. **International impact for government planning after mass casualties.**
Turning the tide together: final report of the Mass Casualty Commission / the Joint Federal/Provincial Commission into the April 2020 Nova Scotia Mass Casualty.: CP32-166/2-2023E-PDF ; CP32-166/2-2023E-0-PDF ; CP32-166/2-2023E-1-PDF ; CP32-166/2-2023E-2-PDF ; CP32-166/2-2023E-3-PDF ; CP32-166/2-2023E-4-PDF ; CP32-166/2-2023E-5-PDF ; CP32-166/2-2023E-6-PDF ; CP32-166/2-2023E-7-PDF Publications - Canada.ca
Joint Federal/Provincial Commission into the April 2020 Nova Scotia Mass Casualty (Canada) author, issuing body. on April 1st 2020. (See pages 396, 404, 413 for referencing)

I. **Comprehensive report for the TF-CBT studies 2008-2023.**
Birkeland, M.S., Blestad, C., Granly, L.B., **Knutsen**, M.L., **Ormhaug**, S.M., **Solheim Skar,** A-M., **Jensen**, T. K. (2024). Femten år med forskning på og implementering av traumefokusert kognitiv atferdsterapi (TF-CBT) i Norge. [Fifteen years studying and implementing TF-CBT in Norway]. NKVTS rapport 1/2024. Available at: www.nkvts.no.

J. User reference.
Liv Kleve - Director at Child and Adolesent Mental Health Services, Haukeland University Hospital. Responsible for implementing TF-CBT in Helse Vest.

PSI 4

Institution: University of Oslo
Administrative unit: Faculty of Social Sciences, Department of Psychology
Title of case study: A new conceptualization of the long-term impact of human prenatal opioid exposure
Period when the underpinning research was undertaken: 2005-present
Period when staff involved in the underpinning research were employed by the submitting institution: 2005 - present
Period when the impact occurred: 2007- present, most clearly evidenced in 2017 and 2019

1. Summary of the impact

Opioid addiction affect many(1) women of child-bearing age, making it critical to understand how fetal opioid exposure affects brain and cognitive development long term, and how negative effects can be mitigated. PSI researchers have been pioneers in impacting the understanding of effects of human prenatal opioid exposure and tapering of opioids during pregnancy. We believe our research in this area has contributed to improved treatment of mothers addicted to opioids and follow-up of their children. Part of this impact is seen in changing Norwegian national guidelines on this (compare (2, 3), following the report of a Consensus panel in 2017(4)).

2. Underpinning research

Kari Slinning and Vibeke Moe, then PhD students supervised by professor Lars Smith, all at PSI, initiated the cognitive and behavioral follow-up of a group of children born to mothers using opioids and other drugs in pregnancy, in the late-80s-early-90s(5-7). In 2004, then PhD student at PSI, Kristine B Walhovd, initiated the first ever quantitative brain imaging study of children born to mothers using opioids during pregnancy, in collaboration with Slinning and Moe. For this cohort of children (n ~70 exposed and ~50 controls), then in the age range 8-13 years, the majority of exposed children were in foster care. The Ministry of Health and Care decided that foster parents could not consent to MRI for the children. However, even with scans from only 14 adopted prenatally drug-exposed and 14 controls, major differences between the groups in terms of neuroanatomical characteristics were uncovered(8). This was new knowledge, as it was then assumed that, contrary to e.g. alcohol exposure, prenatal opioid exposure did not confer macrostructural brain effects. The group with opioid- and polydrug exposure had significantly smaller neuroanatomical volumes and lesser, or altered white matter maturation(8, 9). In part, brain and functional cognitive and behavioral differences were related (8). In 2009, PSI researchers wrote a commentary to Nature Reviews neuroscience (10), calling for attention to the problem, as at this time, opioids were not mentioned among drugs for which human prenatal exposure could cause later problems to brain and behavior(11). In a new study, again initiated by Moe (then associate professor) and Slinning, PSI researchers, now accompanied by PhD student Kristin Haabrekke, followed a group of children born to mothers addicted to opioids and other drugs, but hospitalized and detoxified during pregnancy. This study showed improved perinatal outcomes(12) relative to controls and the previous group not undergoing detoxification, and no miscarriages. At age 4, part of the sample had MRIs. Walhovd (now professor), and PSI colleagues professors Moe, Fjell, and Bjørnerud, ass. prof Due-Tønnesen, post docs Torill Siqveland and Egil Nygaard, showed no indication of lesser neuroanatomical volumes relative to controls in the children born to opioid-addicted mothers who were detoxified during pregnancy(13). This was, like the first study(8), a

small sample, but the relative absence of group differences in either neuroanatomical or neurocognitive outcomes in the detoxified group, was clear. However, the group only partly exposed, still showed lesser visual acuity compared to controls, and visual problems can be a persistent problem with prenatal opioid exposure. More fine-grained visual problems in children born to mothers on OMT were simultaneously documented by another PSI professor, Annika Melinder (14, 15)

Causal mechanisms cannot be readily identified in human opioid exposure, where it is hard to separate different pre- and post-natal environmental risks. Collectively, these studies, with the majority of the first sample exposed to drugs through pregnancy being adopted at an early age and deemed to not have major postnatal risk, and the second sample with the detoxified group largely remaining in the care of biological parents, with lessened prenatal risk, are valuable.

The PSI researchers, including several professors at PSI, Nygaard, Moe and Walhovd, have continued their follow-up of children born to mothers addicted to opioids (16-20). These studies are funded by RCN and internal funds, and draw on multi- and transdisciplinary fields at PSI spanning different sections at PSI. The findings indicate that brain, cognitive and mental health differences between prenatally opioid- and polydrug-exposed children persist into youth and young adulthood.

3. References to the research (indicative max 6 references)

Moe, V. Foster-placed and adopted children exposed in utero to opiates and other substances: prediction and outcome at four and a half years. *J Dev Behav Pediatr* **23**, 330-339 (2002). https://www.ncbi.nlm.nih.gov/pubmed/11885759

Slinning, K. (2004) Foster placed children prenatally exposed to poly-substances--attention-related problems at ages 2 and 4 1/2. *European child & adolescent psychiatry* 13, 19-27. https://www.ncbi.nlm.nih.gov/pubmed/14991428

Walhovd, K. B. *et al.* Volumetric cerebral characteristics of children exposed to opiates and other substances in utero. *Neuroimage* **36**, 1331-1344 (2007). http://www.ncbi.nlm.nih.gov/pubmed/17513131

Walhovd, K. B. *et al.* Effects of prenatal opiate exposure on brain development--a call for attention. *Nature reviews. Neuroscience* **10**, 390 (2009). https://www.ncbi.nlm.nih.gov/pubmed/19377504

Haabrekke, K. J., Slinning, K., Walhovd, K. B., Wentzel-Larsen, T. & Moe, V. The perinatal outcome of children born to women with substance dependence detoxified in residential treatment during pregnancy. *Journal of addictive diseases* **33**, 114-123 (2014). http://www.ncbi.nlm.nih.gov/pubmed/24717065

Melinder A, Konijnenberg C, Sarfi M. Deviant smooth pursuit in preschool children exposed prenatally to methadone or buprenorphine and tobacco affects integrative visuomotor capabilities. Addiction. 2013;108(12):2175-82. http://www.ncbi.nlm.nih.gov/pubmed/25595574

Walhovd, K. B. *et al.* Child neuroanatomical, neurocognitive, and visual acuity outcomes with maternal opioid and polysubstance detoxification. *Pediatric neurology* **52**, 326-332 e323 (2015). http://www.ncbi.nlm.nih.gov/pubmed/25595574

Nygaard, E. *et al.* Neuroanatomical characteristics of youths with prenatal opioid and poly-drug exposure. *Neurotoxicol Teratol* **68**, 13-26 (2018). https://www.ncbi.nlm.nih.gov/pubmed/29679636

4. Details of the impact

In the Norwegian national guidelines for follow-up of pregnant women on medically assisted therapy (OMT) and their children until school-age in 2011(3), the empirical studies of Slinning, Moe and Walhovd were cited(5, 8, 21, 22), but the guideline was that pregnant

women addicted to opioids should maintain taking opioids during pregnancy, and concerns were raised in this guideline, primarily that tapering opioids could lead to complications not only for the mothers, but also the fetus, e.g. stillbirth. PSI researchers have been contributing to meetings and the hearing for the revision of the Norwegian national guidelines for follow-up of pregnant women medically assisted therapy (OMT) and their children until school-age in 2011(3), and the revised guideline as of 2019(2) now lists an option for mothers addicted to opioids to taper off in pregnancy, also citing the detoxification study with the improved perinatal outcomes. Prior to this revision of the guideline, PSI researchers actively contributed the Consensus Conference on OMT and pregnancy arranged by the Directorate of Health in 2017. In the public report from the consensus panel(4), both publications from the detoxification studies, on the perinatal outcomes and the brain and cognitive and visual acuity outcomes, as well as the long-term follow-up studies of the cohort exposed throughout pregnancy, are cited(12, 13, 17, 20). Note that also studies of a cohort born to mothers on OMT, by another PSI professor, Annika Melinder, are cited, underpinning visual system problems with opioid exposure(14, 15).

Specifically, the revision of the guidelines in 2019, states that the Consensus panel and the Directorate of health assess that treatment without opioid medicaments ideally is best for the child, given that such treatment does not increase risk of relapse to use of heroin and other drugs. While the previous guideline advised against tapering in pregnancy, the current guideline is that pregnant women in OMT who with an OMT physician assess that tapering is correct, should do so with follow-up, and those who assess that this is not the correct thing to do, should not taper. The revised guideline emphasizes that the risk for the pregnant woman and the fetus should be balanced, and needs to be an individualized decision for each woman. The revised guideline also acknowledges that some women have felt after pregnancy that they were not well-enough informed about the risks of taking opioid medication during pregnancy, and the current guideline seems to better consider the need for expecting mothers to make informed choices themselves.

However, as also concluded by the various panels, reports and guidelines, current studies are too small and limited to draw secure conclusions regarding best practice regarding opioids in pregnancy, OMT and consequences to mother and child. Since our initial studies, several later imaging studies have shown smaller neuroanatomical volumes, and differences in white matter and functional connectivity in children and adolescents exposed to opioids in utero, in part related to cognitive and behavioral differences (8, 16, 19, 23-25). In recognition of the challenges posed to society, and the potential intergenerational transmission of risk, in the US, the Healthy Brain and Child Development (HBCD) study (26) has been launched, prompted by the opioid crisis. HBCD will investigate the associations of adverse environments – beginning in pregnancy – with development of brain and cognition through childhood. Data from 7000 children and their families, in which 25% of the children will have prenatal opioid exposure, will be collected. The Norwegian cohorts by PSI researchers are not powered to disentangle effects of different risk factors, as can be done in HBCD, but are unique in follow-up time. In continued collaboration with Anders M Dale, who was a primary collaborator on the first quantitative brain imaging study of prenatally opioid exposed children, and who is now a director of the HBCD Data Coordinating Center, PSI researchers (PI:Walhovd) are currently following up on the Norwegian prenatally opioid exposed children who are now adults in their 30s, and will connect the findings to those form the HBCD cohort, to further impact a lifespan understanding of prenatal risk in this area. Our prospective cohort studies suggest that effects persist or even become more pronounced with age(16-20). We need to follow the same persons over time with quantitative assessments of brain and

cognitive effects to know whether these are stable, decreasing or increasing in adulthood, further impacting societal understanding and policy in this important domain.

5. Sources to corroborate the impact (indicative maximum of ten references)

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PSI 5

Institution: University of Oslo
Administrative unit: Department of Psychology
Title of case study: Children in the legal system
Period when the underpinning research was undertaken: 2012-2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2012-2022
Period when the impact occurred: 2012-2022

1. Summary of the impact

In addition to citations in 55 policy documents, the specific impact includes three lines:

1. Results of *memory development and investigative interviewing* are integrated in the post graduate study at the Police University College to police officers interviewing children as part of their crime investigation and prosecutors who lead these interviews. The research impacted the law change in 2015.
2. A video presenting research of *credibility evaluations, memory, and confirmations bias* is created by the Attorney General, used in all public prosecutor districts for continuing education.
3. Results from our study of child protective´s *removal and the effect of stress from these removlas* were implemented in new guideline and Melinder was appointed in the expert group preparing this for the Directorate for Children and Family Affairs.

2. Underpinning research

Melinder was PI in the granted (22 000 000 NOK) project '*Establishing the Cognitive Developmental Research Unit*' (2008-2012), and the granted (22 000 000 NOK) '*Developing the Cognitive Developmental Research Unit into applied areas of witness psychology*' (2012-2018), both funded by the Norwegian Ministry of Children and Families. All key researchers were affiliated in 2008-2018. The grant qualified to conduct several studies of relevance for the societal impact.

The project resulted in 34 published papers, three book chapters and one book in the years 2012-18 (and additional papers before 2012). All papers, except from the surveys, have a quasi- or experimental design and were either naturalistic or lab based:

1. The *memory development and investigative interviewing* concerns a) lab studies of mock situations testing children's capacities to resist suggestions, provide detailed responses, and recall different stimuli (Melinder et al., 2010). Furthermore b) field studies of real investigative interview testing interviewers´ questions, techniques, children´s responses, and the bidirectional influence (Johnson et al., 2015; Melinder et al., 2020; Thoresen et al., 2009). **Main findings:** Investigative interviews should be age adjusted, relatively short in time, use WH-questions and pictures for enhanced recall, and build on an established contact with the interviewer to reduce erroneous information, which demands a solid training of and feedback to those conducting the interviews (e.g., the police). Our concept is 'child friendly'. **Key researchers Dept. of Psych., Oslo Univ**: professors Melinder, Magnussen, left 2016, PhD student Johnson, left 2015.
2. The *credibility evaluations and memory* regards a) experimental work on judgements of child witnesses' credibility (Melinder et al., 2016) as well as surveys of professionals' knowledge of relevant memory factors in forensic work (Melinder & Magnussen, 2014), and the tendency to confirm existing knowledge, i.e., confirmation bias (Melinder et al., 2020), b) an edited handbook (Melinder, 2014; 2022). **Main findings:** Child´s emotional expression is indicative for the judgement of child credibility; expected emotions to verbal utterances highly influence the decision maker (confirmation bias) why professionals must

unlearn automatic responses. Presentation modus (e.g., transcripts, audio, or video) is less important in terms of credibility judgements. Confirmation bias is positively related to openness and negatively to neuroticism. Finally, psychologists serving as experts for the court are not by default experts in all memory aspects and may perform as good or bad as a judge with some training in memory science. **Key researchers Dept. of Psych., Oslo Univ**: professors Melinder, Magnussen, Brennen, and postdoc Wessel, left 2014.

3. The *removal and the effect of stress* composes a) a series of field studies of CPS actions in real removal cases, observed by a researcher who documented every step and reaction in the parties (child and parents) during the removals and as later tested against their memory and individual factors (Melinder et al., 2013). Additional b) studies of maltreated children´s cognitive functions related to stress (Augusti & Melinder, 2013). **Main findings:** Acute removals are sign more stressful for all parties than planned, so preventive work should be prioritized within the CPS. Secured attached children report more correctly from stressful events than insecure, even if the consistency in their recall may vary. Maltreated children may have some difficulties with executive functions, but the causal relationship is not concluded. **Key researchers Dept. of Psych., Oslo Univ**: professor Melinder, PhD stud and postdocs Augusti, left 2017 and Baugerud, left 2015.

References to the research

Melinder, A.M.D; Alexander, K; Cho, Y. I; Goodman, G.S; Thoresen, C; Lønnum, K. & Magnussen, S. (2010). Childrens' eyewitness memory: A comparison of two interviewing strategies as realized by forensic professionals. *Journal of Experimental Child Psychology*, *105*(3), s 156- 177 doi: 10.1016/j.jecp.2009.04.004

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Augusti, E.-M., & Melinder, A. M. D. (2013). Maltreatment is associated with specific impairments in executive functions: A pilot study. *Journal of Traumatic Stress, 26*, 780- 783. doi: 10.1002/jts.21860

4. Details of the impact (indicative maximum 750 words)

Melinder started her research in child witness area in 2000 and earned her PhD in 2004 with the first Norwegian doctoral thesis on the subject: "Perspectives on Children as Witnesses" (Melinder, 2004), which got attention from the legal field (e.g., police officer, attorney general, and the court administration). Grants from the 'Ministry of Children and Families' in 2008-2012 enabled her to start the Cognitive Developmental Lab' and continue this line of research (Melinder & Gilstrap, 2009), adding specifically stress related effects on memory development (Baugerud & Melinder, 2012) and professionals' competence (Magnussen et al., 2010; Magnussen & Melinder, 2012) to the program. Three PhD students (*Fikke, Augusti*, and *Baugerud*) and one researcher (*Gredebäck* who left the dept. in 2011) joined the group, and professors *Magnussen, Landrø*, and *Smith* were associated as senior advisors. In 2010 Melinder became professor and applied for further support from the Ministry as the Norwegian Research Council did not offer any relevant program at that time. The research underpinning the present case to be evaluated is thus entirely produced within the Dept., with contributions from Professor *Goodman* with students (theme 1 and 3), UC Davis, associate professors *Magnusson* (theme 1), Gothenburg University, and *Gilstrap* (theme 1), Colorado Spring.

In addition to the specific outcomes below, Melinder have given an extensive number of lectures and seminars to practicians within the Ministry, Directorate, Police, Court, Judges, lawyers, and the Children's house regarding the themes in the present case. For the specific themes the nature and extent as follows:

1. The nature of the impact in terms of dissimilation includes scientific papers (articles and book chapters) that are an integrated part of the candidates' curriculum in the education of police officers and prosecutors described above. During a full day lecturing on every course (once a year), I describe developmental aspects relevant for their work (memory development, attachment aspects, and age-specific relational requests) as well as techniques, and deliberate practice. All grounded in the research conducted at PSI, and the research also impacted a law change in 2015 (Regulation on questioning of children and other particularly vulnerable victims and witnesses').
2. The research is presented through a produced video that is an integrated part in the public prosecutors' continuous learning process and launched to each of the 11 districts once a year. The content covers confirmation bias, everyday memory errors, and experts' competency and limits thereof, which all are part of the research forming the case.
3. A two-year long participation in the Expert group appointed by the Directorate for Children, Youth, and Family Affairs, including four meetings a year with hearings, commenting, writing, and providing research of relevance obviously exploited the knowledge we gathered throughout the program. Specifically, our 'hands-on' insight in factual removals that we transformed to transparent coding of stress, memory, and the comparison between acute and planned removals build the base for several recommendations. The final product, the guideline, is used by all child protective workers around Norway in their daily work with acute removals.

Evidence of the extent of the impact described:

1. We find improvements in the police officers' interviewing approach (Melinder, Magnusson, & Gilstrap, 2020) and a higher level of understanding in the prosecutors' understanding of the interview model that they are responsible for during the investigation (Bakketeig, Stefansen, Andersen & Gundersen, 2021). It further impacted a law change, called: 'Regulation on questioning of children and other particularly vulnerable victims and witnesses' (Lovdata).
2. Feedback to the Attorney General's Office indicates a high satisfaction, but the evaluation is not published yet.
3. See knowledgebased guidline from the Directorate:

https://www.bufdir.no/fagstotte/produkter/akuttarbeid-i-barnevernstjenesten--kunnskapsbasert-retningslinje/
(professional support/products/emergency-work-in-the-child-welfare-service--knowledge-based-guideline)

Future gains, which demonstrate the case's relevance, includes a new Grant to Melinder from the Norwegian Research Council (12 000 000 NOK) concerning experts' reports in child protective cases, see: The use of Expert Reports as evidence in Child Protection Decision-Making - Department of Psychology (uio.no)

The call it was applied from, directly highlights the need for applied research into 'Children in the Legal System' of which the present case is an example of.

References:

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Regulations on questioning of children and other particularly vulnerable victims and witnesses (facilitated questioning) - Legal data
(Forskrift om avhør av barn og andre særlig sårbare fornærmede og vitner (tilrettelagte avhør) - Lovdata)

Guidelines from the Directorate:

https://www.bufdir.no/fagstotte/produkter/akuttarbeid-i-barnevernstjenesten--kunnskapsbasert-retningslinje/(professional support/products/emergency-work-in-the-child-welfare-service--knowledge-based-guideline)

4. **Sources to corroborate the impact**
   1. Police University College: Senior Police officer Inger-Lise Brøste can corroborate the research´s impact. Her e-mail: Inger.Lise.Broste@phs.no
   2. Attorney General office: Senior attorney Berit Johannessen confirms the impact in her letter. Her e-mail: berit.johannessen@riksadvokaten.no
   3. The Norwegian Directorate for Children, Youth, and Family Affairs: Senior consultant and project manager Tone Viljugrein provides a letter describing the impact of the research on the work with the new guidance for acute removals. Her e-mail: tone.viljugrein@bufdir.no

See also:
Overview - Sage Policy Profiles (sagepub.com)
Documents Melinder's team Policy Profiles, include:
37citations across 28 policy documents
8 citations in policy documents which cite our work that later have been cited a further 73 times in 27 other policy documents

The 10 most recent public policy documents from within and outside Norway, citing work from PSI and researcher in Melinder´s team in this area (other areas excluded):

https://www.regjeringen.no/no/dokumenter/horing-av-barnevernsutvalgets-nou-20237/id2968371/ (hearing document of CPS´s committee in a Norway´s Public Investigation)

https://www.fafo.no/en/publications/kvalitet-pa-asylintervju (report regarding the quality of asylum interviews)

https://www.sm.ee/media/2670/download (Finnish document of the need to develop the CPS)

https://jamstalldhetsmyndigheten.se/aktuellt/publikationer/uppgifter-om-vald-ar-inget-undantag/ (The Swedish equality authority regarding violence)

https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/artikelkatalog/ovrigt/2021-11-7606.pdf (The Swedish social authority regarding honour-related violence and violence in close relationships)

https://apo.org.au/node/306776 (Expert evidence about memory in New Zealand sexual violence trials and appellate courts 2001 to 2020)

http://publications.gc.ca/site/eng/9.919997/publication.html (Gouvernement of Canada: final report of the Mass Casualty Commission / the Joint Federal/Provincial Commission into the April 2020 Nova Scotia Mass Casualty)

https://www.fhi.no/publ/2020/akuttplassering-i-barnevernsinstitusjoner/ (The Norwegian research institute´s report on removals in institutions within the CPS)

https://www.regeringen.se/rattsliga-dokument/statens-offentliga-utredningar/2018/04/sou-201832/ (The Swedish Minestery of Social affairs: Improving the social security system)

University of Oslo, Institute of Health and Society. Case number 1

Institution: UiO
Administrative unit: HELSAM
Title of case study: Human papillomavirus (HPV) and cervical cancer prevention strategies
Period when the underpinning research was undertaken: 2012-2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2005-2022
Period when the impact occurred: 2012-2022

1. Summary of the impact

The research produced by HELSAM's faculty has informed and impacted national and international recommendations for the prevention and control of human papillomavirus (HPV)-related diseases. Nationally, the changes to Norway's cervical cancer screening and HPV vaccination policies have been influenced by the HELSAM research team. Internationally, researchers at HELSAM were pivotal in designing the WHO's Global Strategy to Eliminate Cervical Cancer, adopted by the World Health Assembly in 2020. Rapid response insights on COVID-related disruptions emphasize the need for adaptive research. Overall, HELSAM's research team, resonates through policy changes, shaping international and national healthcare agendas, and providing timely responses to emerging challenges, exemplifying a transformative influence on both global and local health initiatives.

2. Underpinning research

Cancer places a large burden on individuals, family, and society. Interventions aimed to prevent and control cancer can be targeted towards primary prevention (e.g., vaccination) or secondary prevention (e.g., screening). Disease simulation models can provide decision-support by estimating population and long-term impact of interventions. In addition, new technologies present opportunities to improve cancer prevention programs yet require careful consideration to remain "responsible" (i.e., provide an acceptable harm-benefit balance). For example, the discovery of persistent high-risk HPV infections as the obligate cause of cervical cancer led to the development of HPV testing as an alternative to Pap testing as well as the prophylactic HPV vaccines (preventing six HPV-related cancers).

1. Efficiency and Tailored Approach in Norway's Cervical Cancer Screening:
HPV-based testing for cervical cancer provides opportunities for more effective and efficient cervical cancer screening over at less frequent screening intervals, particularly when complemented by >70% risk reduction through HPV vaccination (**Reference 1**). Research by Burger, Kristiansen, and Pedersen advocates for integrating HPV testing in Norway, emphasizing the value of tailored risk profiles over a mass 'one-size-fits-all' approach. However, the population impact of screening can be limited by barriers to attend and adhere to screening guideline recommendations. Interventions to overcome screening failures (e.g., non-adherence across the screening pathway) can prompt high-value improvements, including home-based testing evaluations. Several evaluations of alternative targeted or more general use of home-based cervical cancer testing by the research team have demonstrated opportunities to reduce cancer burden and simultaneously improve the cost-effectiveness within the Norwegian program. Importantly, home-based testing could provide efficiency gains if implemented more widely in the Norwegian screening program (**Reference 2**).

2. Policies to Eliminate Cervical Cancer Globally:
The research team's international research, including collaboration with the United States Preventive Services Task Force, underscores the long-term health benefits and efficiency of primary HPV testing (**Reference 3**). As a WHO Cervical Cancer Elimination Modelling Consortium member (CCGMC), Burger supported the model-based projections that contributed to identifying the intermediate goals (90% vaccination coverage, 70% screening coverage, and 90% access to treatment) to achieve global elimination of cervical cancer in 78 lower-middle income countries (**Reference 4**). HELSAM's research has also extended research to support planning and accelerating the timeframe for cervical cancer elimination in high-income countries, which indicates the potential elimination of cervical cancer as a public health program in both the U.S. and Norway within the next 20 years (**Reference 5**). For Norway, the projected the timeframe for cervical cancer elimination in under policies implemented over the past decade have expected the elimination timeframe by at least 17 years.

3. COVID-Related Disruptions and Disparity Considerations:
Covid and Cancer Global Modelling Consortium (CCGMC), Burger's research, using simulation modeling, assessed the long-term impacts of COVID-related screening disruptions on cervical cancer screening programs. A series of four covid-related analyses projected minimal long-term health impacts, however, there was potential of widening of disparity gaps for women facing screening barriers due to COVID-related fears (e.g., **Reference 6**).

Involved Researchers:

- Emily Burger, PhD (PhD student, Postdoctoral Fellow, Associate Professor (2010-current)).
- Kine Pedersen, PhD (PhD student, Researcher, Associate Professor (2014-current)).
- Ivar Sønbø Kristiansen, PhD, MD, MPH (Professor 2005-2016).

3. References to the research

Reference 1: **Pedersen K**, **Burger EA**, Nygård M, **Kristiansen IS**, Kim JJ. Adapting cervical cancer screening for women vaccinated against human papillomavirus infections: The value of stratifying guidelines. European Journal of Cancer. 2018 Mar 1;91:68-75. doi: 10.1016/j.ejca.2017.12.018. https://www.duo.uio.no/handle/10852/60031.

Reference 2: **Pedersen K**, Portnoy A, Sy S, Hansen BT, Tropé A, Kim JJ, **Burger EA**. Switching clinic-based cervical cancer screening programs to human papillomavirus self-sampling: A cost-effectiveness analysis of vaccinated and unvaccinated Norwegian women. International Journal of Cancer. 2022 Feb 1;150(3):491-501. doi: 10.1002/ijc.33850. https://www.duo.uio.no/handle/10852/89274.

Reference 3: Kim JJ, **Burger EA**, Regan C, Sy S. Screening for cervical cancer in primary care: a decision analysis for the US Preventive Services Task Force. *JAMA*. 2018 Aug 21;320(7):706-14. doi: 10.1001/jama.2017.19872. https://www.duo.uio.no/handle/10852/72822.

Reference 4: Brisson M, Kim JJ, Canfell K, Drolet M, Gingras G, **Burger EA**, Martin D, Simms KT, Bénard É, Boily MC, Sy S. Impact of HPV vaccination and cervical screening on cervical cancer elimination: a comparative modelling analysis in 78 low-income and lower-middle-income countries. *The Lancet*. 2020 Feb 22;395(10224):575-90. doi: 10.1016/S0140-6736(20)30068-4.

Reference 5: Portnoy A, **Pedersen K**, Trogstad L, Hansen BT, Feiring B, Laake I, Smith MA, Sy S, Nygård M, Kim JJ, **Burger EA**. Impact and cost-effectiveness of strategies to accelerate cervical cancer elimination: A model-based analysis. *Preventive Medicine*. 2021 Mar 1;144:106276. doi: 10.1016/j.ypmed.2020.106276. https://www.duo.uio.no/handle/10852/89273.

Reference 6: Burger EA, de Kok IM, O'mahony JF, Rebolj M, Jansen EE, de Bondt DD, Killen J, Hanley SJ, Castanon A, Regan MC, Kim JJ. A model-based analysis of the health impacts of COVID-19 disruptions to primary cervical screening by time since last screen for current and future disruptions. Elife. 2022 Oct 12;11:e81711. doi: 10.7554/eLife.81711.

4. Details of the impact

The ultimate beneficiaries of HELSAM's research on HPV and cervical cancer are the women and their families in Norway and internationally who benefit from reduced disease burden through improved evidence-based programmatic decisions that have had a transformative influence on both Norwegian and international health initiatives. These impacts using HELSAM's research are delivered through many beneficiaries including WHO, governments, clinical organisations, US Preventive Services Task Force, Cancer Registry of Norway, Norwegian Institute of Public Health, and society at large.

Norwegian National Changes to Cervical Cancer Prevention Policies:
From 2012, Kristiansen was a member of "Gruppe II", a cervical cancer screening algorithm group tasked with evaluating the implementation of primary HPV testing on behalf of the Norwegian Directorate of Health. Stakeholders requested that Kristiansen, Burger and Pedersen conducte an analysis to inform capacity and budget implications for implementation. The Cancer Registry of Norway, who is responsible for the guidelines, management, and quality assurance of the Norwegian Cervical Screening Program, implemented changes in national guidelines to initiate regional scale-up of primary HPV testing in 2015 (i.e., **Reference 7**), in line with HELSAM's early research findings. Similarly, since 2017, Pedersen has been a member of the Norwegian Directorate of Health's advisory committee considering changes to the screening program for HPV vaccinated women (**Reference 8**) and expanding the use of primary HPV testing for all women (**Reference 9**).

In 2021, Burger and Pedersen were members of two separate advisory committees for the Norwegian Directorate of Health tasked with evaluating implementation of 1) direct-mail home-based testing for women who have not screened in 10 or more years (**Reference 10**) and 2) novel triage methods for the newly implemented primary HPV-based program. Factors such as capacity constraint consideration, illustrated by the research findings, help inform advisory group discussion about feasible algorithms that align with priority-setting guidelines in Norway. Consequently, the financing of self-sampling was approved by Ministry of Health (**Reference 11**) and added to the annual national budget based on estimates from the HELSAM research team; implementation is currently underway. As of 2022, the decision to implement novel triage methods for the newly implemented primary HPV-based program were still underway.

International Changes to Cervical Cancer Prevention Policies:
Burger's international research in the U.S. contributed to the 2018 U.S. Preventive Services Task Force guidelines, recommending for the first time, the use of primary HPV testing as a screening modality (**Reference 12**). Globally, the WHO Elimination work led to the World Health Assembly's adoption of the WHO's Global Elimination strategy in November 2020, which outlined intermediate 2030 targets of 90% vaccination coverage, 70% screening coverage twice per lifetime, and 90% access to cancer treatment (**Reference 13**). The adoption of a global strategy has spurred countries worldwide to develop ambitious plans to accelerate elimination faster. For example, in Norway, HELSAM's research on the Norwegian cervical cancer elimination timeframe contributed to the Norwegian Cancer Registry to recommend ambitious changes to expedite the current timeline of cervical cancer elimination in Norway (**Reference 14**). Contributions from the analysis that Norway is on track to eliminate cervical cancer by 2039 were cited at the end of a

statement by the Minister of Health in support of the effect of ongoing national prevention policies (**Reference 15**).

Support decision-making in cancer control both during and after acute COVID-pandemic phase: In 2020, Burger was asked to co-lead Working Group 2 of the newly formed Covid and Cancer Global Modelling Consortium (CCGMC), which was jointly formed by IARC and WHO. The CCGMC aimed to connect modelling groups and other experts around the world to address challenges in cancer control as a result of and beyond the COVID-19 era. Between 2020 and 2022, as co-lead, Burger disseminated consortium findings in biannual consortium meetings to global stakeholders (**Reference 16**). As of 2022, the group's work continues under the newly renamed consortium, I-PARCs.

5. Sources to corroborate the impact

Reference 7: Cancer Registry of Norway: https://www.kreftregisteret.no/globalassets/hpv-test-i-primarscreening-mot-livmorhalskreft-gruppe-ii.pdf

Reference 8: Cancer Registry of Norway announces considerations for expanding HPV testing to younger women: https://www.kreftregisteret.no/globalassets/livmorhalsprogrammet/rapporter/andre-rapporter/vedlegg1_rapport-hpvscreening-for-kvinner-25_33-ar.pdf

Reference 9: Cancer Registry of Norway announces considerations for screening vaccinated women: https://www.kreftregisteret.no/globalassets/livmorhalsprogrammet/dokumenter/2020_notat-vedr-screeningalgoritme-for-hpv-vaksinerte-kvinner.pdf

Reference 10: Cancer Registry Report announcing plan for implementation of HPV self-sampling: https://www.kreftregisteret.no/globalassets/livmorhalsprogrammet/rapporter/andre-rapporter/hdir_prosjektforslag-copy_offentlig.pdf

Reference 11: Announcement by the Ministry of Finance that HPV self-sampling have been granted funding in Norway's National Budget: https://www.regjeringen.no/no/statsbudsjett/2023/statsbudsjettet-2023-a-til-a/id2928125/?expand=2929646

Reference 12: U.S. Preventive Services Task Force recommendations that include the findings from the decision analysis that support recommended changes to include primary HPV testing: https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/cervical-cancer-screening

Reference 13: WHO elimination strategy: https://www.who.int/publications/i/item/9789240014107

Reference 14: White paper recommendation interventions to expedite the projected elimination timeline of 2039: https://www.kreftregisteret.no/Generelt/Rapporter/white-paper-raskere-eliminering-av-hpv-og-livmorhalskreft/

Reference 15: The Ministry of Health and Care Services is responding to a proposal from parliamentary representatives aimed at offering an enhanced HPV vaccine: https://www.stortinget.no/globalassets/pdf/innstillinger/stortinget/2020-2021/inns-202021-407s-vedlegg.pdf

Reference 16: Covid and Cancer Global Modeling consortium https://ccgmc.org/

University of Oslo, Institute of Health and Society. Case number: 2

Institution: UiO
Administrative unit: Institute of Health and Society – HELSAM
Title of case study: Improving antibiotic prescribing in primary care
Period when the underpinning research was undertaken: 2012 – 2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2012 – 2022
Period when the impact occurred: 2012 – 2022

1. Summary of the impact

To avoid individual and societal side effects, antibiotic use should be as low and as narrow-spectrum as possible. Until 2012, the use of antibiotics increased in Norwegian primary care. In the period since 2012, researchers at the Department of General Practice (ALLMED) have carried out clinical RCTs, educational RCTs, register studies and qualitative studies that have contributed to changed antibiotic guidelines and the creation of national antibiotic stewardship programs in Norwegian primary care. In the same period, the use of antibiotics has been reduced, and the proportion of narrow-spectrum antibiotics has increased.

2. Underpinning research

Quality improvement/educational RCTs

Quality improvement activities have previously been rarely occuring in Norwegian primary health care. In the RCN-supported research project

Prescription Peer academic detailing (Rx-PAD) study (2004-2013, project leader: Jørund Straand
https://www.med.uio.no/helsam/english/research/projects/rx-pad/index.html ,

we developed a new method for conducting quality improvement work, especially adapted to Norwegian general practice. Through an educational randomized controlled trial, the method proved to be highly effective when it came to achieving more correct antibiotic use in general practice.

The main elements of the educational intervention were:

- Personal prescribing reports, where each individual doctor got an overview of their own antibiotic prescriptions compared to the average for the Continuing medical education (CME) group, the county and the country
- Discussion of own prescribing together with a group of colleagues the prescribers were confident in (CME group)
- Academic lectures adapted to the reports
- Repeated CME group meetings

RxPAD was an expensive intervention. Based on the good results, researchers at ALLMED developed a cheaper intervention where we used units that are already funded to contribute to quality improvement; the municipal medical service and the Norwegian Prescription Database https://www.norpd.no/ . This was tried out in a smaller number of municipalities through an RCN-funded postdoctoral grant:

ENORM – Educational intervention in Norwegian Municipalities for antibiotic treatment in line with guidelines (2014 – 2020, project leader; Sigurd Høye, RCN funded
https://www.med.uio.no/helsam/english/research/projects/quality-improvement-program_RAK/index.html ,

demonstrating the feasibility of implementing an antibiotic stewardship program nationally.

Out-of-hours primary care services account for a significant proportion of antibiotic use, but were not affected by the intervention developed in RxPAD and ENORM. We therefore wanted to develop and test a quality improvement/antibiotic management program for out-of-hours services. In the project
Use of out-of-hours services for respiratory tract infections (2016 – 2022, researcher Bent Håkan Lindberg, project leader Sigurd Høye
https://www.med.uio.no/helsam/english/research/projects/acute-respiratory-tract-infections-use-of-out-of-hours-GP-cooperatives/index.html)
we developed and tested a tailored program for out-of-hours nurses in an educational RCT. The intervention showed no effect on the use of out-of-hours services for respiratory tract infections, but contributed to a better understanding of how quality improvement can be implemented in the out-of-hours services.

As part of a governmental action plan (see section 4), researchers at ALLMED developed and implemented a quality improvement intervention, similar to an antibiotic stewardship program, for long term care facilities. Parts of the implementation was carried out as an educational RCT: *RASK – Riktigere Antibiotikabruk i Sykehjem/Kommunale helseinstitusjoner («More correct use of antibiotics in nursing homes/municipal health institutions») (2016 – 2024, researcher Nicolay J. Harbin, project leader Morten Lindbæk/Maria Romøren), funded by the Norwegian General Practice Research Fund.* The intervention resulted in a decrease in the use of antibiotics for urinary tract infections.

Alongside the RASK project, researchers at ALLMED, together with colleagues from Sweden, the Netherlands and Poland, developed and implemented an intervention similar to the RASK intervention: *ImpresU – Improving rational prescribing for Urinary tract infections in frail elderly Work Package 1-2 (2019 – 2023, researcher Silje R. Heltveit-Olsen, project leader Morten Lindbæk/Sigurd Høye, RCN/EU funded*
https://www.med.uio.no/helsam/english/research/projects/impresu-improving-rational-prescribing-for-uti-frail-elderly/index.html *)*
The intervention resulted in a decrease in the use of urinary tract antibiotics for frail elderly in the four countries.

Clinical RCTs
Clinical studies have also been rare in Norwegian primary health care. In many cases, it is absolutely necessary to carry out clinical studies in general practice in order to get relevant answers to the GPs' challenges. For example, antibiotic guidelines are to a large degree based on old studies of low quality, carried out in the specialist health service in countries with a different antimicrobial resistance situation than in Scandinavia.
Hence, ALLMED has developed experience and competence in carrying out relevant clinical RCTs within infections and antibiotic use in general practice:

Delayed prescribing – a feasible strategy to lower antibiotic use for respiratory tract infections in primary care? (2007 – 2013, researcher Sigurd Høye, project leader Morten Lindbæk
https://www.med.uio.no/helsam/forskning/prosjekter/vent-se/index.html) demonstrated that promoting delayed prescribing contributed to a reduced use of antibiotics in primary care.

Comparison of phenoxymethylpenicillin, amoxicillin, and doxycycline for erythema migrans in general practice. A randomized controlled trial with a 1-year follow-up (2010 – 2016, researcher Knut Eirik Eliassen, project leader Morten Lindbæk, RCN-funded
https://www.med.uio.no/helsam/forskning/aktuelt/arrangementer/disputaser/2017/eliassen-knut-eirik-ringheim.html) demonstrated that narrow spectrum penicillin was as effective and safe as more broad spectrum antibiotics in treating erythema migrans.

Imuti – Ibuprofen versus mecillinam in the treatment of uncomplicated urinary tract infections (2013 – 2021, researcher Ingvild Vik, project leader Morten Lindbæk, RCN-funded https://www.med.uio.no/helsam/english/research/projects/imuti/)
demonstrated that antibiotics were superior to antiinflammatory drugs in uncomplicated urinary tract infections (UTIs), but that a substantial proportion of women with UTIs did well without antibiotics.
In addition, there are two ongoing clinical drug RCTs within infections and antibiotic use in general practice at ALLMED.

Both the educational and clinical RCTs have been followed by qualitative studies, both to inform the implementation of the trials, to understand the effects of the interventions, and to support dissemination and implementation of the results. Alongside, large registry studies have been conducted to investigate any negative effects of reduced antibiotic use. The qualitative and registry studies are not reported here.

3. References to the research

a) Gjelstad S, Høye S, Straand J, Brekke M, Dalen I, Lindbæk M et al. Improving antibiotic prescribing in acute respiratory tract infections: cluster randomised trial from Norwegian general practice (prescription peer academic detailing (Rx-PAD) study) BMJ 2013; 347 :f4403 doi.org/10.1136/bmj.f4403

b) Harbin NJ, Lindbæk M, Romøren M. Barriers and facilitators of appropriate antibiotic use in primary care institutions after an antibiotic quality improvement program - a nested qualitative study. BMC Geriatr. 2022 May 27;22(1):458. doi: 10.1186/s12877-022-03161-w.

c) Eide TB, Øyane N, Høye S. Promoters and inhibitors for quality improvement work in general practice: a qualitative analysis of 2715 free-text replies. BMJ Open Qual. 2022 Oct;11(4):e001880. doi: 10.1136/bmjoq-2022-001880.

d) Høye, Sigurd; Gjelstad, Svein & Lindbæk, Morten. Effects on antibiotic dispensing rates of interventions to promote delayed prescribing for respiratory tract infections in primary care. British Journal of General Practice. 2013 63(616), s. E777–E786. doi: 10.3399/bjgp13X674468..

e) Eliassen KE, Reiso H, Berild D, Lindbæk M. Comparison of phenoxymethylpenicillin, amoxicillin, and doxycycline for erythema migrans in general practice. A randomized controlled trial with a 1-year follow-up. Clin Microbiol Infect. 2018 Dec;24(12):1290-1296. doi: 10.1016/j.cmi.2018.02.028.

f) Vik I, Bollestad M, Grude N, Bærheim A, Damsgaard E, Neumark T, Bjerrum L, Cordoba G, Olsen IC, Lindbæk M. Ibuprofen versus pivmecillinam for uncomplicated urinary tract infection in women-A double-blind, randomized non-inferiority trial. PLoS Med. 2018 May 15;15(5):e1002569. doi: 10.1371/journal.pmed.1002569.

(Three of the educational RCTs mentioned above (ImpresU, RASK, Out-of-hours RCT) delivered impact in the relevant period, but the main articles were published in 2023. They are therefore omitted from this list.)

4. Details of the impact

Quality improvement/educational RCTs, establishment of quality improvement programs and improved antibiotic use

Partly based on the results from the Rx-PAD study, Center for quality in medical services (SKIL https://www.skilnet.no/) was established in 2014. SKIL offers quality improvement courses in different clinical areas for Norwegian clinicians outside hospitals. The main elements from the Rx-PAD study equals the methods used by SKIL.
In 2016, the government published an action plan against antibiotic resistance in the health service with the aim of a 30% reduction in the use of antibiotics https://www.regjeringen.no/contentassets/915655269bc04a47928fce917e4b25f5/handlingsplan-antibiotikaresistens.pdf . Among the very few measures funded through the action plan was a national implementation of the intervention developed in RxPAD and ENORM. The Antibiotic Centre for Primary Care, a national centre of competence belonging to ALLMED, was assigned the task of implementing this measure together with SKIL, and did so in the period 2016 – 2022, engaging 40 – 50% of all Norwegian GPs. The national implementation was named RAK – Riktigere Antibiotikabruk i Kommunene ("More correct use of antibiotics in the municipalities").

The aim of the governmental action plan – a 30% reduction in the use of antibiotics – was reached in 2021. In the action plan evaluation report from the Norwegian Directorate of Health, https://www.helsedirektoratet.no/rapporter/handlingsplan-mot-antibiotikaresistens-i-helsetjenesten--evalueringsrapport-2022/handlingsplanens-kapittel-4-tiltak-rettet-mot-fastleger-og-legevaktsleger , RAK was assessed as successful and effective, and it was recommended that the measure be made a permanent program.

Also, the antimicrobial stewardship program for nursing homes/long term care facilities was deemed successful and recommended as a permanent program. In addition, a similar antimicrobial stewardship program for the out-of-hours service was recommended to be introduced.

To sum up: ALLMED has developed, tested and implemented several quality improvement/antimicrobial stewardship programs through educational RCTs in Norwegian primary care. There is reason to believe that these interventions have contributed to the significant improvement in antibiotic use and thus a reduction in the burden of antibiotic resistance in Norway in the period 2012 – 2022. The Directorate of Health recommends that the interventions be made permanent programs.

Clinical RCTs, changed treatment guidelines and the establishment of a research network in primary care
Based on the mentioned clinical RCTs, the Norwegian antibiotic guidelines recommend

- The use of delayed prescribing for certain diagnoses and situations
- The use of phenoxymethylpenicillin for erythema migrans
- To avoid antibiotics for uncomplicated UTIs for motivated women

The clinical RCTs have

- impacted on Norwegian and international antibiotic guidelines
- contributed to more correct and narrow-spectrum antibiotic use
- contributed to developing expertise and experience in conducting clinical drug studies in Norwegian general practice. As far as we know, ALLMED is the only independent research institution that regularly conducts drug studies in Norwegian primary care.
- contributed to the establishment of the RCN-funded Norwegian Primary Care Research Network, through experienced and documented lack of research infrastructure in primary care, and the experienced and documented need for high quality clinical research in general practice

To sum up: ALLMED has implemented several clinical drug RCTs in Norwegian primary care, comparing antibiotics with less resistance driving treatment options. The results have had direct influence on Norwegian and international guidelines, and may arguably have contributed to less use of antibiotics in general, and broad spectrum antibiotics in particular.

5. Sources to corroborate the impact (indicative maximum of ten references)

a. The governmental action plan against antimicrobial resistance 2016 (in Norwegian): https://www.regjeringen.no/contentassets/915655269bc04a47928fce917e4b25f5/handlingsplan-antibiotikaresistens.pdf
b. Simonsen GS, Berdal JE, Grave K, Hauge K, Juvet LK, Lunestad BT, Riisberg I, Rørtveit G, Urdahl AM. Årdal CO. Antibiotikaresistens - Kunnskapshull, utfordringer og aktuelle tiltak. Status 2020. [Antimicrobial resistance – knowledge gaps, challenges and relevant measures. Status 2020. Rapport 2020. Oslo: Folkehelseinstituttet, 2020. https://www.fhi.no/globalassets/dokumenterfiler/rapporter/2020/amr-kunnskapshull-rapport.pdf *(Recommends that ALLMED's antimicrobial stewardship programs are made permanent)*
c. The governmental action plan against antimicrobial resistance – evaluation report from The Directorate of Health 2022 (in Norwegian): https://www.helsedirektoratet.no/rapporter/handlingsplan-mot-antibiotikaresistens-i-helsetjenesten--evalueringsrapport-2022 *(Recommends that ALLMED's antimicrobial stewardship programs are made permanent)*
d. The Directorate of Health: National antibiotic guideline for primary care https://www.helsedirektoratet.no/retningslinjer/antibiotika-i-primaerhelsetjenesten
e. NORM/NORM-VET 2019. Usage of Antimicrobial Agents and Occurrence of Antimicrobial Resistance in Norway. Tromsø / Oslo 2020. ISSN:1502-2307 (print) / 1890-9965 (electronic). https://www.unn.no/4a5886/siteassets/documents/kompetansetjenester--sentre-og-fagrad/norm---norsk-overvakingssystem-for-antibiotikaresistens-hos-mikrober/rapporter/norm-norm-vet-2019.pdf *(Documents the reduction in antibiotic use and the role of ALLMED's antimicrobial stewardship programs)*

University of Oslo, Institute of Health and Society. Case number 3

Institution: University of Oslo
Administrative unit: HELSAM
Title of case study: Transformation to Digital Health information
Period when the underpinning research was undertaken: 2005 – 2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2012 – 2022
Period when the impact occurred: 2012 - 2022

1. Summary of the impact

The societal impact of our extensive investigations into ongoing transformation to digital health information is demonstrated in published national guidelines, white papers, EU policy and international interoperability standards. This impact is achieved through participatory research methodologies to understand information practices and health systems transformation, grounded in studies of **a)** interdisciplinary information practices, and information flows across levels of care, incorporating patients', families' and health professionals' perspectives; and **b)** engaging and empowering citizens, with complex care requirements, disabilities and/or chronic diseases, to co-create digital services with trusted health information and personal health data to improve understanding of offered information (digital literacy).

2. Underpinning research

The underpinning research builds on extensive multistakeholder public-private collaboration with health sector, industry, care sites, professionals, patients, people with chronic conditions and/or disabilities. The impact can be summarized as contributions from the following converging, underpinning research:

i. *Health information flow for patient centred service coordination and health professionals' cooperation across levels of care and health sectors (2008 –)*

This research contributes to understand information production and use to fully exploit digital transformation for quality care and to understand what supports, emphasizes, or underpins ICT as an integral tool for health care services. The research has uncovered health information use and requirements to implement evidence-base collaborative models in the health care service. We have especially addressed integrated care models that connect patients and providers, improve access and coordinate care across levels of care (specialist and community) and health care services (e.g., medicine, nursing, dentistry) for patients with long-term conditions. The research highlight health care capacity building, curriculum development and continued professional education.

ii. *Community resources and self-care interventions to foster wellbeing and living well with chronic conditions (2009 – 2022)*

This research emphasizes holistically development of community resources, especially promote wellbeing by identifying and utilizing the plethora of local resources that can support self-care for people with chronic/ long term condition or disabilities. Aggregating insights from in-depth qualitative research led to recommendations for utilisation of resources and assessment of "fit for purpose" in self-care interventions for people who live in deprived circumstances. Engaging multi-stakeholder communities in co-creation to optimize interventions for wellbeing and sense of independence further harness cooperation between relevant private and public sector actors. The research has led to community care service development, rooted in participation, co-creation and iteratively incorporate analytic insights.

iii. *Co-creation and inclusive user engagement, to foster active use of personal health data and trusted health information and knowledge sources (2009 –)*

This research is rooted in co-creation of services and inclusive user engagement, engaging citizens with complex care requirements, disabilities and/or chronic diseases, their support network and health professionals. The research identifies and uses available knowledge resources to co-create services and digital tools that integrates health information from trusted sources and personal health data for self-care, empowerment, and management of chronic health conditions. The impact is seen in digital tools with new approaches to utilize health information from trusted sources and personal health data in structured, accessible and active ways to address significant health systems burdens and personal or public health challenges, e.g., healthy eating and undernutrition, physical and social activity, medication management or use of available, understandable health data. The research combines best evidence and accumulated expertise as trusted sources when developing and deploying digital services as interventions that supports collaboration between patients and health professionals, advance digital health literacy, improve quality of life as well as risk minimization and treatment adherence / concordance and health service quality.

Names of the key researchers and what positions they held at the administrative unit

Professor Anne Moen (2006 –)
Professor Ragnhild Hellesø (2007 –)
Professor Marit Kirkevold (1996 – 2023)
Professor Hilde Wøien (2015 –)
Associate professor Randi Opheim (2015 –)
Associate professor Line Kildal Bragstad (2014 – 2023)

2. References to the research

Melby, L., Hellesø, R. (2014) Introducing electronic messaging in Norwegian healthcare: Unintended consequences for interprofessional collaboration. International Journal of Medical Informatics, Vol. 83, Issue 5; 343-353 https://doi.org/10.1016/j.ijmedinf.2014.02.001

Rogers A, Vassilev I, Pumar MJ, Todorova E, Portillo MC, Foss C, Koetsenruijter J, Ratsika N, Serrano M, Knutsen IA, Wensing M, Roukova P, Patelarou E, Kennedy A, Lionis C. (2015) Meso level influences on long term condition self-management: stakeholder accounts of commonalities and differences across six European countries. BMC Public Health. Jul 8;15:622. https://doi.org/10.1186/s12889-015-1957-1

Kumlin, M, Berg, GV, Kvigne, KJ & Hellesø, R (2020). Elderly patients with complex health problems in the care trajectory: A qualitative case study. BMC Health Services Research. ISSN 1472-6963. 20. https://doi.org/10.1186/s12913-020-05437-6

Svensberg, K, Kalleberg, BG, Rosvold, EO, Mathiesen, L, Wøien, H. & Hove, LH m.fl. (2021). Interprofessional education on complex patients in nursing homes: a focus group study. BMC Medical Education. ISSN 1472-6920. 21(1). https://doi.org/10.1186/s12909-021-02867-6

Fuglerud, K.S.; Schulz, T.; Janson, A.L.; Moen, A. (2020) Co-creating Persona Scenarios with Diverse Users Enriching Inclusive Design. in Universal Access in Human-Computer Interaction. Design Approaches and Supporting Technologies. HCI, Lecture Notes in Computer Science, vol. 12188. Springer, Cham https://doi.org/10.1007/978-3-030-49282-3_4

Aure, C. F., Kluge, A., Moen, A., (2021) Older Adults' Engagement in Technology-Mediated Self-Monitoring of Diet: A Mixed-Method Study. Journal of Nursing Scholarship Jan;53(1):25-34 https://doi.org/10.1111/jnu.12619

Turk, E., Wontor, V., Vera-Munos, C., Comnes, L., Rodrigues, N., Ferrari, G., Moen, A. (2022) Human-centered integrated care pathways for co-creating a digital, user-centric health information solution. Journal of Integrated Care, 30:4, 296 – 309 https://doi.org/10.1108/JICA-01-2022-0007

4. Details of the impact

To further detail the impact of this research, allow us to add:
Outputs of research in the case study is incorporated in national guidelines for nutritional practice (2017 – 2021), and "LEVE HELE LIVET" - recommendations for healthy aging and quality of life (Meld St. 15, 2017 – 2018). The research is recognized and awarded as innovative and ground-breaking to mitigate significant public health challenges coming with risk of undernutrition among home dwelling older adults (APPETITT; 2016), and for application of advanced international interoperability standards (HL7 FHIR resources) in a personalized, universally designed digital tools that enables patient/citizen to utilize their health information in structured, accessible, and active ways (CAPABLE - Trillium II; 2019). The impact of the research to co-create services that harness access to and active use of personal health data in structured, accessible and active ways, such as the research and innovation activities in APPETITT and CAPABLE, is further advanced at UiO via SPARK Social Innovation and continued research.

National impact of the case study's research activities is seen in capacity building to strengthen interdisciplinary collaboration and information practices is demonstrated in the first curriculum for "Advanced Nurse Practitioner", established, deployed and evaluated by us pr. request by Department of Health and Care (HOD). This impact is further demonstrated in the recent national, educational guideline for Advanced Nurse Practitioners, adopted in all ANP-master program offered nationally. Graduates from ANP programs following the guideline can seek national certification offered by Helsedirektoratet. The research on the case study added to "SamPraks", the innovative educational program led by Faculty of Medicine and offered in cooperation with multiple Faculties at UiO. SamPraks is a transdisciplinary innovative capacity building program where students from a broad specter of professions; nursing, medicine, pharmacology, odontology, psychology, clinical nutrition, education and theology, comes together to solve problems and co-create solutions/interventions to complex, real-world health problems, e.g. medication management or oral health, via interdisciplinary collaboration. SamPraks was led by the unit. Findings and experiences from Sampraks approach to learning have become an integral part of excellence in sustainable inter-disciplinary, educational curriculum for future health professionals, and is adopted at the satellite sites for medical education in Norway.

Internationally, the impact of our research into "Transformation to Digital Health information" has been recognised in several ways. A publication on "electronic messaging" was recognized as top 3 papers by IMIA (International Medical Informatics Association) in the IMIA Yearbook 2015. Visions for active use of personal health data underpinning research on the impact case led to early conceptualisations of every citizens' right to collect, complement/curate and control personal health data, building on the GDPR legislation which represented a clear impetus for new services. The impact was further advanced when Prof Moen served as rapporteur in the EU eHealth Stakeholder Group (DG Sante and DG CNECT and selected expert communities) for topical area "Citizens and Health Data" (during tenure/ membership 2016 – 2019). The conceptualisation of Citizens and Health Data for the EU eHealth Stakeholder Group served as early input leading up to the proposal for primary use of personal health data under the European Health Data Space (EHDS) (proposed as legislation in 2021, passed December 2023).

The impact of research to co-create services that harness access to and use of personal health data in structured, accessible and active ways, such as the research and innovation activities in APPETITT and CAPABLE, is further demonstrated at European level in the transdisciplinary IMI JU2 Gravitate-Health (2020 – 2025) and IMIJU2 BEAMER (2021 – 2026) Public-Private Partnerships. Gravitate-Health and BEAMER are projects funded under the IMI - Innovative Medicines Initiative and receives funding from European Commission (Horizon2020), EFPIA (European Federation of Pharmaceutical Industries and Associations) and IMI Associated partners. The impact of the research in this case study also led to confidence by consortium members to serve in the role as Coordinator (Prof Moen and University of Oslo) of Gravitate-Health Public-Private Partnership, with 41 members in 15 countries, total budget 19 400 000 Euro. The Gravitate-Health project elaborates on the impact in this case study by developing and testing an integrated, standards-based, user-centred digital

solution for improved access and understanding of health information, safe use of medicines, risk minimization and quality of life, starting with regulator-approved medicinal Product Information (ePI) and International Patient Summary Standard (IPS). Late 2022 the research and collaborative activities in Gravitate-Health led to acceptance of the HL7 FHIR® ePI Implementation Guide, which is an advanced interoperability standard for global use, fully aligned with EU ePI common standard, issued by European Medicine Agency and supported by FDA. The BEAMER project focuses more broadly on adherence to treatment, and identification of key behavioral and structural factors that can drive adherence and stimulate change, mindful of capabilities and digital health literacy is anticipated as outcome.

5. Sources to corroborate the impact

- White paper, "Nasjonal handlingsplan for bedre kosthold (2017 – 2021) (section 5.4, p .96) and synopsis (p 18),
- Meld. St. 15 "LEVE HELE LIVET" En kvalitetsreform for eldre (2017 – 2018, p. 112ff.).
- Trillium II award for CAPABLE's innovative application of advanced international interoperability standards, HL7 FHIR® International Patient Summary Standard, in a personalized, universally designed digital tools that enables patient/citizen to utilize their health information
- *Best Innovative Idea* 2016, for APPETITT application and project, Sykepleierkongressen 2016, Gardermoen, Norway
- Forskrift om nasjonal retningslinje for masterutdanning i avansert klinisk allmennsykepleie, 2020
- Spesialistgodkjenning i klinisk allmennsykepleie
- Sampraks
- Recognized internationally as top 3 papers on "electronic messaging", IMIA (International Medical Informatics Association) Yearbook 2015 for Melby, L., Hellesø, R. (2014) Introducing electronic messaging in Norwegian healthcare: Unintended consequences for interprofessional collaboration. International Journal of Medical Informatics, Vol. 83, Issue 5; 343-353
- www.gravitatehealth.eu and www.beamerproject.eu
- International Interoperability Standards: FHIR ePI Implementation Guide

University of Oslo, Institute of Health and Society. Case number: 4

Institution: UiO
Administrative unit: Helsam
Title of case study: Establishing clinical ethics support in Norway
Period when the underpinning research was undertaken: 2000-2022
Period when staff involved in the underpinning research were employed by the submitting institution: 1996-
Period when the impact occurred: 1996-2022

1. Summary of the impact

Work by researchers at CME has resulted in *the establishment of a system of clinical ethics committees (CEC)* in all Norwegian hospital trusts. In 2021, Norway became the first European country to mandate hospital CECs by law.

The research in clinical ethics has also *contributed substantially to policy development* in several morally challenging areas of healthcare practice such as end-of-life decision making, euthanasia, advance care planning, assessment of competence to consent, use of coercion in healthcare, involvement of next of kin in mental health care, abortion, and priority setting.

The impacts described here originate from the clinical ethics group at CME. Through its work this group has *established clinical ethics as a field of practice and research in Norway.*

2. Underpinning research

The relevant research is summarized under three headings:

1. *Evaluation research on clinical ethics support (2000–)*

Norwegian hospital clinical ethics committees (CECs) were established as a trial project in three hospitals in 1996. CECs are interdisciplinary bodies of 8-12 members. CECs discuss ethical challenges from the clinic and give advice as to how these might be handled, provide training for staff and have also contributed to guideline development. Thus, they contribute to service innovation, sustainability, and the quality improvement work of the hospitals. Over the years, researchers at the Centre for Medical Ethics (CME) have evaluated the work and impact of the CECs and other ethics support with different methods, including:

- Qualitative evaluation through interviews with stakeholders (clinicians, next of kin, CEC members) and analyses of CEC case reports.
- Quantitative evaluation of case deliberations and other activities, by assessment of stakeholder satisfaction and other outcomes.

Overall, the evaluation research has often indicated that the CECs have an impact in the handling of concrete cases and on ethics competence in the hospitals, and that stakeholder satisfaction is high. However, many areas for improvement of CEC practices have also been identified. Such areas have then been emphasized in CME's training for CEC members.

2. *Implementation research, spanning from description of practices, to development and tailoring of interventions, to implementation and rigorous evaluation.*

In cooperation with other Helsam researchers, CME researchers have studied healthcare practices in need of improvement, and have designed, tailored, implemented and evaluated specific

interventions. Three notable examples are *Mental health care, ethics and coercion* (2011-2015), *Advance care planning in nursing homes* (2013-2017) and in acute geriatric care in hospitals (2019-2025), and *Family involvement during severe mental health problems (2017-2023)*.

3. *Research into clinical ethics issues: descriptive, normative/analytic*

In addition, an important part of CME's work in clinical ethics has been research into specific clinical ethics areas/issues. This research has contributed to identifying and raising awareness of healthcare practices in need of ethical analysis. Examples of topics are home ventilator treatment, priority setting in the clinic, and the scope and limits of patient autonomy in clinical ethics.

Key researchers:
Professor Reidun Førde (1996-)
Professor Reidar Pedersen (2003-)
Researcher Lillian Lillemoen (2008-2019)
Researcher Elisabeth Gjerberg (2009-2019)
Research professor Bert Molewijk (2011-)
Associate professor Morten Magelssen (2014-)
Researcher Berit Hofset Larsen (2018-)

CME's work in clinical ethics has received annual funding from the Norwegian Directorate of Health throughout the evaluation period. In addition, several medium- and large-scale projects have sprung from the clinical ethics work and received specific funding from the NRC etc (examples given above).

3. References to the research

Kalager, G., Førde, R., & Pedersen, R. (2011). Is the discussion of patient cases in clinical ethics-committees useful? *Journal of The Norwegian Medical Association*, *131*(2), 118-121. *DOI: 10.4045/tidsskr.10.0183 Early evaluation study of the Norwegian CECs.*

Førde, R., & Linja, T. (2015). "It scares me to know that we might not have been there!": a qualitative study into the experiences of parents of seriously ill children participating in ethical case discussions. *BMC Med Ethics*, *16*(1), 40. https://doi.org/10.1186/s12910-015-0028-6. *Seminal article based on in-depth interviews, showing how next of kin might contribute to and benefit from a CEC deliberation.*

Magelssen M, Pedersen R, Miljeteig I, Ervik H, Førde R. "Importance of systematic deliberation and stakeholder presence: a national study of clinical ethics committees". *Journal of Medical Ethics* 2020; 46(2): 66-70. *Reports results of national evaluation study of the Norwegian CECs, showing how their work is highly appreciated by stakeholders.*

Magelssen M, Pedersen R, Førde R. "Four Roles of Ethical Theory in Clinical Ethics Consultation". *American Journal of Bioethics* 2016; 16(9): 26–33. *Article about normative underpinnings of CEC case deliberations, published in the most prestigious bioethics journal globally.*

Sævareid, Thoresen, Gjerberg, Lillemoen, Pedersen.
Improved patient participation through advance care planning in nursing homes—A cluster randomized clinical trial - ScienceDirect *Patient Education and Counseling* 2019; 102(12): 2183-

2191. *Main outcome article from this ACP trial reporting positive outcomes for the patients. To our knowledge the first high quality ACP-study (cluster randomization) using a whole ward approach and that also included patients with cognitive impairment.*

Hestmark, Romøren, Heiervang, Hansson, Ruud, Benth, Norheim, Weimand, Pedersen. Implementation of Guidelines on Family Involvement for Persons with Psychotic Disorders (IFIP): A Cluster Randomised Controlled Trial - PubMed (nih.gov) *Adm Policy Ment Health* 2023 May;50(3):520-533. *Sub-study from the IFIP-trial reporting positive implementation outcomes. To our knowledge, the first large-scale high quality (cluster randomization) implementation study on family involvement, paving the way for large-scale implementation of evidence-based treatment for severely and chronically ill patients.*

Hem, Molewijk, Gjerberg, Lillemoen, Pedersen. The significance of ethics reflection groups in mental health care: a focus group study among health care professionals - PubMed (nih.gov) *BMC Med Ethics* 2018 Jun 5;19(1):54. doi: 10.1186/s12910-018-0297-y. *One of the first articles assessing the value of ethics reflection groups as clinical ethics support in mental health care.*

4. Details of the impact

To explain how the impacts occurred, it is important to convey the basics of how the clinical ethics group at CME has worked. The group's basic funding is an annual government grant with which the group is expected to increase knowledge of clinical ethics and improve the handling of ethics problem in the health services. The hospital CECs is a special area of responsibility, and CME's work and network for the CECs serves as a "R&D hub" for the CECs and the services.

The clinical ethics group at CME has developed a very fertile interplay between teaching, supervision and counselling of individual CECs, development of teaching materials (e.g., the CME 6-step ethics reflection model), and research close to and driven by clinical practice. This has enabled researchers to gain better insight into how ethical problems play out in clinical practice, thus informing and inspiring our teaching and research.

This strong connection to practice has also enabled spin-off projects such as the examples given in section 2 above.

A main impact highlighted in this impact case is the establishment of a system of CECs in all Norwegian hospital trusts, and the 2021 legislation mandating every hospital trust to have a CEC. In 2000, The Ministry of Health and Care Services appointed CME as the academic centre in charge of the CECs, with special responsibility for education of CEC members, networking, development, and evaluation research. CME researchers have had annual meetings with Ministry representatives and have also published a yearly report on the work of the CECs. As stated above, evaluation research has not only pointed to areas for improvement of the CECs' work, but also confirmed that the CECs in fact do play an important role in finding new and better solutions. Based on these evaluations, the Ministry in 2004 required all hospital trusts to have a CEC and in 2011 issued a national mandate for the CECs based on a draft from CME researchers. In 2021, the requirement of a CEC was enshrined in law.

As the evaluation research has shown, CECs benefit Norwegian hospitals e.g. by constituting an arena where health professionals, patients and next of kin can get a thorough discussion of a difficult case, and where solutions can be formulated and justified ethically. CEC deliberations can thus contribute to better handling of ethical problems in the clinic, and to increased understanding and agreement between stakeholders. Thus, the research also confirms well-functioning CECs'

roles in the capacity building and quality assurance work of the hospitals. Internationally, CECs are established in more and more countries and hospitals.

CME's work in clinical ethics has also directly contributed to national guidelines on morally charged areas of healthcare practice. A prominent example is the guideline on "decision-making processes in the limitation of life-prolonging treatment" (2009; revised in 2013). This work was chaired by CME's prof. Reidun Førde, and prof. Reidar Pedersen also made key contributions. Here, CME's work in clinical ethics directly informed the guidance presented and contributed to make the guideline more applicable and relevant. Furthermore, CME and the CECs contributed to the successful implementation of this guideline. CME's research and CME researchers have contributed to many other guidelines, government "green papers" (NOU; e.g., priority setting, abortion, use of coercion) and legislative preparations. When the topic concerns clinical ethics it is more the rule than the exception that a CME researcher is invited to contribute. In this way the clinical ethics research at CME and the work of the CECs inform government/health service inquiries and policy development, and also support the implementation of new policies. Together, the clinical ethics group and CECs constitute an important infrastructure for identifying unmet challenges and needs, developing innovative and more sustainable solutions, capacity building, dissemination and continuous and lifelong learning for health professionals and leaders in health care.

Finally, CME researchers have also raised and influenced public and professional awareness of clinical ethics through numerous interviews and media contributions on clinical ethics topics, and through the 2020 textbook "Etikk i helsetjenesten" which is widely used (>4,000 copies sold) in Norwegian health care services and educations. Other examples of user-oriented publications are online courses e.g. on competence assessments in psychiatry, and on clinical ethics in cooperation with the Norwegian Medical Association, and a manual for systematic ethics reflection in municipal healthcare. The work at CME has also influenced research in and development of ethics support internationally, e.g. through CME researchers' participation in the European Clinical Ethics Network. Thus, through this work CME researchers have had major impact on the development of Norwegian health care services and educations, and beyond.

5. Sources to corroborate the impact

The main page for the clinical ethics project at CME is in Norwegian only. Here is a link to the English page.

2021 law mandating clinical ethics committees

English version of Guideline "Decision-making processes in the limitation of life-prolonging treatment

Project: Mental health care, ethics and coercion

Project: Family involvement during severe mental health problems

Project: Implementing Advance Care Planning - A Cluster Randomised Controlled Study

University of Oslo, Institute of Health and Society. Case number 5

Institution: UiO
Administrative unit: Helsam
Title of case study: Vitamin D and immigrant health
Period when the underpinning research was undertaken: 2004-2021
Period when staff involved in the underpinning research were employed by the submitting institution: 2004-2021
Period when the impact occurred: 2012-2022

1. Summary of the impact

Against the backdrop of an increased risk of rickets and prevalent vitamin D deficiency in some immigrant groups, we conducted an intervention study laying the foundation for Norwegian health authorities to provide free vitamin D-drops for infants with immigrant background. Subsequently, we documented that rickets and serious vitamin D-deficiency currently are a manageable problem in children with immigrant background.
Previous studies in adults have suggested that immigrant populations may tolerate lower vitamin D-concentration than Caucasian populations, which could help explaining why we did not observe any effects of vitamin D supplementation in our randomized controlled trial in adults.
The results of our research have contributed to the knowledge base for recommendations and information to the public.

- 2. Underpinning research

In the late 1990-ties an increased number of children with rickets were registered at Norwegian hospitals, and most of them had Pakistani background. In addition, several studies reported that some immigrant groups had a high prevalence of serious vitamin D deficiency. Based on this, the Norwegian Directorate of Health funded a cluster randomized trial performed at child health clinics in Oslo by PhD-student Ahmed Madar and prof. Haakon E. Meyer in collaboration with the public health nurses at the child health clinics (ref. 1, published in 2009). A cluster randomized design was chosen as it was not feasible to employ individual randomization of mothers/infants. We were able to show that provision of free vitamin D-drops to 6-week-old infants with immigrant background together with tailor-made information handouts (translated to Somali, Urdu and Turkish) significantly improved vitamin D status over 7-weeks compared to usual care (mean increase in s-25-hydroxyvitamin D of 28.0 nmol/l (p=0.002) in the intervention group compared to the control group). Whereas the intervention had a clear effect on the infants, the information provided had no effect on the mother's vitamin D-status despite widespread vitamin D-deficiency at baseline. However, unlike the infants, the mothers were not provided with any supplements (ref. 2).
As direct follow-ups to the study, we have, conducted:

- A study on the incidence of rickets in Norway published in 2017 (prof. Haakon Meyer and researcher Ahmed Madar) (ref 3). We utilized nationwide data from the Norwegian Patient Registry, and in collaboration with pediatricians at Oslo University Hospital the diagnoses were verified in medical records. This study shows that nutrition-related rickets is rare in Norway, even among children with immigrant backgrounds. Still, almost all children with nutrition-related rickets had background from Asia/Africa. The article also described a decrease in rickets cases between 1998 and 2012.

- A study on vitamin D status in children aged 9-16 months with immigrant backgrounds in Oslo who were born after the implementation of the offer of free vitamin D drops. It showed that although nearly half of the children were below the recommended s-25(OH)D sufficiency level of ≥50 nmol/l, only 3% had vitamin D-deficiency (ref. 4). The study was published in 2017 and performed by researcher Ahmed Madar and prof. Haakon Meyer.

Furthermore, we have carried out a double-blinded randomized controlled trial titled 'Effect of Vitamin D Supplementation on Muscular Strength, Musculoskeletal Pain, and Headache' among adults (ref. 5, published in 2014). Previous studies have suggested that vitamin D deficiency may have many effects on health in adults, including impacting muscle strength and the risk of falling. Given the potential preventive benefits, we conducted a trial including 251 healthy adult females and males aged 18-50 years with background from Asian, African and the Middle East living in Oslo to test the effect of daily supplementation with vitamin D for 16 weeks (Postdoc Ahmed Madar and prof. Haakon Meyer in collaboration with colleagues at the Department of General Practice).

Results: Mean serum 25-hydroxyvitamin D concentration at baseline was only 26 nmol/l. However, despite the anticipated increase in 25-hydroxyvitamin D, daily supplementation with vitamin D compared to placebo did not improve muscle strength or power as measured by the jump test, handgrip test, or chair-rising test (ref 5). In addition, we did not find an effect on the predetermined additional endpoints of musculoskeletal pain and headache, HbA1C or BMI, iron status, or thyroid autoimmunity. Since baseline concentration of 25-hydroxivitamin D was in the deficit range it was not least interesting to assess if supplementation with vitamin D had an influence on bone turnover markers, but no effect was detected (ref. 6). This result agrees with other research we have performed (not detailed here) showing that South-Asians living in Norway have a substantially lower risk of osteoporotic fractures compared to the majority population despite a much higher prevalence of vitamin D-deficiency.

3. References to the research (indicative maximum of six references)

1. **Madar AA**, Klepp KI, **Meyer HE**. Effect of free vitamin D(2) drops on serum 25-hydroxyvitamin D in infants with immigrant origin: a cluster randomized controlled trial. Eur J Clin Nutr. 2009 Apr;63(4):478-84. doi: 10.1038/sj.ejcn.1602982. Epub 2008 Jan 30. PMID: 18231120.

2. **Madar AA**, Klepp KI, **Meyer HE**. The effect of tailor-made information on vitamin D status of immigrant mothers in Norway: a cluster randomized controlled trial. Matern Child Nutr. 2011 Jan;7(1):92-9. doi: 10.1111/j.1740-8709.2009.00238.x.

3. **Meyer HE**, Skram K, Berge IA, **Madar AA**, Bjørndalen HJ. Nutritional rickets in Norway: a nationwide register-based cohort study. BMJ Open. 2017 May 29;7(5):e015289. doi: 10.1136/bmjopen-2016-015289. PMID: 28554929; PMCID: PMC5729986.

4. **Madar AA**, Gundersen TE, Haug AM, **Meyer HE**. Vitamin D supplementation and vitamin D status in children of immigrant background in Norway. Public Health Nutr. 2017 Nov;20(16):2887-2892. doi: 10.1017/S136898001700180X. Epub 2017 Aug 9. PMID: 28789713; PMCID: PMC10261310.

5. Knutsen KV, **Madar AA**, Lagerløv P, Brekke M, Raastad T, Stene LC, **Meyer HE**. Does vitamin D improve muscle strength in adults? A randomized, double-blind, placebo-controlled trial among ethnic minorities in Norway. J Clin Endocrinol Metab. 2014 Jan;99(1):194-202. doi: 10.1210/jc.2013-2647. Epub 2013 Dec 20. PMID: 24248184.

6. **Madar AA,** Knutsen KV, Stene LC, Brekke M, Lagerløv P, **Meyer HE**, Macdonald HM. Effect of vitamin D3-supplementation on bone markers (serum P1NP and CTX): A randomized, double blinded, placebo controlled trial among healthy immigrants living in Norway. Bone Rep. 2015 May 21;2:82-88. doi: 10.1016/j.bonr.2015.05.004. eCollection 2015 Jun.

4. Details of the impact

- Our cluster-randomized trial on free vitamin D-drops served as the basis for the Norwegian Directorate of Health's nationwide offer of free vitamin D supplements (+ informational brochures in 6 languages) for infants aged 0-6 months with parents from Africa, Asia, South and Central America. The information brochure developed in our trial was slightly modified and translated into 6 languages and was an integrated part of the intervention. This was implemented in 2008, and still exists.

Our follow-up studies on rickets and vitamin D-status in children with immigrant background were also funded by the Directorate of Health. The results are reassuring. Under the influence of current measures, the incidence of rickets is low, and the number of rickets cases decreased substantially between 1998 and 2012. During the same period, several measures were implemented to prevent vitamin D deficiency. This includes the above-mentioned free distribution of vitamin D supplements, vitamin D-fortified infant formula and baby food, as well as significant information work conducted by public health nurses to prevent vitamin D deficiency.
In our study among small children with immigrant background few had vitamin D-deficiency.

Based on our body of research on vitamin D, we have contributed extensively to advisory and dissemination work. In general, we have emphasized the very high prevalence of vitamin D-deficiency in some immigrant groups with corresponding recommended measures to correct that. At the same time, the observations regarding the potential greater tolerance for low vitamin D-status in immigrant populations compared to the Caucasian majority population influence the way we address this issue. It is important to maintain a balanced perspective and avoid excessive emphasis on the problem at hand.

In 2018, the report 'Vitamin D i Norge: Behov for tiltak for å sikre god vitamin D-status?' ('Vitamin D in Norway: The need for measures to ensure adequate vitamin D status?') was published by the National Council for Nutrition. Researcher Ahmed Madar and prof. Haakon Meyer were two of four members of the working group (ref 7 - unfortunately, the report is only available in Norwegian). The report highlights the high prevalence of low vitamin D status in immigrant groups originating from Asia and Africa (a combination of sun habits, skin pigmentation and a low intake). Accordingly, strategies to increase intake were suggested, including specific recommendations for supplementation for people with immigrant background and food fortification. It could be added that Haakon Meyer served as the leader of the National Council for Nutrition from 2006 to 2012, while Ahmed Madar was a member of the council from 2012 to 2023.

Other relevant advisory and dissemination works:

- The perspectives piece 'High-dosage vitamin D supplements are unnecessary' published in the Journal of the Norwegian Medical Association (ref. 8)
- The article 'Vitamin D status and current policies to achieve adequate vitamin D intake in the Nordic countries' from 2021 (ref. 9)
- The commissioned paper 'Should vitamin D supplements be recommended to prevent chronic diseases?' published in BMJ (ref. 10)
- We have frequently featured in various media outlets, including national radio and television, as part of our efforts for advocacy and dissemination

5. Sources to corroborate the impact

7. Brustad M, Madar AA, Meyer HE, Holvik K. Vitamin D i Norge – Behov for tiltak for å sikre god vitamin D-status.pdf (helsedirektoratet.no). Nasjonalt råd for ernæring. IS-2772 11/2018

8. Holvik K, Meyer HE, Madar AA, Brustad M. High-dosage vitamin D supplements are unnecessary. Tidsskr Nor Legeforen. 2019 Apr 8;139(7). Norwegian, English. doi: 10.4045/tidsskr.18.0749. PMID: 30969046.

9. Itkonen ST, Andersen R, Björk AK, Brugård Konde Å, Eneroth H, Erkkola M, Holvik K, Madar AA, Meyer HE, Tetens I, Torfadóttir JE, Thórisdóttir B, Lamberg-Allardt CJE. Vitamin D status and current policies to achieve adequate vitamin D intake in the Nordic countries. Scand J Public Health. 2021 Aug;49(6):616-627. doi: 10.1177/1403494819896878. Epub 2020 Jan 9. PMID: 31916497.

10. Meyer HE, Holvik K, Lips P. Should vitamin D supplements be recommended to prevent chronic diseases? BMJ. 2015 Jan 29;350:h321. doi: 10.1136/bmj.h321.

11. Nordic nutrition recommendations 2023. Scoping review on Vitamin D. Magrit Brustad, Haakon E. Meyer

Impact case guidelines

Each case study should include sufficiently clear and detailed information to enable the evaluation committee to make judgements based on the information it contains, without making inferences, gathering additional material, following up references or relying on members' prior knowledge. References to other sources of information will be used for verification purposes only, not as a means for the evaluation committee to gather further information to inform judgements.

In this evaluation, impact is defined as an effect on, change or benefit to the economy, society, culture, public policy or services, health, the environment or quality of life, beyond academia.

Timeframes

- The impact must have occurred between 2012 and 2022
- Some of the underpinning research should have been published in 2012 or later
- The administrative units are encouraged to prioritise recent cases

Page limit

Each completed case study template will be limited to **five pages** in length. Within the annotated template below, indicative guidance is provided about the expected maximum length limit of each section, but institutions will have flexibility to exceed these so long as the case study as a whole remains no longer than **five pages** (font Calibri, font size 11). Please write the text into the framed template under the sections 1–5 below. The guiding text that stands there now, can be deleted.

Maximum number of cases permitted per administrative unit

For up to 10 researchers: one case; for 10 to 30 researchers: two cases; for 30-50 researchers: three cases; for 50-100 researchers: four cases, and up to five cases for units exceeding 100 researchers.

Naming and numbering of cases

Please use the standardised short name for the administrative unit, and the case number for the unit (1,2,3, etc) in the headline of the case. Each case should be stored as a separate PDF-document with the file name: [Name of the institution and name of the administrative unit] [case number]

Publication of cases

RCN plans to publish all impact cases in a separate evaluation report. By submitting the case the head of the administrative units consents to the publication of the case. Please indicate below if a case may not be made public for reasons of confidentiality.

If relevant, describe any reason to keep this case confidential:

N/A

[University of Oslo, Institute of Basic Medical Sciences] [case number 1]

Institution: University of Oslo (UiO)
Administrative unit: Institute of Basic Medical Sciences (IMB)
Title of case study: 4D epigenetics of adipose tissue stem cells
Period when the underpinning research was undertaken: 2014-2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2009-2022
Period when the impact occurred: 2014-2022

1.Summary of the impact (indicative maximum 100 words)

In a worldwide context of obesity, much as long remained unknown on principles of genome organization which govern fat stem cell differentiation into adipocytes. We describe a scientific impact on the 4-dimensional (4D; space-time) organization of the adipose stem cell and adipocyte genome. We have identified a new level of spatial chromatin organization, and henceforth have unveiled contributions of two main chromatin organizers to the 4D genome, and their significance in pathophysiological contexts. We have generated and made publicly available epigenomic datasets and bioinformatics pipelines which constitute valuable resources for the scientific community.

2. Underpinning research (indicative maximum 500 words)

The discovery in the early 2000s that adipose tissue stem cells (ASCs) could be isolated from fat tissue has sparked research worldwide on understanding and harnessing their differentiation potential into adipocytes and other cell types. In the same decade, the explosion of transcriptomics and other genomics technologies has enabled unprecedented space-resolved studies of genome (chromatin) organization.

ASCs, isolated from human adipose tissue as a by-product of liposuction, constitute a powerful system to study adipogenesis. Using this system, we and other groups have revealed i) changes in the transcriptome, the 3D genome and chromatin accessibility to transcription factors, ii) acquisition of new epigenetic states, and iii) remodeling of interactions between gene promoters and enhancers.

3D chromatin conformation can change in response to external signals during development, differentiation and tissue homeostasis. This view rests on discoveries of genomic elements and nuclear architectural proteins that structurally shape the genome at multiple levels. At the largest scale, chromosomes are organized in territories broadly divided into euchromatic and transcriptionally active A compartments, and heterochromatic and overall inactive B compartments. Within compartments, topologically-associated domains (TADs) of higher chromatin contact frequencies are important for gene expression regulation, and, as we and others have shown (including in this impact case), establish long-range contacts with other TADs, shaping high-order chromatin architecture. In addition, radial (center-to-periphery) genome organization relies on associations of chromatin with the nuclear lamina, at the nuclear envelope, via lamina-associated domains (LADs). Some LADs change during differentiation or are altered in disease states, and laminopathies, diseases caused by mutations in nuclear lamin A, underscore the importance of maintaining a proper genome organization.

In this context, we have established a research program aiming to map and decipher the genome-wide epigenetics underlying the differentiation potential of ASCs. We have provided evidence of contributions from two main genome organizers (TADs and LADs) to the 4D conformation of chromatin (i.e. in 3D over time), and of their significance in laminopathies. We have made available epigenomic datasets and bioinformatics pipelines, which constitute resources for the scientific community.

The work has largely been undertaken in the Stem Cell Epigenetics Laboratory (www.collaslab.org), part of the Chromatin Biology research group at IMB. The lab has counted 12-

18 people at any time in the 2012-2022 period, and has benefitted from interactions with other groups at IMB and internationally. Through publications and dissemination activities, the impact has occurred continuously throughout the 2013-2022 period, but has culminated in 2029-2022.

Key researchers, dates in the administrative unit, and position:

- Philippe Collas (1999-present), researcher then (2003 -) Professor, Head of research group Head of Department (2016-)
- Julia Madsen-Østerbye (2019-present), postdoc
- Nolwenn Briand (2017-present), postdoc then researcher
- Natalia Galigniana (2021-present), postdoc
- Aurélie Bellanger (2018-present), postdoc then researcher
- Jonas Paulsen (2016-2020), postdoc
- Annael Brunet (2016-2020), postdoc
- Erwan Delbarre (2006-2018), postdoc then researcher
- Anja Oldenburg (2009-2018), researcher
- Evdokiia Potolitsyna (2018-2021), PhD student
- Tharvesh Liyakat-Ali (2016-2020), PhD student
- Frida Forsberg (2017-2020), PhD student
- Jane Spirkoski (2014-2017), PhD student
- Akshay Shah (2014-2017), PhD student
- Torunn Rønningen (2013-2016), PhD student
- Eivind Lund (2013-2015), PhD student
- Engineers in the lab (Anita Sørensen, Kristin Vekterud, Mohamed Abdelhalim [bioinfo])

Relevant key contextual information about this area of research:

Worldwide, over 2 billion adults are overweight, including 1 billion clinically obese. Adipose tissue has there become a major research focus because of its capacity to store energy in the form of lipids in white adipocytes, and dissipate energy by heat in thermogenic adipocytes. In parallel, the past decade has witnessed an explosion of genomics methods enabling studies of regulation of gene expression and cell fate at unprecedented levels, notably (and critical to this research) in the 3D context of genome organization.

3. References to the research (maximum six references):

- Madsen-Østerbye J, Abdelhalim M, Baudement MO, Collas P. 2022. Local euchromatin enrichment in lamina-associated domains anticipates their repositioning in the adipogenic lineage. Genome Biol 23, 91. https://pubmed.ncbi.nlm.nih.gov/35410387/
- Paulsen J, Liyakat Ali TML, Nekrasov M, Delbarre E, Baudement, MO, Kurscheid S, Tremethick D, Collas P. 2019. Long-range interactions between topologically-associating domains shape the 4-dimensional genome during differentiation. Nature Genet 51, 835-843. https://pubmed.ncbi.nlm.nih.gov/31011212/
- Paulsen J, Ali TML, Collas P. 2018. Computational 3D genome modeling using Chrom3D. Nature Protoc 13, 1137-1152. https://pubmed.ncbi.nlm.nih.gov/31011212/
- Paulsen J, Sekelja M, Oldenburg AR, Barateau A, Briand N, Delbarre E, Shah, A, Sørensen AL, Vigouroux C, Buendia B, Collas P. 2017. Chrom3D: three-dimensional genome modeling from Hi-C and nuclear lamin-genome contacts. Genome Biol 18, 21-29. https://pubmed.ncbi.nlm.nih.gov/28137286/
- Oldenburg AR, Briand N, Sørensen AL, Cahyani I, Shah A, Moskaug JØ, Collas P. 2017. A lipodystrophy-causing lamin A mutant alters conformation and epigenetic regulation of the anti-adipogenic MIR335 locus. J Cell Biol 216, 2731-2743. https://pubmed.ncbi.nlm.nih.gov/28751304/

- Lund E.G., Oldenburg A., Collas P. 2014. Enriched domain detector: a program for detection of wide genomic enrichment domains robust against local variations. Nucl. Acids Res. 42, e92. https://pubmed.ncbi.nlm.nih.gov/24782521/

4. Details of the impact (indicative maximum 750 words)

The 3-dimensional epigenome of fat stem cells and adipocytes in health and disease

Cell fate decisions are programmed at several levels of gene expression, including heritable epigenetic modifications. Interactions between chromosomes, and repositioning of genes in the 3D nucleus space, provide a blueprint of temporal gene expression. Aspects of 3D genome organization are regulated in a 4D space where the 4th dimension is time. Nutrient availability also modulates the epigenome, providing another level of complexity of gene regulation and cell fate, particularly in cells from adipose tissue. This case study has over 10 years looked into mechanistic links between a changing 3D chromatin landscape, gene expression and adipose cell metabolic state and function, in health and pathological conditions (lamin A-linked lipodystrophies).

Omics technologies enable investigations of structural properties of the genome in space. As suitable molecular and bioinformatics approaches were lacking to deeply investigate radial genome architecture, we have tailored chromatin assays and developed a bioinformatics pipeline (Enriched Domain Detector; https://github.com/CollasLab/edd) for analyses of interactions of chromatin with the nuclear lamina. We have then developed a 3D genome modeling tool, Chrom3D (https://github.com/CollasLab/Chrom3D; published in *Genome Biology* in 2017 and *Nature Protocols* in 2018) to infer new principles of 3D genome organization, and this can go awry in lamin A-linked lipodystrophies.

Using as model system differentiation of human ASCs into adipocytes, we have combined genomics and computational approaches to show in a 2019 landmark *Nature Genetics* paper that long-range assemblies of topological domains (TADs), which we called TAD cliques, shape the 4D genome during adipogenesis. A relationship between TAD cliques and LADs suggests that cliques stabilize heterochromatin at the nuclear periphery. This and related work show that TAD cliques represent a new level of 4D genome conformation reinforcing the silencing of developmental genes. In a collaboration with Stanford U, we have applied Chrom3D to show that carcinogen susceptibility lies at the origin of genome instability regulated by nuclear architecture.

Implementing theoretical physics, we have in parallel used polymer simulations to provide new insights on the physical properties of chromatin affect its interaction with the nuclear lamina. From this, we have investigated how LADs impinge on adipogenic gene expression. Gains and losses of LADs are prominent features of adipogenic chromatin rearrangement, in that LADs sequester genes irrelevant for fat cell function, while important genes are released from the lamina. Our work also emphasizes a challenging concept of epigenetic heterogeneity at the nuclear lamina. LADs emerge as central features of adipose nuclear architecture which contribute to reinforcing adipose cell type identity.

Chromatin organization in lamin A-linked lipodystrophies. A-type lamins integrate metabolic signals and convey them to the genome. Investigating metabolic aspects of genome organization, we have shown that a lipodystrophy (FPLD2)-causing host-spot lamin A mutation alters conformation and epigenetic regulation, resulting in a loss-of-function of differentiation-dependent lamin A binding to chromatin. This links a laminopathy-causing mutation to an unsuspected deregulation of spatial chromatin conformation, impacting adipose stem cell fate. Using induced pluripotent stem cells derived from FPLD2 patient's fibroblasts, we have connected a lipodystrophic lamin A mutation to defective endothelial differentiation, and propose that the mutation rewires the fate of several lineages, resulting in multi-tissue pathogenic phenotypes.

Our results have impacted science mainly because we have identified a new level of spatial chromatin organization; in doing so we have unveiled contributions of two main genome organizers to the 4D genome (LADs and TAD cliques) and their significance in pathophysiological

contexts. We have generated and made publicly available epigenomic datasets and two bioinformatics pipelines which constitute valuable resources for the scientific community.

How has the process led to the impact:
Wet-lab methods, computational tools and results have been presented at conferences and research institutions (upon invitation) worldwide. They have resulted in the group being contacted for collaborations, tutorials, and wide use by research labs worldwide who also have published using these methods and tools. This case study has amply complemented research at IMB, notably in molecular nutrition, adipose and lipid biology, and clinical nutrition on hypercholesterolemia and childhood obesity, in the Department of Nutrition.

Beneficiaries, nature of the impact:
The primary beneficiaries of the impact are members of the scientific community, given the basic nature of the findings. Significance for industry has been indirect, as our wet-lab methods, computational tools, and researchers who have graduated from the group, have generated strong interest in the biotech sector. Societal significance has to date however been limited due to the very basic nature of the work. Our dissemination plan has included publications in high-ranked journals, reviews, seminars, public lectures, presentations to patient groups at European congresses, and social media. Impact has also been tremendous regarding the amount of funding it has generated, notably from the Research Council of Norway, with at least 5 Research Council projects related to the case study, and 3 PhD and Postdoc stipends plus 1 program grant from Helse Sør-Øst (Norwegian Health Authorities), 3 EU-UiO Scientia fellows, and 1 EAA grant (NO-CZ).

Indicators of impact extent (2013-2022):

- No. Pubmed publications directly related to the impact: 46
- No. Github-released bioninformatics tools: 2
- No. speaker invitations at national and international conferences: 57
- No. speaker invitations at Universities and Institutes worldwide: 44

5. Sources to corroborate the impact (indicative maximum of ten references)

- Potolitsyna E, Hazell Pickering S, Germier T, Collas P, Briand N. 2022. Long non-coding RNA HOTAIR regulates cytoskeleton remodeling and lipid storage capacity during adipogenesis. Sci Rep 12, 10157
- Brunet A, Destainville N, Collas P. 2021 Physical constraints in polymer modeling of chromatin associations with the nuclear periphery at kilobase scale. Nucleus 12, 6-20
- Brunet A, Forsberg F, Fan Q, Sæther T, Collas P. 2019. Nuclear lamin B interactions with chromatin during the circadian cycle are uncoupled from periodic gene expression. Front Genet 10, 917
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- Delbarre, E, Ivanauskiene K, Spirkoski J, Shah A, Vekterud K, Moskaug JØ, Bøe SO, Wong L, Küntziger T, Collas P. 2017. PML protein organizes heterochromatin domains where it regulates histone H3.3 deposition by ATRX/DAXX. Genome Res. 27, 913-921
- Rønningen T., Shah A, Oldenburg AR, Vekterud K, Delbarre E, Moskaug JØ, Collas P. 2015. Prepatterning of differentiation-driven nuclear lamin A/C-associated chromatin domains by GlcNAcylated histone H2B. Genome Res 25, 1825-1835
- Shah, A., Oldenburg, A.R., Collas, P. 2014. A hyper-dynamic nature of bivalent promoter states underlies coordinated developmental gene expression modules. BMC Genomics 15, 1186

- Ivanauskiené K., Delbarre E., McGhie J.D., Küntziger T., Wong L.H., Collas P. 2014. The PML-associated protein DEK regulates the balance of H3.3 loading on chromatin and is important for telomere integrity. Genome Res. 24, 1584-1594
- Lund E.G., Oldenburg A., Collas P. 2014. Enriched domain detector: a program for detection of wide genomic enrichment domains robust against local variations. Nucl. Acids Res. 42, e92
- Oldenburg A.R., Delbarre E., Thiede B., Vigouroux C., Collas P. 2014. Deregulation of Fragile X-related protein 1 by the lipodystrophic lamin A p.R482W mutation elicits a myogenic gene expression program in preadipocytes. Hum. Mol. Gen. 23, 1151-1162
- Lund E., Oldenburg A.R., Delbarre E., Freberg C.T., Duband-Goulet I., Eskeland R., Buendia B., Collas P. 2013. Lamin A/C-promoter interactions specify chromatin state-dependent transcription outcomes. Genome Res. 23, 1580-1589

[University of Oslo, Institute of Basic Medical Sciences] [case number 2]

Institution: University of Oslo (UiO)
Administrative unit: Institute of Basic Medical Sciences (IMB)
Title of case study: The role of sleep in brain waste clearance
Period when the underpinning research was undertaken: 2010–2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2006–present
Period when the impact occurred: 2012–2022

1. Summary of the impact (indicative maximum 100 words)

Research by the group of the late Professor Erlend Nagelhus and his successor Associate Professor Rune Enger at Department of Molecular Medicine, Institute of Basic Medical Sciences has contributed to ground-breaking discoveries that have increased our understanding of how the brain rids itself of harmful waste. Apart from a substantial academic impact, the findings have paved the way for foundational and applied research across the globe and in collaborating groups in the clinic that has changed patient diagnostics of brain fluid disorders. Moreover the findings have increased public awareness of the importance of sleep for brain health neurodegeneration in the general public.

2. Underpinning research (indicative maximum 500 words)

In 2012 Professor Nagelhus had a central contribution to a milestone paper by Professor Maiken Nedergaard in Rochester, NY, USA. They demonstrated that the cerebrospinal fluid flows along the brain's vasculature, and that this flow contributes to the clearance of waste products from the brain, and is dependent on water channels – *Aquaporins* – in perivascular astrocyte endfoot processes. The system was coined 'the glymphatic system', due to its functional analogy to the lymphatic system in the rest of the body, and its dependency on the astrocyte subtype of glial cells. The system was shown to remove for instance amyloid beta from the brain and thus may play a role in preventing neurodegenerative disease. In 2013 follow-up work in the Nedergaard lab demonstrated that this system primarily is active in sleep.

The original reports on the glymphatic system from the Nedergaard lab were enabled by use of advanced in vivo optical imaging techniques called two-photon microscopy. In Oslo, Nagelhus and his group had established similar technology and were refining this technique over the next decade to enable studies in naturally sleeping head-fixed mice, to try to elucidate mechanisms that regulate the glymphatic system. A key step was establishing in vivo two-photon microscopy in anesthetised and later unanesthetized mice. Then PhD student (2013–2016) and later postdoctoral researcher (2016–2019), and finally associate professor Rune Enger had the prime responsibility of establishing these techniques in the group. This led to the first study using genetically encoded Ca^{2+} sensors in both astrocytes and neurons at the same time in a single preparation in (Enger et al 2017, Cerebral Cortex). Laura Bojarskaite (PhD student 2015–2020, now a senior postdoctoral researcher in the group) had the major responsibility of setting up two-photon microscopy of naturally sleeping head fixed mice. Concurrently, PhD students Daniel M. Bjørnstad (PhD student from 2016-2022) and Knut S. Åbjørsbråten (PhD student from 2016 to 2022) under supervision of Enger developed a pipeline of data analyses of two-photon imaging data, tailored for natural sleep, including novel methods for analysing astrocytic signalling. In January 2020, Nagelhus tragically passed away. Subsequently, under Enger's leadership, the first description of astrocyte signalling in natural sleep was published (Bojarskaite&Bjørnstad et al, Nat Comm 2020). These findings may be important for regulating the glymphatic system, and the study suggested a salient role of astrocytes in maintaining uninterrupted deep sleep. Following up on this work, Enger and his team pursued brain waste clearance

mechanisms in sleep, demonstrating for the first time the dynamics of the vasculature and surrounding endfeet in natural sleep in *Nature Communications* in 2023 (Bojarskaite&Vallet&Bjørnstad et al, Nat Comm 2023).

3. References to the research (indicative maximum of six references)

Iliff, J.J., Wang, M., Liao, Y., Plogg, B.A., Peng, W., Gundersen, G.A., Benveniste, H., Vates, G.E., Deane, R., Goldman, S.A., Nagelhus, E.A. and Nedergaard, M., 2012. A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid β. Science translational medicine, 4(147), pp.147ra111-147ra111.https://doi.org/10.1126/scitranslmed.3003748

Rune Enger, Didrik B. Dukefoss, Wannan Tang, Klas H. Pettersen, Daniel M. Bjørnstad, P. Johannes Helm, Vidar Jensen, Rolf Sprengel, Koen Vervaeke, Ole P. Ottersen, Erlend A. Nagelhus, Deletion of Aquaporin-4 Curtails Extracellular Glutamate Elevation in Cortical Spreading Depression in Awake Mice, Cerebral Cortex, Volume 27, Issue 1, January 2017, Pages 24–33. https://doi.org/10.1093/cercor/bhw359

Bjørnstad, Daniel M., Knut S. Åbjørsbråten, Eivind Hennestad, Céline Cunen, Gudmund Horn Hermansen, Laura Bojarskaite, Klas H. Pettersen, Koen Vervaeke, and Rune Enger. 2021. "Begonia—A Two-Photon Imaging Analysis Pipeline for Astrocytic Ca^{2+} Signals." Frontiers in Cellular Neuroscience 15: 176. https://doi.org/10.3389/fncel.2021.681066

Bojarskaite, Laura, Daniel M. Bjørnstad, Klas H. Pettersen, Céline Cunen, Gudmund Horn Hermansen, Knut Sindre Åbjørsbråten, Anna R. Chambers, et al. 2020. "Astrocytic Ca^{2+} Signaling Is Reduced during Sleep and Is Involved in the Regulation of Slow Wave Sleep." Nature Communications 11 (1): 1–16. https://doi.org/10.1038/s41467-020-17062-2

Knut Sindre Åbjørsbråten, Gry HE Syverstad Skaaraas, Céline Cunen, Daniel M Bjørnstad, Kristin M Gullestad Binder, Laura Bojarskaite, Vidar Jensen, Lars NG Nilsson, Shreyas B Rao, Wannan Tang, Gudmund Horn Hermansen, Erlend A Nagelhus, Ole Petter Ottersen, Reidun Torp, Rune Enger (2022) Impaired astrocytic Ca2+ signaling in awake-behaving Alzheimer's disease transgenic mice eLife 11:e75055 https://doi.org/10.7554/eLife.75055

Bojarskaite, Laura, Alexandra Vallet, Daniel M. Bjørnstad, Kristin M. Gullestad Binder, Céline Cunen, Kjell Heuser, Miroslav Kuchta, Kent-Andre Mardal, and Rune Enger. 2023. "Sleep Cycle-Dependent Vascular Dynamics in Male Mice and the Predicted Effects on Perivascular Cerebrospinal Fluid Flow and Solute Transport." Nature Communications 14 (1): 953. https://doi.org/10.1038/s41467-023-36643-5

4. Details of the impact (indicative maximum 750 words)

Professor Nagelhus as part of the research environment led by Professor Ole Petter Ottersen in Oslo demonstrated in the late 1990s the location of aquaporin-4 water channels in the astrocytic endfeet in the central nervous system. This interest and the development of aquaporin-4 knockout mouse lines laid the groundwork for the work leading up to the first description of the glymphatic system in 2012. The discovery and publication of the glymphatic system as a way the brain rids itself of waste products in *Science Translational Medicine* received some attention, but it was only the year after when this system was found to be considerably more active in sleep than wakefulness that a lot of attention was given to this line of research. The paper (Xie et al 2013, *Science*) demonstrating that the glymphatic system is active in sleep and certain types of anaesthesia was highlighted as one of the top ten scientific breakthroughs of 2013 by *Science Magazine* and opened up a new field of research. The paper was picked up by a range of international news outlets and was proposed to be an explanation of the universal need for sleep: for the brain to rid itself of harmful waste products. Importantly it was shown that beta-amyloid, an important player in Alzheimer's disease and other

neurodegenerative disorders, is cleared by the glymphatic system, linking the amount and quality of sleep with a potential future risk of neurodegenerative disease. This whole research field that sprung out of the interest of aquaporins in astrocytes in the brain and collaboration with Maiken Nedergaard is a very active field of research that has already changed diagnostics, but potentially will also change treatment for a range of brain disorders in the not too distant future. Today, a Pubmed search of 'glymphatic' reveals around 1500 articles, and a number of patents aimed for treatment of human disease have been registered.

Nagelhus' role in the original descriptions of the glymphatic system received a lot of attention in Norway, both in academia and in the general population, and spurred an interdisciplinary research effort in Oslo studying the glymphatic system with clinical, neuroimaging, and biophysical modelling approaches. Importantly, this work led to the first study demonstrating the glymphatic system in humans using intrathecal MRI contrast by collaborators Professor Per Kristian Eide and Dr. Geir Ringstad at Oslo University Hospital (Eide & Ringstad, Acta Radiologica Open 2015). This new imaging modality has now changed patient diagnostic procedures for patients with normal pressure hydrocephalus, where tracer clearance distribution is used as a means to quantify CSF flow disturbances in these patients.

Following the initial papers on the Glymphatic system, Nagelhus established infrastructure and know-how to further study the sleeping brain. To establish optical imaging of natural sleep in rodents represented a challenge. The initial steps included establishing in vivo microscopy at the lab in Oslo, and extending these imaging models to the study of unanesthetized mice. After Nagelhus' passing in 2020, associate professor Rune Enger led the further development of the research. In 2020 Enger and his lab were able to for the first time describe astrocytic signalling across the natural sleep-wake state of mice. The paper was published in *Nature Communications* and listed as Editor's pick of the month. Importantly, these signalling mechanisms across the sleep-wake state could be a part of the explanation of how the glymphatic system is regulated. The results received broad recognition in the field, and in the general population: news outlets like *Verdens Gang* (the largest newspaper in Norway) reported the study, raising awareness of the importance of sleep for proper brain functioning. The authors were invited to contribute to a range of public outreach events where focus has been to raise public awareness on the detrimental effects of sleep loss on brain health. The group also featured in *Solaris Naturfag* 3–4 textbook for elementary school, raising awareness of the need for sleep in children, an important public health focus given the potential detrimental effects of personal smart devices and social media.

In the following years, the group continued investigating mechanisms underpinning the glymphatic system and were for the first time able to show in 2023 that sleep-specific dynamics of the arteries and arterioles of the brain serve as pumps that likely drives fluid and solute movement in the brain in sleep. The study was a collaboration with Simula Research Laboratory and Department of Mathematics at UoO and published in *Nature Communication* in 2023. These findings could explain how brain health and vascular health seems to both strongly correlate with Alzheimer's dementia. The findings received widespread attention in the news and through various popular science outlets, including the front page and 2 full pages in *Verdens gang*, as well as radio interviews in NRK EKKO, national radio.

5. Sources to corroborate the impact (indicative maximum of ten references)

Kaalstad, Jørn. 2023. “Kan Hindre Alzheimers.” Verdens Gang, March 25, 2023.

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“Astrocytes Help to Maintain Slow Wave Sleep” Neuroscience News, July 15, 2020
https://neurosciencenews.com/astrocytes-slow-waves-sleep-16652/

“Astrocytes Play an Important Role in Maintaining Slow Wave Sleep” Technology Networks, August 5, 2020.
https://www.technologynetworks.com/neuroscience/news/astrocytes-play-an-important-role-in-maintaining-slow-wave-sleep-338295

“Dementia and Sleep: It’s Not Just Deep Sleep That Counts” in the podcast The Snooze Button by Neil Hedley with Laura Bojarskaite, PhD. September 7, 2020.

Isachsen, Henriette Bertheussen. 2023. “Norsk studie kan bidra til å forebygge Alzheimers: Fant at søvn gir mer effektiv «hjernevask»”, Dagens Medisin, April 3, 2023.
https://www.dagensmedisin.no/alzheimers-sykdom-forskning-universitetet-i-oslo-uio/norsk-studie-kan-bidra-til-a-forebygge-alzheimers-fant-at-sovn-gir-mer-effektiv-hjernevask/558638

Munkebye, E., K. Skage, and A. Munkebye. "Solaris-Naturfag (3-4)." (2022): “Hvorfor må vi sove?”, s. 131.

Laura Bojarskaite on Lithuanian national TV morning show “good morning” talking about the research in the research group
https://www.lrt.lt/mediateka/irasas/2000211890/neuromokslininke-musu-smegenys-keiciasi-ir-del-skirtingu-metu-laiku-ir-sviesos-kiekio?fbclid=IwAR1zLZDRUlA2slgoibV5KO1MA8WU06PGbRnIbQdsKHZQM_eACPhJvU2Araw

NRK EKKO, “Hjerneforskere får millioner til Alzheimerforskning”
https://radio.nrk.no/program/MDFP02018123

Public outreach through Hjernehelsekonferansen og Hjernerådet:
https://www.hjerneradet.no/hapet-pa-1000-svar-har-hittil-fatt-18-000-2-2-4-2-4/

[University of Oslo, Institute of Basic Medical Sciences] [case number 3]

Institution: University of Oslo (UiO)
Administrative unit: Institute of Basic Medical Sciences (IMB)
Title of case study: Prevention of non-communicable diseases (NCDs) by promoting a healthy diet among children
Period when the underpinning research was undertaken: 2012-2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2007-2022
Period when the impact occurred: 2013-2022

1. Summary of the impact (indicative maximum 100 words)

Several researchers at IMB have for many years focused their research on prevention of non-communicable diseases (NCDs) by promoting a healthy diet. Establishing healthy dietary habits early in life can promote a healthy diet throughout life. The results from our research have had an important academic impact. Additionally, the results add essential knowledge to nutritional policy and implementation of diet-related guidelines, which are developed by the Norwegian Directorate of health. Thus, this impact case describes our research's social impact on policy and public health. Moreover, the findings have increased public awareness of the importance of healthy dietary habits early in life.

2. Underpinning research (indicative maximum 500 words)

Together with the Norwegian Institute of Public Health/Directorate of Health, Prof Frost Andersen regularly conduct **national dietary surveys**. The most recent surveys among children aged 9 and 13 years (UNGKOST 3 rapport, 2015) showed that children ate too much saturated fat and added sugar, and they ate less fruit, vegetables and fish than recommended. This is a dietary pattern, which is associated with increased risk of obesity and cardiovascular diseases (CVD). In the project**, the BRA-study** funded by the Research Council of Norway, profs. Lien and Frost Andersen et al. aimed to increase vegetable intake among 3–5-year-olds by changing the food environment in the kindergartens and at home. Important non-academic partners were the Information bureau for fruit and vegetables and Geitmyra culinary centre for children. There were no significant differences in the parent reported vegetable intake of the children the intervention and control groups, but the amount of vegetable consumed in the intervention kindergartens were higher than the control group. There were also greater amounts and variation in vegetables served in the intervention kindergartens, but there were no changes at home. In the project "**The school as a public health actor: Strategies for successful implementation of guidelines for food and meals**" funded by the Research Council of Norway and the Norwegian Directorate of Health, the focus on shaping the food environment of children by public policy was further studied by Prof Lien et al. A questionnaire for measuring guidelines adherence was developed. Theory-guided qualitative interviews revealed several factors affecting guideline implementation at macro, school, and individual levels. The project RØRE (Move) in the county of Østfold was an important non-academic partner.

The national dietary surveys also include infants and small children (spedkost and småbarnskost). Prof. Holven et al., conducted a **sub study to investigate the prevalence of elevated cholesterol levels among infants and small children**. The study was funded by IMB and Throne Holst foundation for nutrition research, UiO. They found a large variation in plasma cholesterol levels in infants and small children aged 6, 12 ad 24 months, and 20% of these infants had total cholesterol above 5 mmol/l which is the current recommended level. The cholesterol levels at 6 and 12 months were significantly correlated, and other studies have shown that the cholesterol levels track further through life meaning that children with high cholesterol will become adults with high cholesterol

and these children will therefore have a higher risk for CVD later in life unless lifestyle changes are made.

References to the research (indicative maximum of six references)

1. Iodine intake among children and adolescents in Norway: Estimates from the national dietary survey Ungkost 3 (2015-2016).Medin AC, Carlsen MH, Andersen LF**.**J Trace Elem Med Biol. 2020 Mar;58:126427. doi: 10.1016/j.jtemb.2019.126427.

2. Effects of a kindergarten intervention on vegetables served and staff's food-related practices: results of a cluster randomised controlled trial - the BRA study.
Himberg-Sundet A, Kristiansen AL, Frost Andersen L, Bjelland M, Lien N. Public Health Nutr. 2020 Apr;23(6):1117-1126.

3. Kristiansen, Anne Lene; Bjelland, Mona; Himberg-Sundet, Anne; Lien, Nanna; Holst, René & Andersen, Lene Frost (2019). Effects of a cluster randomized controlled kindergarten-based intervention trial on vegetable consumption among Norwegian 3–5-year-olds: the BRA-study. BMC Public Health. ISSN 1471-2458. 19(1), s. 1–10. doi: 10.1186/s12889-019-7436-3.

4. Randby, Jorunn Sofie; Meshkovska, Biljana; Holbæk, Helene & Lien, Nanna (2021). An Exploration of Implementation Enablers and Barriers for Norwegian School Meal Guidelines. Global Implementation Research and Applications. ISSN 2662-9275. 1, s. 122–134. doi: 10.1007/s43477-021-00010-7.

5. Cholesterol at ages 6, 12 and 24 months: Tracking and associations with diet and maternal cholesterol in the Infant Cholesterol Study. Øyri LKL, Bogsrud MP, Kristiansen AL, Myhre JB, Astrup H, Retterstøl K, Brekke HK, Roeters van Lennep JE, Andersen LF, Holven KB. Atherosclerosis. 2021 Jun;326:11-16. doi: 10.1016/j.atherosclerosis.2021.04.017.

4. Details of the impact (indicative maximum 750 words)

An unhealthy diet is one of the major causes of NCDs, and overweight/obesity is a direct risk factor for many NCDs, including CVDs. In addition, it is well known that plasma cholesterol is an important risk factor for CVD. Although diet is an individual behaviour, there is an increased recognition that this behaviour to a great extent is driven by an unhealthy food environment and that policies should target these environments to prevent overweight/obesity and reduce plasma cholesterol to reduce risk of NCDs in the general population. Both dietary habits, overweight/obesity and cholesterol levels have been shown to track from childhood to adulthood. Establishing healthy dietary habits and weight status among children is thus important to prevent NCDs. To assess the overall impact of policies and societal changes on diets of children, we need to monitor what children are eating. The results from national dietary surveys are important for policy makers and white papers, and the Norwegian Directorate of Health needs this information to make action plans and dietary guidelines for the general population. The results from our national survey have been an important basis for the white paper "Nasjonal handlingsplan for bedre kosthold (2017-2021).". Moreover, the Directorate of health use the national survey data to promote health in the Norwegian population and make action plans for dietary habits in their yearly report "Utviklingen i norsk kosthold - Helsedirektoratet". The national survey data is also used by the Norwegian Scientific committee for Food and environment in their risk assessments. The results from the BRA-study have been taken forward by the Information bureau for fruit and vegetables in their "5 a day Kindergarten" scheme. Furthermore, in January 2017 a workshop to discuss food and meals in kindergarten was initiated by the project and jointly organised with the Norwegian Directorate of Health and Centre for food, health and physical activity. This was an important input for the revised guidelines for kindergartens published in December 2017 where the project is referred to under the recommendation about serving fruit and vegetables every day with a link to the material. The questionnaire for measuring guideline adherence was taken up by the public health project RØRE (Move) in the county of Østfold

in order to evaluate on of the aim of their projects. This led to a collaboration for the development and testing of the implementation intervention in the project. Thus, the project has influenced both the practice in Østfold county and the practice of the Norwegian Directorate of Health with regards to implementation of the guideline. Furthermore, these results can be directly transferable to implementation of other guidelines which the Norwegian Directorate of Health is responsible for and especially the ongoing work on a possible implementation of a free school meal. The impact of measuring cholesterol early in life is that it is the total cholesterol burden who define the risk of CVD. If we can detect children with high cholesterol early in life, lifestyle changes can be made in order to prevent CVD later in life. Our findings are in line with many European projects where initiatives have been initiated to start cholesterol screening among infants. We have discussed this in the national nutrition council and aim to suggest that a working group is started with the mandate of investigating the impact, feasibility, and economic benefit of initiating such a screening program in Norway. Several countries in Europe have already initiated a universal cholesterol screening program among children (Slovenia, Croatia, Luxembourg) or have started up large pilot studies (Germany and UK). Identifying children with high lipid levels and intervene with lifestyle counselling will favourably impact lifetime cardiovascular risk.

5. Sources to corroborate the impact (indicative maximum of ten references)

1.Data from the National surveys has been disseminated in the largest newspaper in Norway, Aftenposten Barn drakk dobbelt så mye brus for 16 år siden (aftenposten.no),
2. Data from the National surveys have also been used by the Norwegian Scientific Committee for Food and Environment in their risk benefit analysis of fish intake in the Norwegian population Benefit and risk assessment of fish in the Norwegian diet (alsaker.no)
3. Children and cholesterol measurements; Bør jobbe med kolesterolet allerede hos barn; Dagens Medisin, 2021**.** Bør jobbe med kolesterolet allerede hos barn (dagensmedisin.no)
4. Children and cholesterol measurements; was shown at the national news, 2022; Professor Kirsten Holven mener alle barn bør få tilbud om kolesterolmåling – NRK Norge – Oversikt over nyheter fra ulike deler av landet
5. Children and kindergartens and at home to increase intake of vegetables; interview with Nanna Lien at national radio 2014; 90 Vestfold-barnehager med på undersøkelse – NRK Vestfold og Telemark – Lokale nyheter, TV og radio
6. Increase intake of vegetables among children**;** Skal få barn til å spise mer grønt (forskning.no)
7. Increase intake of vegetables among children; Deltar i et grønnsakprosjekt; interview with Anne Lene Kristiansen at national radio 2015**;** Den som spiser gulrøtter ... – NRK Vestfold og Telemark – Lokale nyheter, TV og radio
8. Increase intake of vegetables among children; interview with Nanna Lien in local newspaper. Vil ha mer grønnsaker til barna (sandeavis.no)
9. Mat og måltider i barnehagen - Helsedirektoratet

[University of Oslo, Institute of Basic Medical Sciences] [case number 4]

Institution: University of Oslo, Faculty of Medicine
Administrative unit: Institute of Basic Medical Sciences, Department of Behavioural Medicine
Title of case study: Well-being among students and professionals
Period when the underpinning research was undertaken: 1993-2022
Period when staff involved in the underpinning research were employed by the submitting institution: 1995-2022
Period when the impact occurred: 2012-2022

1. Summary of the impact (indicative maximum 100 words)

The NORDOC and NORVET studies have yielded new knowledge that has informed interventions and preventive measures both in undergraduate and postgraduate training. The NORVET study has had a particularly large impact in the general media from 2020-22, and there has been increased awareness about work stress in trainees in medicine and veterinary medicine in Norway. Two important intervention schemes, an RCT of Mindfulness based stress reduction in medical and psychology students, and the Villa Sana intervention to reduce burnout in physicians, have proved effective in long-term follow-up studies, and these studies have had impact in both policymaking and health.

2. Underpinning research (indicative maximum 500 words)

The nationwide NORDOC study (The Longitudinal Study of Norwegian medical students and doctors) involves 1052 medical students in two cohorts, who were followed up in 7 waves during 25 years until 2019. This has resulted in about 50 original publications and altogether 10 PhDs. Five PhDs were awarded during the impact period: Grotmol 2012, Solberg 2017, Hertzberg 2018, Mahmood 2019, and Belfrage 2020. Major findings were a decline in work stress and severe depressive symptoms during the years of the career, with the exception that work home conflict is enduring and that this factor also predicts burnout from 10 to 15 years after medical school. Perceived skills in history taking and writing medical records are an independent predictor of perceived mastery of clinical work 20 years later. Low levels of neuroticism increased the risk of experiencing workplace violence from patients during 20 years follow-up. For NORDOC summary see: Facebook: @docsinrush

The NORVET study involves all 4000 Norwegian veterinarians approached in a postal survey in 2020 with a focus on mental health and individual and work-related factors, but in particular on serious suicidal thoughts and professional help seeking, using several similar measures to those in the preceding NORDOC. The NORVET study found a relatively high rate of suicidal ideation (20% thoughts and 5% serious suicidal thoughts) and reported work problems to be associated with such thoughts. Only half of those with perceived mental health treatment needs had sought help, and this applied even to those with serious suicidal thoughts.

Both NORDOC and NORVET had relatively high response rates, NORDOC, 60-80%, and NORVET, 75%. They are among the most representative studies ever in these professions, in particular with a relatively high rate of female participants.

The NORDOC studies has informed two interventions with long-term follow-up. These studies are also collaborations with other national institutions.

(1) *The Villa Sana study* is a follow-up of physicians seeking a counselling intervention for burnout at Modum Bad Hospital (N=227), and the Institute for Research of the Medical Profession (IRMP), Oslo. A major finding here was a reduction in burnout at 1 and 3 years follow-up, but also the importance of full time sick leave after the intervention as predictive.

(2) *An RCT of mindfulness training* in psychology and medical students (N=288) was a collaboration between the Department, The Institute of Health and Society at our Faculty, and the University of Tromsø. This study had long-term follow-ups, 4 and 6 years, and found that possible mechanisms for the effect of mindfulness training seem to be an increase in active problem focused coping and a reduction in avoidance coping.

- **Professor Reidar Tyssen** (2012-2022) leads the research team of Health Professions at the Department and has directed the NORDOC survey during the impact period. He received grants for the NORVET study for **PhD Helene Seljenes Dahlum** who was with our department (2019-2022). Other members: **Professor Erlend Hem** (2018-2022), p**rofessor emeriti Per Vaglum** (2012-2018), **Tore Gude** (2012-2020) and **Torbjørn Moum** (2012-2022). Dr **Karin Isaksson Rø, had her PhD** with us and affiliated member of the team.
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3. References to the research (indicative maximum of six references) Authors in bold are in positions/associates at the Dept Behav Med/Institute of Basic Medical Sciences at the time of the research

Isaksson Rø KE, Tyssen R, Gude T, Aasland OG: Will sick leave after a counselling intervention prevent later burnout? A 3-year follow-up study of Norwegian doctors. *Scandinavian Journal of Public Health* 2012; 40:278-285

Hertzberg TK, Rø KI, Røvik JO, Ekeberg Ø, Gude T, Moum T, Vaglum P, Tyssen R. Work-home interface stress: and important predictor of emotional exhaustion 15 years into a medical career *Industrial Health* 2016; 54:139-58 (accept. online 2015)

De Vibe M, Solhaug I, Rosenvinge J, **Tyssen R**, Hanley A, Garland E. Six-year positive effects of mindfulness-based intervention on mindfulness, coping and well-being in medical and psychology students: results from a randomized controlled trial. *PLoS One*. 2018, 24;13(4):e0196053

Nøland ST, Taipale H, Mahmood JI, Tyssen R. Analysis of Career Stage, Gender, and Personality and Workplace Violence in a 20-Year Nationwide Cohort of Physicians in Norway. *JAMA Netw Open*. 2021 Jun 1;4(6):e2114749

Dalum HS, Tyssen R, Hem E. Prevalence and individual and work-related factors associated with suicidal thoughts and behaviours among veterinarians in Norway: a cross-sectional, nationwide survey-based study (the NORVET study). *BMJ Open*. 2022 Jan 3;12(1):e055827.

Dalum HS, Tyssen R, Moum T, Thoresen M, Hem E. Professional help-seeking behaviour for mental health problems among veterinarians in Norway: a nationwide, cross-sectional study (The NORVET study). *BMC Public Health*. 2022 Jul 7;22(1):1308. doi: 10.1186/s12889-022-13710-y.

4. Details of the impact (indicative maximum 750 words)

Education and training in medicine and school

Our team has made a major contribution to research in medical education. Tyssen (26 articles), Vaglum (25) and Gude (16) are the three most productive authors of such research in Norway. For instance, Belfrage et al found the importance of communication skills training in medical school. Perceived medical recording skills (including history taking) at the end of medical school predicted perceived mastery of clinical work 10 and 20 years later, also when controlled for personality and other factors.

Tyssen has also been at the editorial board on BMC Medical Education (Associate Editor) 2009-2018 and a member of the Research Committee in AMEE (Association of Medical Education Europe) 2014-2018.
In 2015, OECD invited Tyssen to the Expert Panel of the ongoing programme for upper secondary school, OECD Education 2030, much because of research on mindfulness training in students. In the panel and Focus group 2B, he emphasized the importance of flexibility and change in a VUCA world (Volatile-Uncertain-Complex-Ambiguous). "Transformative competencies" (creating new value, taking responsibility, and reconciling tensions and dilemmas) have become an important part of the Learning compass developed by this OECD programme.

Physician personality and well-being

NORDOC is one of very few projects in epidemiology that included a measurement of personality traits (BCI-36). NORDOC studies have shown the independent predictive validity of personality for mental health and work. Tyssen is the only Non-American author in a Springer textbook about Physician Mental Health and Well-being with a chapter on Personality traits. Tyssen was also the only European invited to the summit "Joy in Medicine" arranged by the American Medical Association in 2016. The burnout rate among physicians in the USA is high, but they lack longitudinal research such as NORDOC.
The Villa Sana programme runs week-long schemes for doctors and their partners with burnout, and our research team has been active in studying the effects of this programme (Isaksson Rø, Gude, Tyssen, Vaglum) in collaboration with the IRMP. The lectures at Villa Sana refer to many findings from the NORDOC studies, both with respect to the preventive importance of colleague support and balancing life, and in addition, the programme includes mindfulness training.
Both Isaksson Rø and Tyssen have given several plenary talks at national conferences for physicians, and they have given several interviews to the general media in the period. As such, they have had an important impact on the increased awareness about work and mental health among physicians in Norway. At the end of the impact period, there was an increased number of physicians seeking support at Villa Sana, particularly young female physicians.
Tyssen has given plenaries at several international conferences, the last two in 2019: a plenary at YES (Young European Scientists) in Porto and a keynote at the 21st Nordic Congress of General Practice, Aalborg, "Well-being for GPs and practice staff"
A NORDOC study published in JAMA Network Open (IF=13.8) in 2020 received much attention also in general media, news report in NRK P1, other newspapers, and a podcast with the Norwegian Medical Association ("Stetoskopet")

Veterinarians' mental health and well-being

There is a known increased risk of suicide among veterinarians, even higher than that among physicians in many countries. Dr. Dalum, who is a veterinarian herself, has been very active in the media and contributed to about 50 newspaper reports. Even before the start of her PhD project she gathered 350.000 NOK of grants for running expenses from veterinary organization and the industry. She headlined "Dagsrevyen" in NRK TV and a large report in Dagens Næringsliv, a recommended Norwegian newspaper.
The finding that one out of three Norwegian vets finds that life is not worth living was the second most read report on "forskning.no" from the University of Oslo in 2022. She has also contributed to several podcasts, among those in USA and Australia.
She and a colleague has started Psycho-Vets. They tour both in Norway and abroad to disseminate knowledge about prevention of burnout.
Another important impact is the implementation of mental health and communication skills training in the curriculum for veterinary students in Norway.

5. Sources to corroborate the impact (indicative maximum of ten references)

Medisinsk pedagogikk som forskningsfelt i Norge – en bibliometrisk studie.
Kvernenes M, Armitage CS, Almeland SK, Birkeli CN.Tidsskr Nor Laegeforen. 2023 Nov 28;143(18). doi: 10.4045/tidsskr.23.0398

OECD Education 2030 Learning compass: https://www.oecd.org/education/2030-project/teaching-and-learning/learning/learning-compass-2030/OECD_Learning_Compass_2030_concept_note.pdf

Tyssen R. Personality traits. In: KJ. B, MB. R, editors. Physician Mental Health and Well-being: Research and Practice. Integrating Psychiatry and Primary Care. USA: Springer; 2017. p. 211-34. https://link.springer.com/chapter/10.1007/978-3-319-55583-6_10

NRK P1 12.06.2021: Vold mot leger: https://www.nrk.no/norge/ny-studie_-hver-syvende-lege-har-blitt-angrepet-av-pasient-1.15570669

Suicide among veterinarians – Headline Dagsrevyen NRK : Dagsrevyen 21 – 10. desember 2020 · Selvmord blant veterinærer – NRK TV

Mange veterinærer sliter med selvmordstanker - Institutt for medisinske basalfag (uio.no)

Flynn's Talk | Ep 23 - Psycho Vets; the NORVET Project | Flynn's Talk (podbean.com)

Fighting Burnout Across the Globe (galaxyvets.com)

Hverdagspsyken: Veterinærer og psykisk helse m/ Maria Tysnes, Reidar Tyssen & Helene Seljenes Dalum on Apple Podcasts

Veterinærer sliter med tanker om selvmord og at livet ikke er verdt å leve (khrono.no)

[University of Oslo, Institute of Basic Medical Sciences] [case number 5]

Institution: University of Oslo (UiO)
Administrative unit: Institute of Basic Medical Sciences (IMB)
Title of case study: Models for the management of the covid pandemics in Norway
Period when the underpinning research was undertaken: 2015-2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2015-2022
Period when the impact occurred: 2020-2023

1. Summary of the impact

OCBE's research has been essential for the management of the covid pandemic in Norway. From the very start of the pandemic, we have developed and run our mathematical and statistical models to (1) estimate the reproduction number R in each region of Norway, (2) to perform prediction of the number of hospitalised covid patients; and (3) to perform what-if studies on the efficacy of interventions (vaccines, lockdown and re-opening strategies …). Our results were regularly used by the National Institute of Public Health (NIPH), the Health Directorate, hospitals, national and local governments, to take key decisions. During the pandemic, OCBE and NIPH had a joint modelling team constantly on duty, also responsible for communication with the public (weekly reports) and the media. Norway's handing of the pandemic is recognised as very successful, and this is also thanks to our contribution.

2. Underpinning research

State-of-the-art by 2015: *Stochastic compartmental metapopulation models* were known to be useful for situation awareness, forecasting and scenario simulation in epidemics. Informed by multiple sources of data (incidence of cases, hospital admissions), they allow to quantify the strength of viral transmission (reproduction number R), to estimate the number of infected individuals, and to predict the future number of infected and of hospitalized patients. *Individual-based models* were known as mathematical representation of an interacting population, with their demography and transmission networks in different social layers (households, schools, workplaces).

Our contribution per 2019: OCBE and NIPH, within our sfi BigInsight, had projects and PhD students in models for epidemics, which turned out to be essential for our Covid work:

R1. We developed a new spatio-temporal stochastic model for the spread of an infection based on mobile phone mobility and a sequential Approximate Bayesian Computation (ABC) for efficient inference. (2019 PhD Solveig Engebretsen, then started at Norsk Regnesentral (NR).)

R2. We developed an individual-based model, reproducing the Norwegian population's sociodemography, representing households, hospitals and nursing homes, calibrated to 2008–2015 and applied to MRSA bacteria. (2019 PhD Francesco Di Ruscio, started at NIPH.)

Our contribution during the Covid pandemic 2020-2022: Already in February 2020, OCBE, NIPH, NR and Telenor formed the Oslo Covid-modelling group. Throughout the pandemic, our relentless efforts, built on expertise and new scientific findings, allowed us to produce essential modelling results for Norway. Below, key methods developed during this period, which were in daily use and turned out to be powerful instruments for epidemic management for Norway:

- We extended R1 to Norway, using the Norwegian Telenor mobile phone mobility data (updated every six hours during the whole pandemics).
- Real-time inference was crucial, with data arriving on Monday mornings and results required by Wednesday mornings. Existing algorithms couldn't handle time-piecewise constant reproduction numbers (changing every 2-3 weeks). To address this, we created a novel

sequential ABC, named split-seqABC, enabling efficient use of our stochastic metapopulation models with a high parameter count.

- Daily changing reproduction numbers are more precise than time-piecewise constant reproduction numbers. We developed a new model with daily-varying reproduction number, to quantify the viral transmission in real time. We proposed a state-space formalisation of the model and a sequential Monte Carlo approach which also runs in real-time.
- Throughout the COVID years, we routinely received specific inquiries from the government and others, involving decisions on optimal interventions. To address these what-if scenarios, we enhanced our individual-based model R2, dividing Norway into 13,521 cells, each with the actual population. The model incorporated various age-structured contact routes, such as community, household, school, and workplace, utilizing Telenor mobility data. This refined model proved instrumental in guiding decisions, including optimizing vaccination strategies and post-Omicron lockdown reopening. It stands as the most advanced individual-based model for Norway, surpassing the level of detail found in comparable models, such as the UK ones.
- In addition, we produced results on specific aspects of covid epidemiology, which had impact on the management of the pandemics. For example:
  - We compared Omicron's epidemic growth to Delta's, using December 2021 - January 2022 contact tracing data. We found increased Omicron susceptibility despite three-dose vaccination, with infected individuals efficiently spreading the virus, while three-dose vaccinated contacts had lower infection risk.
  - We criticised for major shortcomings in design and methodology, a randomised trial on Covid transmission in fitness centres in Oslo, suggesting that these were not a place of special spread.
  - We established an international multidisciplinary research group to develop a questionnaire for patients with or after covid disease, including long-covid, to assess their health-related quality of life. The questionnaire has been used in many clinical studies, and for example help to conclude that Baricitinib should not be used to treat Covid patients.

Our contribution after the Covid pandemic: We continue publishing our methods and findings, to document our work and to prepare for future pandemics. For example, our analysis revealed that mandating recommendations to reduce contacts did not result in fewer contacts compared to just recommendations. Consequently, less intrusive and costly non-mandatory measures may prove effective in Norway in the future.

Funding: BigInsight, NFR, Nordforsk; In-kind: UiO, NIPH, Telenor, NR; Supercomputing: UiO, Sigma2.

- Oslo Covid-modelling group, included:
• Birgitte Freiesleben de Blasio – NIPH and OCBE (20%) (leader)
• Arnoldo Frigessi – OCBE (leader)
• Francesco Di Ruscio – OCBE (PhD) and NIPH
• Solveig Engebretsen – OCBE (PhD) and NR.
• Chi Zhang – OCBE (PhD) and NIPH.
• David Swanson (OCBE)

- Contributors from OCBE in additional activities:
Jon Michael Gran, Marissa Erin LeBlanc, Morten Valberg, Corina Silvia Rueegg, Ragnhild Sørum Falk

3. References to the research

Engebretsen, S., Engø-Monsen, K., Aleem, M.A., Gurley, E.S., Frigessi, A. and De Blasio, B.F., 2020. Time-aggregated mobile phone mobility data are sufficient for modelling influenza spread: the case of Bangladesh. *Journal of the Royal Society Interface*, *17*(167), p.20190809.

Di Ruscio, F., Guzzetta, G., Bjørnholt, J.V., Leegaard, T.M., Merler, S. and De Blasio, B.F., 2019. Quantifying the transmission dynamics of MRSA in the community and healthcare settings in a low-prevalence country. *Proceedings of the National Academy of Sciences*, *116*(29), pp.14599-605.

Engebretsen, S., Diz-Lois Palomares, A., Rø, G., Kristoffersen, A.B., Lindstrøm, J.C., Engø-Monsen, K., Kamineni, M., Hin Chan, L.Y., Dale, Ø., Midtbø, J.E. and Stenerud, K.L., Di Ruscio, F., White, R., Frigessi, A., De Blasio, B.F., 2023. A real-time regional model for COVID-19: Probabilistic situational awareness and forecasting. *PLOS Computational Biology*, *19*(1), p.e1010860.

Storvik, G., Diz-Lois Palomares, A., Engebretsen, S., Rø, G.Ø.I., Engø-Monsen, K., Kristoffersen, A.B., de Blasio, B.F. and Frigessi, A., 2023. A sequential Monte Carlo approach to estimate a time-varying reproduction number in infectious disease models: the Covid-19 case. With discussion. *Journal of the Royal Statistical Society* *Series A*, *186*(4), pp.616-632.

Chan, L.Y.H., Rø, G., Midtbø, J.E., Di Ruscio, F., Watle, S.S.V., Juvet, L.K., Littmann, J., Aavitsland, P., Nygard, K.M., Berg, A.S. and Bukholm, G., Kristoffersen, A.B., Engø-Monsen, K., Engebretsen, S., Swanson, D., Diz-Lois Palomares, A., Lindstrøm, J.C., Frigessi, A. De Blasio, B.F.,2023. Modeling geographic vaccination strategies for COVID-19 in Norway. Accepted by PLOS *Computational Biology*, available on *medRxiv*

Jalali, N., Brustad, H.K., Frigessi, A., MacDonald, E.A., Meijerink, H., Feruglio, S.L., Nygård, K.M., Rø, G., Madslien, E.H. and De Blasio, B.F., 2022. Increased household transmission and immune escape of the SARS-CoV-2 Omicron compared to Delta variants. *Nature Communications*, *13*(1), p.5706.

Kamineni, M., Engø-Monsen, K., Midtbø, J.E., Forland, F., de Blasio, B.F., Frigessi, A. and Engebretsen, S., 2023. Effects of non-compulsory and mandatory COVID-19 interventions on travel distance and time away from home, Norway, 2021. *Eurosurveillance*, *28*(17), p.2200382.

Günther, F., Brustad, H.K., Frigessi, A. and Britton, T., 2024. Quantifying the impact of social activities on SARS-CoV-2 transmission using Google mobility reports. Submitted to PNAS, available on *medRxiv*.

Valberg, M., Gran, J. M., Rueegg, C. S., & LeBlanc, M. (2022). Letter to the editor regarding "Covid-19 transmission in fitness centers in Norway-a randomized trial". *BMC public health*, *22*(1), 1-2.

4. Details of the impact

OCBE was a founder and key part of the Oslo Covid-modelling group: key scientific results originated from OCBE, De Blasio and Frigessi were joint leaders of the group, with their ex-PhD students fully active. The impact was during the whole pandemic (2020-2022) and continues today in terms of preparedness for future pandemics. We were part of the NIPH pandemic management during the whole period, with responsibility for all modelling and predictions. The groups included about 15 researchers, including system and data engineers and epidemiologists, in addition to us statisticians. We were responsible for all methodology and algorithms, including weekly runs. Typically, our week started Monday at 8 am, when we froze the current data and started running our models, with results ready on Wednesday morning, when the report was prepared and submitted at 12:00. The modelling group had a meeting on Monday at 8:00 to decide what algorithms to run, on Wednesday to discuss results and on Friday to critically discuss and decide about needed improvements and planning the specialised reports, with hard work all week long, often including weekends: week after week, taking turns during vacations. In addition, we were responsible for communication with the public and media on all modelling and prediction. Meetings were also organised with health authorities that used our results and regularly with all the Nordic health authorities.
Our results reached immediately the health authorities and the government. The R-number was used in the public discourse, including uncertainties in estimating it. We experienced several times to hear the minister or the health directors to cite from our reports during press conferences on tv, just few hours after publication.

It is difficult to quantify the impact of our results. We dare to say that the beneficiaries is the whole Norwegian population, in terms of lives saved, reduced hospitalisation and illness, increased economical benefits. Norway as a country, has been able to manage the pandemics well, citing from the national Coronavirus Commission: "The country's population and its authorities have

handled the pandemic well overall. Norway has had one of Europe's lowest mortality rates, least restrictive infection control regimes and smallest declines in economic activity." One reason for this is the timeliness with which the national and the local governments have introduced interventions, to prevent the spread to explode. Our estimates and predictions were making this possible.

In order to give evidence of the importance of our work, we cite (our translations) from the report of the Coronavirus Commission, "Evaluering av pandemihåndteringen - Rapport fra Koronautvalget, 29. april 2022, for å gjennomgå og trekke lærdom fra koronapandemien i Norge", see section 12.3.5 on "Matematisk infeksjonsmodellering": "The situational understanding included mathematical modelling to estimate the disease burden of the epidemic in the coming weeks. Mathematical infection modelling was part of a comprehensive knowledge base, and NIPH's professional advice was always provided based on a holistic assessment. - By quantifying health loss and the burden of measures, the [modelling] group could highlight the societal consequences of reducing imported infections, differentiating measures geographically, or illustrating how characteristics of the virus variant influenced the choice of strategy. - Throughout the pandemic, projections of infection numbers, hospitalizations, and sick leave were crucial parts of the government's decision-making basis. The committee believes that such projections have clear utility as decision-making tools and should, therefore, be used in future crises."
The report in section 12.3.5 also includes two statements, here translated: Prime Minister Støre described his relationship with the models and that these results were useful in "challenging decision-makers to consider what to do with hospital capacity … that must be scaled up if [the predictions would] materialize." Espen Nakstad, Assistant Director of the Norwegian Directorate of Health, said on the role of models and predictions: "It has probably influenced political decision-makers, both locally and nationally, especially to see alarming models. It is important to say. But we have contributed to seeing it not as forecasts but possible scenarios. In that sense, I don't think it has always been very decisive."

In addition, we believe that a further impact of our work, of more long term and educational type, is the increased understanding by the general population of uncertainty quantification of predictions. We think that recognising the presence of uncertainty in decision making, can more generally help to increase the trust in government and politics – important in our current world.

OCBE also participated (with JM Gran) to the national commission responsible for deciding whether to stop the use of the Astra-Zeneca vaccine.

Mistakes we did in the covid period also made an impact, not only our correct results: we failed to explain well enough the assumptions of our three-week ahead predictions. These were such that we predicted the number of new covid hospitalisations, given that no new intervention would be implemented, and given that the population would continue to have the same mobility. Aftenposten, the main Norwegian newspaper, found that our predictions were pessimistic when the spread was increasing, and this was the main news on 15 June 2021. The reason for this difference was that when our predictions were alarming, then governments often would introduce additional restrictions and people would naturally behave more carefully, thus leading to less hospitalisations than predicted. We tried to explain this, but it was difficult.

Finally, we mention possible long term impacts of our work: We are preparing scientific papers which use the Norwegian and Nordic data to explain if and how interventions were useful, with the hope to increase knowledge for future situations. We mention that while NIPH had to cut their staff significantly, their modelling team was not reduced, recognising the importance of our work.

5. Sources to corroborate the impact

Weekly reports *Situational awareness and forecasting for Norway,* published from 14.4.2020 until 25 may 2023 (Tidligere publiserte rapporter):
https://www.fhi.no/ss/korona/koronavirus/koronavirus-modellering/
An example is here, for 24 November 2022:

https://www.fhi.no/contentassets/e6b5660fc35740c8bb2a32bfe0cc45d1/vedlegg/nasjonale-og-regionale-rapporter/2022-11-24-national_regional_model_22.pdf

The NIPH published also a weekly report which always included a summary of our results, which then were seen in a global perspective ("Alle ukerapporter 2020-2023", in Norwegian) https://www.fhi.no/publ/statusrapporter/luftveisinfeksjoner/#alle-ukerapporter-2020-2023

Example of report prepared to answer a specific question of the government, here on the possible vaccination of children between 12 and 15 years (in Norwegian), 26 August 2021: https://www.fhi.no/contentassets/3596efb4a1064c9f9c7c9e3f68ec481f/2021-09-02-oppdrag-45_vedlegg-2_modelleringsrapport_rettet.pdf

Example of report where modelling was a major component: Socio-economic assessment, 15 February 2021, see for example tables V.1 and V.7, among many results from our models: https://www.fhi.no/contentassets/3596efb4a1064c9f9c7c9e3f68ec481f/2021-09-02-oppdrag-45_vedlegg-2_modelleringsrapport_rettet.pdf

Example of impact of our quality-of-life questionnaire, to stop using a certain treatment: https://www.helsedirektoratet.no/veiledere/koronavirus/vaksiner-smittevernutstyr-og-legemidler/legemiddelbehandling-behandling-av-covid-19/bruk-av-baricitinib-olumiant

Selection from the media (in Norwegian):

- Into the Unknown, Klassekampen, 17 March 2020: https://klassekampen.no/utgave/2020-03-17/inn-i-det-ukjente
- The FHI expert does not think we will get the R-number below 1 again, NRK, 24 march 2021, https://www.nrk.no/norge/fhi-ekspert-tror-ikke-vi-far-r-tallet-under-1-igjen-1.15431839
- Aftenposten makes mistakes on forecasts. Again and again. Aftenposten, 18 June 2021, https://www.aftenposten.no/meninger/kronikk/i/7KbAKo/aftenposten-bommer-om-prognoser-igjen-og-igjen, answer to the article on Aftenposten of 15 June 2021: https://www.aftenposten.no/norge/i/0KLBLG/prognosene-bommet-fullstendig-paa-antallet-pasienter-igjen-og-igjen
  Posted on social media (17.000 impressions; Frigessi had 1500 followers during the pandemics) https://x.com/freeges/status/1472596466686386186?s=43
- More recently: Mandates during the pandemic had a greater effect in large cities, Finansavisen, 1 may 2023, https://www.finansavisen.no/samfunn/2023/05/01/8004900/pabud-under-pandemien-hadde-storre-effekt-i-store-byer?zephr_sso_ott=Oq3Qk7
- In English: COVID-19: The Norwegian model, The UNESCO Courier, 15 December 2022, https://courier.unesco.org/en/articles/covid-19-norwegian-model

During the pandemic, we gave many ZOOM presentations, including for example:

- Alan Turing Institute, London, 17 March 2022: https://www.turing.ac.uk/people/guest-speakers/arnoldo-frigessi
  https://www.turing.ac.uk/events/probabilistic-approach-situation-awareness-and-forecasting-covid-19-pandemics-norway
- Data Science in the Post-Covid World, University of Helsinki, 11 May 2021 https://www.helsinki.fi/en/faculty-science/news/hidata-webinar-data-science-post-covid-world-11-may-2021

"Evaluering av pandemihåndteringen - Rapport fra Koronautvalget, oppnevnt ved kongelig resolusjon 29. april 2022 for å gjennomgå og trekke lærdom fra koronapandemien i Norge" https://www.regjeringen.no/contentassets/b1dace9390054c85a5a87c7bbf1bc384/no/pdfs/nou20232320230016000dddpdfs.pdf

Camilla Stoltenberg, director of NIPH, thanks BigInsight for the work during Covid times, in Norwegian, subtitled; her video is the first linked in this page: https://www.biginsight.no/news/2023/11/21/biginsight-celebration-day-was-fun

Impact case guidelines

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Timeframes

- The impact must have occurred between 2012 and 2022
- Some of the underpinning research should have been published in 2012 or later
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Page limit

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Maximum number of cases permitted per administrative unit

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Naming and numbering of cases

Please use the standardised short name for the administrative unit, and the case number for the unit (1,2,3, etc) in the headline of the case. Each case should be stored as a separate PDF-document with the file name: [Name of the institution and name of the administrative unit] [case number]

Publication of cases

RCN plans to publish all impact cases in a separate evaluation report. By submitting the case the head of the administrative units consents to the publication of the case. Please indicate below if a case may not be made public for reasons of confidentiality.

If relevant, describe any reason to keep this case confidential:

Please write the text here

[University of Oslo _ The Centre for Molecular Medicine Norway] [1]

Institution: University of Oslo
Administrative unit: The Centre for Molecular Medicine Norway
Title of case study: Drug development for ischemia-reperfusion injury in myocardial infarction
Period when the underpinning research was undertaken: 2007 to 2020
Period when staff involved in the underpinning research were employed by the submitting institution: Kjetil Tasken - Director - 2007 to 2018 Ana Isabel Costa Calejo - Post-doctoral fellow - 2013 to 2019 Birgitte Lygren - Post-doctoral fellow - 2008 to 2011 Ellen Østensen - PhD fellow - 2012 to 2019 Jens Prebens Morth - Group Leader - 2010 to 2019
Period when the impact occurred: 2016 - onwards

1. Summary of the impact (indicative maximum 100 words)

In this case, we present how basic research in understanding molecular mechanisms in cardiovascular disease can lead to identifying a drug target. The work undertaken by the research group, from mechanistic studies to the development of a small molecule showing cardioprotective effect in rats with ischaemia-reperfusion injury, led to the establishment of a pharmaceutical company, SERCA Pharmaceuticals AS. A co-development agreement was further established with Cadila, an Indian FDA-approved company, to open opportunities for clinical trials.

2. Underpinning research (indicative maximum 500 words)

Heart attack, also known as myocardial infarction, is a major health concern globally. According to the World Health Organization, in 2017, an estimated 17.9 million people died from cardiovascular diseases, representing 31% of all global deaths. Out of these, heart attacks were responsible for nearly 85% of deaths. If the coronary artery is blocked, a procedure known as a percutaneous coronary intervention (PCI) may be performed where a catheter is threaded into the blocked artery to open it up. After PCI, Ischemia-reperfusion (IR) injury, which triggers additional damage such as an increase of lesions and cell dysfunction, with an increased risk of arrhythmia, can occur when blood supply is restored. Understanding the mechanisms behind IR injury is crucial in developing therapeutic strategies to prevent or minimise tissue damage after myocardial infarction.

A key protein in normal cardiac function is the Sarcoplasmic/Endoplasmic Reticulum Calcium ATPase 2 (SERCA2). It is an ATP-driven pump embedded in the sarcoplasmic or endoplasmic reticulum (SR/ER) membrane. It is responsible for the active transport of calcium ions (Ca^{2+}) from the cytosol into the SR/ER lumen. Regulation of SERCA2 activity is essential for normal cardiac function, and phospholamban (PLN), a regulatory protein, can inhibit SERCA2 in its non-phosphorylated form, reducing calcium uptake into the SR and consequently affecting muscle relaxation. Conversely, when PLN is phosphorylated, it dissociates from SERCA2, increasing the pump's activity.

AKAP18, a member of the A-Kinase Anchoring Proteins (AKAP) family, plays a significant role in regulating calcium re-uptake into the sarcoplasmic reticulum, a key component of muscle cell

relaxation and contractility. It forms a signalling complex by binding to protein kinase A (PKA) and the enzyme PLN, creating an efficient and localised signalling environment. The phosphorylation of PLN induced by PKA inhibits its function, which is to restrain the action of SERCA2, so it enhances SERCA2 activity, accelerating the re-uptake of Ca2+ to enhance muscle relaxation and subsequent contraction. In 2007, the researchers showed that, by using genetically modified mouse models, disruption of AKAP-PLN complex formation impaired Ca2+ transport and further signalling in heart cells [1]. This work then led to further outputs in 2008 [2] and 2015 [3], where small peptide molecules were investigated to target protein interactions within the AKAP-PLN complex [4]. The work was supported by a study using crystallographic methods showing that when malonate binds to the nucleotide-binding site of AKAP18γ/δ, it induces a unique conformational state not previously seen in this protein. It suggested that trapping AKAP18γ/δ in this unusual conformation by small molecules like malonate could be a novel strategy for therapeutic interventions targeting SERCA2 to improve cardiac function in IR injury [5]

The research was performed between 2007 to 2016 by the following key individuals: Kjetil Tasken (director, 2007 to 2018), Ana Isabel Costa Calejo (post-doctoral fellow, 2013 to 2019), Birgitte Lygren (post-doctoral fellow, 2008 to 2011), Ellen Østensen (PhD fellow, 2012 to 2019) and Jens Prebens Morth (group leader, 2010 to 2019).

3. References to the research (indicative maximum of six references)

[1] Lygren B, Carlson CR, Santamaria K, Lissandron V, McSorley T, Litzenberg J, Lorenz D, Wiesner B, Rosenthal W, Zaccolo M, Taskén K, Klussmann E. AKAP complex regulates Ca2+ re-uptake into heart sarcoplasmic reticulum. EMBO Rep. 2007. doi: 10.1038/sj.embor.7401081. https://www.embopress.org/doi/full/10.1038/sj.embor.7401081

[2] Lygren B, Taskén K. The potential use of AKAP18delta as a drug target in heart failure patients. Expert Opin Biol Ther. 2008. doi: 10.1517/14712598.8.8.1099. https://www.tandfonline.com/doi/full/10.1517/14712598.8.8.1099

[3] Calejo AI, Taskén K. Targeting protein-protein interactions in complexes organized by A kinase anchoring proteins. Front Pharmacol. 2015. doi: 10.3389/fphar.2015.00192. https://www.frontiersin.org/articles/10.3389/fphar.2015.00192/full

[4] Patent: SERCA2-PDE3A Interaction Peptides And Uses Thereof, 2015: https://patents.google.com/patent/WO2015181631A1/en

[5] Bjerregaard-Andersen K, Østensen E, Scott JD, Taskén K, Morth JP. Malonate in the nucleotide-binding site traps human AKAP18γ/δ in a novel conformational state. Acta Crystallogr F Struct Biol Commun. 2016. doi: 10.1107/S2053230X16010189. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4973299/

4. Details of the impact (indicative maximum 750 words)

The research described earlier significantly contributed to knowledge by identifying and detailing the protein interactions involving SERCA2 in calcium transport and cardiac functions. The publication of this knowledge contributed to more than 200 citations and 5 patents. The research work involved collaborators in Germany, Italy, and the USA. The work was disseminated through the media with the help of the communications team at the administrative unit's institution. It generated collaboration with the healthcare sector, primarily OUH.

Importantly, the innovative aspect of the research generated interest. One of the main contributors, Ana Isabel Costa Calejo, secured a place in the innovation scheme, SPARK Norway, to develop a novel therapy for ischaemic reperfusion injury. This work led to establishing SERCA Pharmaceuticals AS with private investment to the value of 7.9 million NOK (Inven2 and Sarsia Seed being the biggest investors). The company entered in 2018 a co-development agreement with Cadila Pharmaceuticals - an FDA-approved Indian Pharma company with some 6000 employees. The development agreement with Cadila Pharmaceuticals was signed in New Delhi, overseen by the Prime Minister of Norway, Erna Solberg, during her official visit to India in 2019.

With researchers moving on from the administrative unit due to the EMBL-recruitment model and to career opportunities, the outcome and impact of the work originally undertaken at the administrative are being furthered out-with the unit. The SERCA Pharmaceuticals company continues to raise funds to develop molecular and clinical trials. In 2020, the company raised 33 million NOK (16 million NOK from RCN) to undertake further projects.

In summary, the research conducted at the administrative unit was pivotal in developing 13-M, a novel small-molecule drug. This drug, created by Serca Pharmaceutical AS, is currently in preclinical stages and is aimed at treating acute myocardial infarction in patients eligible for PCI. Cadila Pharmaceuticals is investigating the drug's safety, pharmacokinetics, and ADME (Absorption, Distribution, Metabolism, and Excretion) profiles, while pharmacological studies in animal models are underway at European Contract Research Organizations under Serca Pharmaceutical's direction. Thus, the impact of this original work can further be measured by the contribution to the pharmaceutical industry in Norway and internationally, with the potential for improved patient treatment.

5. Sources to corroborate the impact (indicative maximum of ten references)

Innovation project SPARK:

- https://www.uio.no/english/research/strategic-research-areas/life-science/norway-life-science-conference/oslo-life-science-2018/video/spark/130218_uio_anaisabelcostacolejo.mp4?vrtx=view-as-webpage

SERCA Pharmaceutical AS:

- https://sercapharmaceuticals.com/rd/
- https://sercapharmaceuticals.com/myocardial-infarction/

SERCA Pharmaceuticals AS agreement with Cadila:

- https://www.med.uio.no/ncmm/english/news-and-events/news/2019/research-by-tasken-group-at-the-heart-of-internati.html
- https://www.ous-research.no/home/ous/news/19189
- https://www.cadilapharma.com/news-release/cadila-inks-agreement-with-norway-based-serca-pharmaceuticals-for-better-treatment-of-heart-patients/

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If relevant, describe any reason to keep this case confidential:

Under "Sources to corroborate the impact", we have provided the Disclosure of Invention (DOFI) title and number, and the executive summary. For confidentiality reasons, the full DOFI is not provided. When the Impact Case is being published, the removal of the executive summary would be appreciated.

Please note that the consultancy agreement with Sanofi cannot be disclosed for privacy reasons.

[University of Oslo _ The Centre for Molecular Medicine Norway] [2]

Institution: University of Oslo

Administrative unit: The Centre for Molecular Medicine Norway

Title of case study: Developing a diagnostic process and a new pathway for treating rare immune disorders.

Period when the underpinning research was undertaken: 2012 - 2022

Period when staff involved in the underpinning research were employed by the submitting institution:

Janna Saarela: 2019 - now
Emma Haapaniemi: 2019 - now
Monika Szymanska: 2019 - now
Johanna Marianna Lehtonen: 2020 - now
Inkira Soppa: 2020
Ganna Reint: 2017 - 2022
Zhuokun Li: 2019 - 2023
Katariina Mamia: 2019 - now

Period when the impact occurred: 2018 - 2022

1. Summary of the impact (indicative maximum 100 words)

Understanding the genetic and molecular basis of rare immune diseases can ultimately improve patients' quality of life and outcomes. The research undertaken here, from basic molecular research to implementation in the clinical environment, contributes to improved diagnostics and personalised treatments, including the development of gene therapies. The outcome of these studies is the possibility of targeted interventions for patients displaying rare immune diseases, including developing novel therapeutical technology such as using CRISPR/Cas9 and advice on drug repositioning.

2. Underpinning research (indicative maximum 500 words)

Inborn errors of immunity (IEI) are typically caused by damaging germline variants in single genes (i.e., they are monogenic diseases). IEIs are a subset of rare diseases characterised by abnormal or absent immune system function, many of which are life-threatening. Individuals with IEIs are more susceptible to infections, autoimmune conditions, dysregulated immune responses, and cancer. While individually rare, the aggregated number of patients with an IEI represents a significant health burden worldwide (3.5% to 5.9% of the worldwide population is affected). This rate equates to an estimated 300 million individuals, with 220,000 cases in Norway. The diagnostic rate of IEI patients is among the lowest, with the diagnostic rate even lower than that of rare diseases in general, with only 25% of children and less than 10% of adults receiving a definitive diagnosis. However, securing a molecular diagnosis in patients with rare diseases provides major benefits to the patients, their families, health care and society: end of time-consuming and expensive diagnostic odyssey, knowledge-based prognosis and genetic counselling for the family, and selection of and access to more efficient/targeted treatments.

Researchers at NCMM have focused on identifying novel genetic causes for IEIs to shed light on the mechanisms of the diseases and to increase the diagnostic yield. Despite over 300 novel genes described since 2012, a large proportion of IEI-causing genes are yet to be identified. Characterising rare genetic defects leading to immune dysfunction provides an understanding of the function of critical molecules of the human immune system and molecular mechanisms underlying the cellular defects, and enables the development of novel therapeutic approaches.

Since 2012, the researchers have discovered several gene defects causing IEI. These include DIAPH1, identified through genome sequencing and the application of CRISPR-Cas knockout technology in healthy peripheral blood mononuclear cells [1]. Another significant gene, NFKB1, was studied using genetic linkage analysis, next-generation sequencing, functional and immune signalling analyses of NFKB1 and its mutated alleles [2].

Improving the understanding of the molecular aetiologies underlying IEI opens up the potential of reversing disease processes by targeting the key driving pathways. The increasing numbers of available therapeutics have expanded the repertoire of drugs that can be repurposed for conditions other than the originally designed indications [3]. While pharmacologic therapies primarily dampen unwanted immune responses or activate the remaining functions, several IEI disorders can be cured by cellular therapies, such as hematopoietic stem cell transplantation (HSCT) and gene therapy.

The CRISPR-Cas9 gene-editing technology can introduce custom changes in diverse genomic landscapes. The work undertaken by the researchers has been to investigate ways to render the technology more efficient and safer for patient use [4-5]. As part of the team, a paediatric immunologist from Oslo University Hospital, contracted at 50% at NCMM, together with clinicians from all the university hospitals in Finland, facilitated access to patient samples, enabling the researchers to evaluate the outcome of the CRISPR technology *ex-vivo*.

The research presented here was undertaken by the following key individuals at NCMM Janna Saarela (director, 2019 - onwards), Emma Haapaniemi (group leader, 2019 - onwards), Monika Szymanska (head engineers, 2019 - onwards), Johanna Marianna Lehtonen (research assistant, 2020 - onwards), Inkira Soppa (MSc student, 2020), Ganna Reint (PhD fellow, 2017 - 2022), Zhuokun Li (PhD fellow, 2019 - 2023) and Katariina Mamia (PhD fellow and researcher, 2019 - now).

The work was undertaken collaboratively with Meri Kaustio, Henrik Almusa and Anna-Maija Sulonen, scientists from FIMM (Institute for Molecular Medicine Finland).

3. References to the research (indicative maximum of six references)

[1] Kaustio M, Nayebzadeh N, Hinttala R, Tapiainen T, Åström P, **Mamia K**, Pernaa N, **Lehtonen J**, Glumoff V, Rahikkala E, Honkila M, Olsén P, Hassinen A, Polso M, Al Sukaiti N, Al Shekaili J, Al Kindi M, Al Hashmi N, Almusa H, Bulanova D, **Haapaniemi E**, Chen P, Suo-Palosaari M, Vieira P, Tuominen H, Kokkonen H, Al Macki N, Al Habsi H, Löppönen T, Rantala H, Pietiäinen V, Zhang SY, Renko M, Hautala T, Al Farsi T, Uusimaa J, **Saarela J**. Loss of DIAPH1 causes SCBMS, combined immunodeficiency, and mitochondrial dysfunction. J Allergy Clin Immunol. 2021 Aug;148(2):599-611. DOI: 10.1016/j.jaci.2020.12.656
https://www.sciencedirect.com/science/article/pii/S0091674921003456?via%3Dihub

[2] Kaustio M, **Haapaniemi E**, Göös H, Hautala T, Park G, Syrjänen J, Einarsdottir E, Sahu B, Kilpinen S, Rounioja S, Fogarty CL, Glumoff V, Kulmala P, Katayama S, Tamene F, Trotta L, Morgunova E, Krjutškov K, Nurmi K, Eklund K, Lagerstedt A, Helminen M, Martelius T, Mustjoki S, Taipale J, **Saarela J**, Kere J, Varjosalo M, Seppänen M. Damaging heterozygous mutations in NFKB1 lead to diverse immunologic phenotypes. J Allergy Clin Immunol. 2017 Sep;140(3):782-796. DOI: 10.1016/j.jaci.2016.10.054.
https://www.sciencedirect.com/science/article/pii/S0091674917300532?via%3Dihub

[3] Keskitalo S, **Haapaniemi E**, Einarsdottir E, Rajamäki K, Heikkilä H, Ilander M, Pöyhönen M, Morgunova E, Hokynar K, Lagström S, Kivirikko S, Mustjoki S, Eklund K, **Saarela J**, Kere J, Seppänen MRJ, Ranki A, Hannula-Jouppi K, Varjosalo M. Novel TMEM173 Mutation and the Role of Disease

Modifying Alleles. Front Immunol. 2019 Dec 5;10:2770. DOI: 10.3389/fimmu.2019.02770. https://www.frontiersin.org/articles/10.3389/fimmu.2019.02770/full

[4] **Reint G., Li Z.,** Labun K.I., Keskitalo S., **Soppa I., Mamia K.**, Tolo E., **Szymanska M.**, Meza-Zepeda L.A., Lorenz S., **Cieslar-Pobuda A.**, **Hu X.**, Bordin D.L., **Staerk J.**, Valen E., Schmierer B., Varjosalo M., Taipale J. and **Haapaniemi E.** Rapid genome editing by CRISPR-Cas9-POLD3 fusion. Elife, 2021 Dec 13:10:e75415. DOI: 10.7554/eLife.75415. https://elifesciences.org/articles/75415

[5] **Haapaniemi E.**, Botla S., Persson J., Schmierer B.,Taipale J. CRISPR-Cas9 genome editing induces a p53-mediated DNA damage response. Nat Med, 2018 Jul;24(7):927-930. DOI: 10.1038/s41591-018-0049-z. https://www.nature.com/articles/s41591-018-0049-z

4. Details of the impact (indicative maximum 750 words)

Identification of novel gene mutations and increasing awareness of NGS technology to improve diagnosis of IEI:

The research described earlier has significantly improved the detection of relevant mutations to diagnose IEI more effectively. The Saarela group, under the umbrella of the Nordic-EMBL Partnership at NCMM and FIMM, and in collaboration with the FIMM sequencing unit and doctors treating IEI patients in all university hospitals in Finland, started a translational research project providing exome sequencing-based diagnostic services in 2012, before the service was available in any clinical laboratory in Finland. During 2012 - 2018, the analysis results were returned to the doctors providing over 100 molecular diagnoses for the patients, of which at least 7 have received an HSCT, one entered a clinical enzyme replacement trial, and for over 50%, a repurposed immune modifying treatment was tested. In 2018, the technology was transferred to the Helsinki University Hospital. Importantly, one of the trained researchers from the team was recruited to operate the platform and train the geneticists at the hospital unit. This shows the transferability of skills of the researchers between the labs and the clinic. The information about the new genes has been communicated to clinical laboratories and private companies providing sequencing-based diagnostics for IEI in Finland and Norway before being published. The work undertaken by the Saarela group has gained exposure to the public. Prof. Saarela has been invited to participate in podcasts on IEI and gene sequencing [1]. She serves as a rare disease expert for the Sanofi-Genzyme rare disease awareness program, as part of which she has given lectures on NGS technologies in rare disease diagnostics in Oslo, Bergen, and all major Finnish hospitals during 2018 - 2020. Moreover, the researchers are paving the way to enhancing diagnosis by exploring RNA biology in immune cells, which holds promise for identifying novel IEI-causing genes and disease mechanisms, potentially improving diagnostic capabilities.

A step closer to precision medicine:

The research underpinning this impact case remains ongoing. However, the identification of novel genes, combined with the design and optimisation of new protocols for gene editing, demonstrates the potential of precision medicine for treating and curing IEI. Indeed, the CRISPR-Cas9 gene-editing tool has been optimised for personalised therapy by the Haapaniemi group. A significant contribution to gene-editing protocols has been made by screening the effect of 450 DNA repair protein-Cas9 fusions on editing outcomes. As a result, the Cas9-POLD3 fusion has been shown to enhance gene editing by speeding up the initiation of DNA repair. This allows for faster and more efficient gene editing, reducing the risk of errors, increasing the safety of the technology. Importantly, optimising high-throughput protocols for efficient gene editing in T cells and hematopoietic progenitor stem cells is being pursued. To that effect, a disclosure of invention (DOFI) for “CRISPR-Cas9 T cell editing pipeline for correcting monogenic mutations” has been

recently filed by NCMM's researchers [2]. This could potentially lead to commercialisation of the technology in the future.

The work by the Haapaniemi group on new therapies for serious diseases in children was disseminated in the national newspaper Aftenposten [3], in the research magazine Apollon [4], and as a case study in NCMM's Annual Report [5], highlighting the societal impact of this work.

Consortium Participation:

Due to their work and expertise, the researchers are participating in international consortia such as the European Network on rare primary immunodeficiency, autoinflammatory and autoimmune diseases (ERN RITA) and ESID Genetics Working Party, ClinGen Immunology Clinical Domain Working Group (CDWG) Executive Committee and ClinGen SCID-CID Gene Curation Expert Panel (GCEP). An important development in the Oslo area, to come in 2023, is the Precision Immunotherapy Alliance (PRIMA), where NCMM's researchers will contribute to developing the next generation of precision immunotherapy [6].

5. Sources to corroborate the impact (indicative maximum of ten references)

[1] Podcast "It's in the genes" - Janna Saarela - https://thehematologypodcast.buzzsprout.com/1767939/8793934-it-s-in-the-genes

[2] DOFI Evaluation Report: DOFI 22087 "CRISPR-Cas9 T cell editing pipeline for correcting monogenic mutations":

EXECUTIVE SUMMARY
- The scientists have developed a streamlined CRISPR-Cas9 based pipeline for primary human T cells to enable rapid CRISPR tool discovery and safety validation for early-stage CRISPR gene therapy projects. Their innovative workflow enables customizable protocols for editing of monogenic mutations causing T cell defects in patients.
- The pipeline can be applied to several monogenic diseases affecting T cells, including rare primary immunodeficiency disorders, most of which are under-researched. There is also a potential for scaling up the production of the corrected T cells and the protocols for cell manufacturing.
- There is an unmet need and the platform has direct applicability in clinical use. Based on the above, Inven2 concludes to establish a commercialization project based on the DOFI.

[3] News items about new therapies for serious diseases in children: https://haapaniemilab.org/research-and-publications/aftenposten-article-ncmm/; original article in Norwegian: https://www.næringslivnorge.no/livsvitenskap/nye-terapier-for-alvorlige-sykdommer-hos-barn/

[4] Fikser sjeldne sykdommer ved å klippe og lime sammen gener *(Fixing rare diseases by cutting and gluing genes together)*, article in Norwegian: https://www.apollon.uio.no/artikler/2022/4_tema_crispr

[5] NCMM Case study: Translating CRISPR from the lab to the clinic: https://www.med.uio.no/ncmm/english/about/facts/annual-reports/ncmm_2022.pdf p.44-45

[6] Consortiums:https://esid.org/Working-Parties/Genetics-Working-Party; https://ern-rita.org/; https://clinicalgenome.org/affiliation/40081/; https://www.prima.uio.no/english/

Section A

Institution: The University of Stavanger (UiS)		
Title of case study: Breast Cancer School – An education arena for enhancing breast cancer survivors' quality of life based on patient participation and interaction with experts and peers		
Period when the underpinning research was undertaken: 2012-2020		
Details of staff conducting the underpinning research:		
Siv Tove Aunan Associate Professor Mail: siv.t.aunan@uis.no Tel.: +47 51 83 24 89	Britt Sætre Hansen Professor Mail: britt.s.hansen@uis.no Tel.: +47 51 83 42 56	Gry C. Wallgren Assistent Professor Mail: gry.c.wallgren@uis.no Tel.: +47 51 83 12 34
Period when the claimed impact occurred: 2014-2020		

Section B

1. Summary of the impact

UiS researchers at the Faculty of Health has identified the urgent need to develop an educational program for Breast Cancer (BC) survivors, which has by far the largest incidence among women in Norway. The educational program serves as an arena for learning from experts and fellow patients, which make cancer-affected people feel safe and motivated during and after receiving the treatment. Referring to as Breast Cancer School (BCS), the 2-day educational program has given rise to similar arenas for other types of cancer, including Prostate and Colorectal cancer, where all together have provided about 50 courses for more than 650 patients (as of the end of 2019) at the Patient Education Center, Stavanger University Hospital.

In addition to improving patients' quality of life through strengthening their psychosocial resilience and supporting their wellbeing, the cancer schools has enabled healthcare providers to tailor their support to individual patients' needs and adapt their communication throughout patient encounters during the entire treatment pathway. The particular research at UiS on follow-up and evaluation of these cancer schools has resulted in concrete changes in clinical practice related to effectively engaging with cancer survivors in the design and implementation of patient education programs.

2. Underpinning research

This case story is centered upon the work of Siv Tove Aunan and Britt Sætre Hansen at the Department of Quality and Safety in Health Care Systems, and Gry Ciekals Wallgren at the Department of Caring and Ethics, Faculty of Health Sciences, University of Stavanger. The story of Cancer Schools (CS) at UiS started back in 2012 when Siv Tove Aunan was carrying out her master's thesis on BC patients and their description of quality of life from diagnosis and through adjuvant treatment. This study has highlighted the critical role of providing individually tailored information to patients and creating meeting places for women in the same life situation [1]. In terms of clinical practice, the results have suggested that establishing a dedicated educational program will standardize the information transfer process occurring between patients and healthcare providers, and hence ensure the consistency of communication between these two groups.

Since the launch of the BCS as the first CS in Stavanger in the spring of 2014, Aunan and Hansen has been conducting follow-up surveys and investigations in order to evaluate the educational programs and contribute to the continuous improvement of CSs building upon the patients' own experiences. In one of these studies that was published in 2018, all BCS participants in the period 2014-2017 were

invited to join focus group interviews, where eventually 20 of them were recruited. Three focus groups containing six or seven participants were organized. They were women with early-stage BC receiving adjuvant treatment and were aged 20–70 years.

According to the content analysis in the above study, BCS is perceived as a balancing act between the need for and fear of information. Lectures from experts and meeting with fellow patients gave additional important information to BC survivors in general, though some of them has also expressed fear of receiving undesirable information or information overload as a reason for avoiding to join such educational programs [2]. Consequently, BCS addresses both a systematic and individual approach to information and communication representing expert information, support from fellow patients, and networking. On the one hand, BCS has proved to be successful in streamlining a systematic approach to information based on the expressed needs of the patients towards making them feel safe and providing them with predictability in an unpredictable life situation. The transition from no structure for cancer patient education to established CS has thus benefited both patients and health-care providers concerning knowledge exchange both within and between their peer groups. On the other hand, the focus group interviews pinpoint that BCS has led to improving the individualized approach to patient monitoring and therapy through continuity of care and staff availability. The interaction with patients during the 2-day program is indeed assisting health-care providers in terms of tailoring their support to individual patients' needs.

In another study, Aunan and Hansen focused on Prostate Cancer School (PCS) and explored how 16 Prostate Cancer (PC) survivors experienced information received specifically at the school and generally along their treatment pathway. This work corroborates the results of their previous study on BCS regarding the importance of a structured, yet informal patient education program that pave the way for effective communication between patients and their direct contacts in the healthcare system as well as with the interprofessional teams. The study also demonstrates that not only the information content of a patient education program but also its timing that affects the effectivity of such communication [3]. According to the PC survivors, PCS has encouraged communication and knowledge exchange about topics such as sexual dysfunction and urinary incontinence in post-treatment phase that are seldom discussed elsewhere. In addition, participants in this study underline the invaluable role of PCS in fulfilling their need for repeating information that they received earlier during diagnosis and early treatment, and that they should be given the possibility to partake in the education program when they feel ready to address the issues that may arise from the undergoing treatment.

Results from these follow-up studies has enabled the UiS researchers to secure funding from Folke Hermansens Fund for a research project on BC survivors' return to work where the amin objective is to identify the factors that may facilitate or hinder this process.

3. References to the research

[1] Aunan, S. T (2012). Livskvalitet hos kvinner med brystkreft under behandling (Master's Thesis). Retrieved from https://uis.brage.unit.no/uis-xmlui/bitstream/handle/11250/184178/Aunan%20Siv%20Tove.pdf?sequence=1&isAllowed=y

[2] Aunan S. T, Wallgren G. C, Saetre Hansen B. (2018) Breast cancer survivors' experiences of dealing with information during and after adjuvant treatment: A qualitative study. Journal of Clinical Nursing;28(15-16):3012-3020. doi: 10.1111/jocn.14700

[3] Aunan S. T, Saetre Hansen B, Wallgren G. C. (in press) The value of information and support: Experiences among patients with prostate cancer. Journal of Clinical Nursing

4. Details of the impact

BCS, and its offshoot education arenas for other types of cancer, support the Norwegian government's obligation for providing patient education to cancer survivors along their treatment pathway. The research underpinning the development and improvement of these CSs has yielded substantial and far-reaching impacts for three groups of beneficiaries: (a) cancer survivors and their families, (b) clinicians, and (c) administrators and directors in the healthcare sector.

Cancer survivors and their families. The educational programs of the CSs have been delivered to more than 650 patients at the Patient Education Center, Stavanger University Hospital (as of the end of 2019). Course evaluation data indicates that 85% of attendees said the course met their training needs, and many of them remark that every cancer patient should join the course. While providing information to the patients is a part of all treatment pathways in Norway, CSs have enabled systematic training where the focus is on interaction with patients and effective communication. As such, the biggest advantage with the latter is exchanging the knowledge so that the information is utilized by both the patients and the clinicians, which is completely different from just making a brochure and handing it out to the patients. In addition, CSs deliver quality assured (research-based) and to-the-point information to cancer survivors, in contrast to the wealth of flawed information that they are exposed to via social media, blogs, relatives etc.

From the start of the BCS, the aim was to create an arena that could not only inform cancer survivors about their diagnosis and treatment, but also enhance their knowledge about various aspects that affect their quality of life during and after the treatment. As mentioned by one participant in the BCS: "I am learning how important it is to give myself more priority and generally how to relax. BCS has motivated us to be more active and exercise on a regular basis, helped us value healthy nutrition and understand how BC influences our sexual function [A]". These variety in the educational programs of the CSs has raised cancer survivors' awareness of the benefits of self-management support for patients, made them aware of a range of welfare services available through the local experts, fellow patients and their networks.

In addition to the generic impact of the present CSs on cancer survivors diagnosed with any of the three types of cancer, some specific cancer groups report additional advantages for their participation in the educational programs. Men diagnosed with PC often feel very isolated as they are reluctant to talk to others about their condition, and as it is so rare, they do not encounter others who have experienced it. PCS has however created informal contacts between PC survivors where different concerns including signs and symptoms of the cancer, the treatment options, recovering from surgery, as well as several sensitive topics such as how to tell other people about their cancer, using the toilet, the effect on sex and relationships, and the impact of surgery on men's sense of masculinity and confidence are brought up. A participant in PCS reports how talking and sharing experiences with fellow PC patients can lead to changes in ways of thinking, thereby improving health and satisfaction: "When we get into a situation as now and have reduced sexual health, we lose some manhood in a way. If I can compare it to women who must remove a breast due to breast cancer, they talk about their challenges in debates and on TV. We are just starting to talk about our challenges now, … and this will help us to reframe our new life [B]".

Even though families of cancer survivors are not joining the CSs (this is indeed a deliberate preference for survivors themselves), they also benefit from the education programs as the patient has now access to a network that helps reduce his/her feelings of isolation, and thus releasing some burden and stress placed upon families whose full attention and energy need to be focused on the care of their patient [C]. This has then reduced the risk of suffering from severe mental illnesses such as

depression or anxiety disorder.

Clinicians. Thanks to a true engagement of front-line staff from a range of professional groups including oncology nurse, radiation therapist, oncologist, nutritionist, physiotherapist and sexologist, CSs are currently incorporated into the self-management support for several types of cancer patients. This engagement has led to quite a few gains for clinicians, including [D]:

- Raised their awareness about that the work they do regarding cancer treatment is connected and not isolated. The course provides the opportunity to get a good connection with other professional groups as well as to patients.
- Increased their insight on what it is like to be diagnosed with and to live with cancer, which has then enhanced how they deal with cancer patients in order to assure availability and continuity of care as important factors for improving cost effectiveness.
- Enabled smoother communication with cancer survivors so that the clinicians can get users' experiences as a prerequisite for developing the quality of their service. During the courses, they may receive questions that they have not thought about before, which turns to be essential for learning and updating themselves.

Administrators and directors in the healthcare sector. The research described above has documented that CSs has transformed the way information is shared and sought. Following the success of the present CSs, more and more directors in the other departments of the Stavanger University Hospital are contacting the Patient Education Center to develop equivalent courses for the patients [E]. This is basically due to the fact that this research has raised the awareness of healthcare administrators about how crucial it is to involve patients in the design, implementation and evaluation of educational programmes to be able to tailor their need for information and support.

5. Sources to corroborate the impact

[A] BC survivors that were interviewed in connection with study [2]
[B] PC survivors that were interviewed in connection with study [3]
[C] Norwegian Breast Cancer Society – local office in Stavanger
[D] Chief oncologist at the Department of blood and cancer diseases, Stavanger University Hospital
[E] Head of Patient Education Center, Stavanger University Hospital

Impact case guidelines

Each case study should include sufficiently clear and detailed information to enable the evaluation committee to make judgements based on the information it contains, without making inferences, gathering additional material, following up references or relying on members' prior knowledge. References to other sources of information will be used for verification purposes only, not as a means for the evaluation committee to gather further information to inform judgements.

In this evaluation, impact is defined as an effect on, change or benefit to the economy, society, culture, public policy or services, health, the environment or quality of life, beyond academia.

Timeframes

- The impact must have occurred between 2012 and 2022
- Some of the underpinning research should have been published in 2012 or later
- The administrative units are encouraged to prioritise recent cases

Page limit

Each completed case study template will be limited to **five pages** in length. Within the annotated template below, indicative guidance is provided about the expected maximum length limit of each section, but institutions will have flexibility to exceed these so long as the case study as a whole remains no longer than **five pages** (font Calibri, font size 11). Please write the text into the framed template under the sections 1–5 below. The guiding text that stands there now, can be deleted.

Maximum number of cases permitted per administrative unit

For up to 10 researchers: one case; for 10 to 30 researchers: two cases; for 30-50 researchers: three cases; for 50-100 researchers: four cases, and up to five cases for units exceeding 100 researchers.

Naming and numbering of cases

Please use the standardised short name for the administrative unit, and the case number for the unit (1,2,3, etc) in the headline of the case. Each case should be stored as a separate PDF-document with the file name: [Name of the institution and name of the administrative unit] [case number]

Publication of cases

RCN plans to publish all impact cases in a separate evaluation report. By submitting the case the head of the administrative units consents to the publication of the case. Please indicate below if a case may not be made public for reasons of confidentiality.

If relevant, describe any reason to keep this case confidential:

Please write the text here

[Name of the institution and name of the administrative unit] [case number]

Institution: UiT the Arctic University of Norway
Administrative unit: Department of Social Education (DSE)
Title of case study: Changing the understanding of disability
Period when the underpinning research was undertaken: 2008-today
Period when staff involved in the underpinning research were employed by the submitting institution: 2008-today
Period when the impact occurred: 2023

1. Summary of the impact (indicative maximum 100 words)

Department of Social Education has for 40 years educated social educators in Harstad and northern Norway. Around 5000 students have graduated with a bachelor's degree in social education. Given that social educators' main purpose is to assist individuals with various needs in managing their own daily lives and making important decisions, has disabilities been a central theme in all our education and research. Our impact case relates to how we have contributed in further developing the understanding of disability from a mere medical aspect to a broader societal understanding.

2. Underpinning research (indicative maximum 500 words)

DSE was established at a time where discussions were on-going about the responsibility for care for people with disabilities. In 1991 the responsibility was moved from counties to municipalities, moving beyond institutions. The purpose was to ensure each individual an independent life with possibilities for work, learning and a meaningful spare time. Our researchers have participated in both evaluations of this reform, in sharing stories from institutional life (https://en.uit.no/ansatte/person?p_document_id=445105), in ensuring work inclusion (https://en.uit.no/ansatte/person?p_document_id=449415), in discussing school participation and leisure time activities (https://en.uit.no/ansatte/person?p_document_id=445866) and in accommodating for, and evaluating, participation in cultural life (https://en.uit.no/ansatte/person?p_document_id=445139). Further, we have evaluated the many reforms in the field (https://uit.no/ansatte/person?p_document_id=445192). And we are now in the forefront nationally related to our inclusive research approaches.

DSE's research has implications for how disability is conceptualized, moving beyond medical or individual models to embrace a more holistic, social model of disability. The social model of disability suggests that disability is caused by the way society is organized, rather than by a person's impairment or difference. It looks at ways of removing barriers that restrict life choices for disabled people. When barriers are removed, disabled people can be independent and equal in society, with choice and control over their own lives.

Put together, our work has contributed in acknowledging that the concept of 'disability' needs to be understood as the interaction between individual impairments and societal barriers. The term 'functional impairment' is used to describe the physical, mental, or cognitive conditions that may limit an individual's activities. Our researchers emphasize that these conditions only lead to disability when they encounter environmental and attitudinal barriers that hinder full participation in society. Our understanding aligns with the social model of disability, which argues that it is not the individual's condition, but rather the lack of societal accommodation, that disables people. This perspective shifts the focus from the medical condition of the individual to the responsibilities of society to remove barriers and create inclusive environments. Researchers at ASVF then claims

that policies must promote accessibility, remove discrimination, and ensure equal opportunities for all, regardless of functional abilities. Further, researchers analyze the work with CRPD (Convention on the Rights of Persons with Disabilities) and how it is implemented locally. Professor Line Melbøe participated in Likestillings- og mangfoldsutvalget which presented NOU 2023:13 På høy tid in May 2023 (https://www.regjeringen.no/contentassets/06e733d054c343af921f6469cb5324c4/no/sved/ensammendrag.pdf). The report suggests that language around disability should reflect a person-first approach, recognizing the individual before their impairment.

DSE is proud of how our research has contributed in moving the understanding of disability forward, and how this culminated in NOU 2023:13's progressive view of disability that calls for societal change to enable individuals with functional impairments to live with dignity and equality.

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3. References to the research (indicative maximum of six references)

Edvardsen, Nanna Kathrine & Gjærum, Rikke Gürgens (2021). The Aesthetic Model of Disability, Chapter 10 in Janse Van Vuuren P, Rasmussen BK, Khala. Theatre and Democracy: Building Democracy in Post-war and Post-democratic Contexts. Cappelen Damm Akademisk p. 193-215, https://munin.uit.no/bitstream/handle/10037/31358/article.pdf?sequence=2&isAllowed=y.

Gjertsen, Hege (2019). People with intellectual disabilities can speak for themselves! A methodological discussion of using people with mild and moderate intellectual disabilities as participants in living conditions studies, Scandinavian Journal of Disability Research 21:1 141-149, https://doi.org/10.16993/sjdr.615.

Gjærum, R.G., Ramsdal, G.H. (2015). Change the Game. In Vettraino, E., Linds, W. (eds) Playing in a House of Mirrors. SensePublishers, Rotterdam. https://doi.org/10.1007/978-94-6300-118-2_12.

Melbøe, Line (2018). Role of the "differently-abled" researcher: Challenges and solutions in inclusive research, *Alter* 12:4 225-237, https://doi.org/10.1016/j.alter.2018.06.005.

Mittner, Lilli; Dalby, Karoline & Gjærum, Rikke Gürgens (2021). Re-conceptualizing the gap as a potential space of becoming: Exploring aesthetic experiences with people living with dementia, *Nordic Journal of Arts, Culture and Health* 3:1-2 63-74, https://doi.org/10.18261/issn.2535-7913-2021-01-02-06.

Rustad, Marit & Kassah, Kwesi A. (2020). Learning disability and work inclusion: on the experiences, aspirations and empowerment of sheltered employment workers in Norway. *Disability & Society* 36:3 399-419, https://doi.org/10.1080/09687599.2020.1749564.

4. Details of the impact (indicative maximum 750 words)

Staff at DSE has a conviction that every single human being possesses the same inherent human dignity, recognizing the very first sentence of the UN Universal Declaration of Human Right from 1948. Central is an understanding that disability or difference does not – and can never - take away anything from your worth. The value or dignity people possesses, on par with all other human beings, resides within them and is given as a fact, independent of human decisions, recognition, or power. With this as DSE's foundation, we have contributed in developing the understanding of intellectual disability.

Our approach on inclusive research started with developing qualitative methods for conducting research with people with intellectual disabilities (https://www.universitetsforlaget.no/usedvanlig-kvalitativ-forskning). And has further developed to include also quantitative methods with people with intellectual disabilities. Further, inclusive research is a topic both in our Master program and as a PhD topic. We have several inclusive research / collaborative projects:

- People with disabilities and Sami background
- Living conditions for persons with developmental disabilities and Sami background
- Art, Dementia and Social innovation
- HealthIntro – a study to increase the successful participation of refuges with health problems in the integration program
- A new PhD project initiated January 1st, 2024 focusing on young people with intellectual disabilities and how they participate in cross-sectorial cooperation, in which the target group also participates in an expert group which will contribute in shaping the research design, in data gathering, in data analysis and in dissemination.

Our co-researchers have participated in NOU 2016:17 På lik linje — Åtte løft for å realisere grunnleggende rettigheter for personer med utviklingshemming (https://www.regjeringen.no/no/dokumenter/nou-2016-17/id2513222/) and in developing the national guidelines «Gode helse- og omsorgstjenester til personer med utviklingshemming» https://www.helsedirektoratet.no/veiledere/gode-helse-og-omsorgstjenester-til-personer-med-utviklingshemming. We believe that participating as co-researchers in our research projects have contributed to their empowerment. This is also our hope from having four people from thw work training company INKO working with us some hours each day. Further, we invited people with Sami background into research as co-researchers. We have trained people with disabilities in participation in school, work life and leisure time, and arranged election courses in connection with Parliament elections. Our staff took active part in the establishment of a user council for people with intellectual disabilities in Harstad municipality, as one of two municipalities in Norway.

We are the only research group in Norway focusing on Sami with disabilities, and our publications are used as curricula in other universities.

4. Sources to corroborate the impact (indicative maximum of ten references)

NOU 2023:13 (2023). *På høy tid. Realisering av funksjonshindredes rettigheter*, NOU 2023:13, https://www.regjeringen.no/contentassets/06e733d054c343af921f6469cb5324c4/no/pdfs/nou20232320230013000dddpdfs.pdf

English summary:
https://www.regjeringen.no/contentassets/06e733d054c343af921f6469cb5324c4/no/sved/ensammendrag.pdf

Overview of the Commission's proposed measures:
https://www.regjeringen.no/contentassets/06e733d054c343af921f6469cb5324c4/no/sved/enoversikt.pdf

Department of Clinical Medicine, UiT. Impacts cases.

Table of contents

DepClinMed at UiT. Impact case number 1 "Anal incontinence: assessing symptoms, improving treatment and surveillance after treatment"

Institution: UiT
Administrative unit: Department of Clinical Medicine
Title of case study: Anal incontinence: assessing symptoms, improving treatment and surveillance after treatment
Period when the underpinning research was undertaken: 2012 – present
Period when staff involved in the underpinning research were employed by the submitting institution: Barthold Vonen (professor II 2000-2013, professor at Department of Community Medicine 2013-2023) Rolv-Ole Lindsetmo (ass. professor II 1999-2009, professor II 2009-present) Stig Norderval (ass. professor II 2012-2018, professor II 2018-present) Steen Buntzen (professor II 2015-2018) Trond Dehli (Ph.dD 2013, ass. professor II 2023-present) Mona Rydningen (Ph.D 2017, ass. professor II 2023-present)
Period when the impact occurred: Progressively from 2012

No 1. Summary of the impact

Obstetric sphincter injuries are the most common etiological factor for anal incontinence (AI). Norderval and Vonen showed in 2005 that anatomical immediate repair of both sphincters yielded good results. This was further explored in a large case control study **(R1)**, and the method is now implemented in national obstetric guidelines **(S1).** The research combined with clinical commitment led to the formation of the Norwegian Registry for Anal incontinence (NRA), from 2014 a national quality registry **(S2)**. Dehli **(R3)** and Rydningen **(R4)** undertook RCTs that participated in changing treatment algorithms for AI **(S3)**. Through national and international collaborations **(R2, R5, R6, R7)** new knowledge has been gained, and some of it implemented in international guidelines (**S3, S4, S7, S9, S10)**

No 2. Underpinning

A mapping of the prevalence of AI after obstetric sphincter tears repaired with different techniques, and the impact of ultrasonic post-repair extent of sphincter defects was carried out by Norderval (Ph.d thesis) and Vonen (professor at IKM) prior to 2012. This led up to a study comparing the traditional repair technique with anatomical sphincter repair showing favourable results after anatomical repair **(Norderval 2012, R1)**. This technique is now implemented in national obstetric guidelines **(S1)**.

The following research focused on treatment options for AI. An RCT by Graf W et al published in the Lancet, had surprisingly shown significant effect on AI by injecting bulk agents deep to the internal anal sphincter. Our group had questioned the efficacy of bulking agents, and Dehli (Ph.D.) carried out an RCT comparing pelvic floor exercises with intersphincteric bulk injections finding no difference in AI between the groups after treatment **(Dehli 2013, R3**). Rydningen (Ph.D.) undertook an RCT comparing injecting bulking agents with sacral nerve modulation (SNM) showing that SNM was superior to bulking agents **(Rydningen 2017, R4)**. Bulking agents are, partly based on this research, not recommended anymore as a treatment option for AI in international guidelines **(S3)**

The experience and research within the field of SNM, a procedure Vonen introduced in Tromsø already in 1999 (first among the Nordic countries) has resulted in several international publications **(Norderval, Rydningen and Lindsetmo,** exemplified with **R2 and R4),** and the results have been implemented in international guidelines **(S3)** and international expert recommendations **(S4).** Based on this activity, **Norderval** was already in 2015 invited for an editorial commentary in British Journal of Surgery **(S5)**, the highest ranked surgical journal in Europe and number 6 worldwide.

The research activity combined with clinical activity concerning all aspects on AI revealed a lack of knowledge among relevant Norwegian health carers, and **Vonen and Norderval** initiated in 2012 a national collaboration among health carers (surgeons, physiotherapists and specialised nurses) in all 4 Norwegian health regions in order to survey the treatment of AI. The Norwegian Registry of Anal incontinence (NRA) was established in 2013, and given status as a national quality register in 2014. In order to record symptoms from two somewhat different scoring systems for AI, **Norderval** established and validated one common questionnaire **(R5)**. The registry had in 2022 a coverage degree of 80% **(S2)**. The registry has led to change of clinical practise, as the surveillance revealed that a hospital which did not follow international guidelines when implanting SNM had inferior results compared to the others. The practice was changed and followed by improved results **(S2).** A master thesis based on data from the registry was finalised in 2022, and a Ph.D. project is now funded and will start this year.

Furtermore, **Buntzen** initiated a national group reviewing the existing knowledge on conservative treatment of pelvic floor disorders, of which AI is a major part. This work resulted in 2019 in the first national guidelines within the field **(S6)**, presenting a comprehensive algorithm for conservative treatment of AI.

Through national **(R3, R4, R5)** and international collaborations (Melbourne, Australia **(R2)**, Auckland, New Zealand **(R6)**, and Europe **(S7, S8, S9, S10)**, new insights on assessment and treatment has been gained during the period.

No. 3. References to the research

(R1) **Norderval S**, Røssaak K, Markskog A, **Vonen B.** Incontinence after primary repair of obstetric anal sphincter tears is related to relative length of reconstructed external sphincter: a case-control study. *Ultrasound Obstet Gynecol.* 2012 Aug;40(2):207-14. doi: 10.1002/uog.10154. https://pubmed.ncbi.nlm.nih.gov/22125165/

(R2) **Norderval S**, Behrenbruch C, Brouwer R, Keck JO. Efficacy of cyclic sacral nerve stimulation for faecal incontinence. *Tech Coloproctol*. 2013 Oct;17(5):511-6. doi: 10.1007/s10151-013-0999-6. https://pubmed.ncbi.nlm.nih.gov/23525966/

(R3) **Dehli T**, Stordahl A, Vatten LJ, Romundstad PR, Mevik K, Sahlin Y, **Lindsetmo RO, Vonen B**. Sphincter training or anal injections of dextranomer for treatment of anal incontinence: a randomized trial. *Scand J Gastroenterol*. 2013 Mar;48(3):302-10. doi: 10.3109/00365521.2012.758770. https://pubmed.ncbi.nlm.nih.gov/23298304/

(R4) **Rydningen M, Dehli T**, Wilsgaard T, Rydning A, Kumle M, **Lindsetmo RO, Norderval S.** Sacral neuromodulation compared with injection of bulking agents for faecal incontinence following obstetric anal sphincter injury - a randomized controlled trial.
Colorectal Dis. 2017 May;19(5):O134-O144. doi: 10.1111/codi.13632.
https://pubmed.ncbi.nlm.nih.gov/28211186/

(R5) **Norderval S**, **Rydningen MB,** Falk RS, Stordahl A, Johannessen HH. Strong agreement between interview-obtained and self-administered Wexner and St. Mark's scores using a single questionnaire. *Int Urogynecol J.* 2019 Dec;30(12):2101-2108. doi: 10.1007/s00192-019-03945-6. https://pubmed.ncbi.nlm.nih.gov/31172220/

(R6) **Norderval S**, Pedersen TK, Collinson RJ. Anal Sphincter Length as Determined by 3-Dimensional Endoanal Ultrasound and Anal Manometry: A Study in Healthy Nulliparous Women. *J Ultrasound Med.* 2021 Feb;40(2):331-339. doi: 10.1002/jum.15407. https://pubmed.ncbi.nlm.nih.gov/32701175/

No. 4. Details of the impact

The work on various repair techniques for anal sphincter reconstruction immediately after obstetric perineal tears showing favourable results with anatomical repair implying separate repair of the internal anal sphincter when injured and reconstruction of the full length of the external anal sphincter has been implemented in the national obstetric guidelines **(S1).**

The research on bulking agents as a treatment option for AI **(Dehli 2013 and Rydningen 2017)** showed that the treatment was not efficient despite previous reports indicating the opposite. Bulking agents are not recommended anymore as a treatment option for AI in international guidelines, in which the works by **Dehli and Rydningen** added strength to this recommendation **(S3)**.

The research activity on SNM has had a substantial impact nationally and internationally, and the results have been implemented in international guidelines **(S3)** and international expert recommendations **(S4).** Based on this activity, **Norderval** was already in 2015 invited for an editorial commentary in British Journal of Surgery **(S5)**, the highest ranked surgical journal in Europe and number 6 worldwide.

The Norwegian registry of anal incontinence has led to change of clinical practise, as the surveillance revealed that one hospital which did not follow international guidelines when implanting SNM had inferior results compared to the others. The practice was changed due to intensive work by **Rydningen and Norderval 2019-2021**, and followed by improved results **(S2).** Furthermore, the registry revealed an unexpected rise in infection rate after implant of sacral nerve stimulators at another hospital. The immediate feedback and consequent action taken at the hospital in order to prevent infections resulted in a documented return to a low infection rate **(S2)**. A master thesis based on data from the registry was finalised in 2022, and the results showed that patients with moderate or low degree of AI had in fact no significant reduction of symptoms one year after anal sphincter repair for AI, and more than one fourth of these patients actually had more severe symptoms ater surgery. The findings are implemented in the annual registry report for 2022 **(S2)** and a manuscript is now being prepared for international publication in which the procedure is advocated abandoned for this group of patients. Furthermore, a Ph.D. project based on data from the registry is now funded by the North Norwegian Health Trust “Helse Nord” and will start this year.

Buntzen initiated in 2016 a national group reviewing the existing knowledge on conservative treatment of pelvic floor disorders, of which AI is a major part. This work resulted in 2019 in the first national guidelines within the field **(S6)**, presenting a comprehensive algorithm for conservative treatment of AI. This guideline is essential for every unit treating patients with AI, and is implemented in the internet-based national Health Library “Helsebiblioteket” **(S10)**, which monthly have about 25 000 e-visitors.

Through national **(R3, R4, R5)** and international collaborations (Melbourne, Australia **(R2)**, Auckland, New Zealand **(R6)**, and Europe **(S7, S8, S9)** undertaken by **Norderval, Rydningen and Buntzen**, new insights on assessment and treatment has been gained during the period.

No. 5. Sources to corroborate the impact

(S1) Nasjonal veileder i fødselshjelp 2020 (National Guidlines in Obstetrics 2020) https://www.legeforeningen.no/foreningsledd/fagmed/norsk-gynekologisk-forening/veiledere/veileder-i-fodselshjelp/perinealskade-og-anal-sfinkterskade-ved-fodsel/

(S2) Årsrapport norsk register for analinkontinens 2022 (Annual report Norwegian Registry for Anal Incontinence 2022) https://www.kvalitetsregistre.no/sites/default/files/2023-09/Årsrapport 2022 Norsk register for analinkontinens.pdf

(S3) Guideline for the diagnosis and treatment of Faecal Incontinence-A UEG/ESCP/ESNM/ESPCG collaboration. Assmann SL, Keszthelyi D, Kleijnen J, Anastasiou F, Bradshaw E, Brannigan AE, Carrington EV, Chiarioni G, Ebben LDA, Gladman MA, Maeda Y, Melenhorst J, Milito G, Muris JWM, Orhalmi J, Pohl D, Tillotson Y, **Rydningen M**, Svagzdys S, Vaizey CJ, Breukink SO. *United European Gastroenterol J.* 2022 Apr;10(3):251-286. doi: 10.1002/ueg2.12213.

(S4) Programming Algorithms for Sacral Neuromodulation: Clinical Practice and Evidence-Recommendations for Day-to-Day Practice. Lehur PA, Sørensen M, Dudding TC, Knowles CH, de Wachter S, Engelberg S, Matzel KE; European SNM Expert Group *Neuromodulation.* 2020 Dec;23(8):1121-1129. doi: 10.1111/ner.13117. PMID: 32153080

(S5) Long-term outcomes of sacral nerve stimulation for faecal incontinence. Br J Surg 2015; 102: 407-415.
Norderval S. *Br J Surg.* 2015 Mar;102(4):415. doi: 10.1002/bjs.9772.

(S6) Faglige retningslinjer for utredning og konservativ behandling av anorektale funksjonsforstyrrelser (Guidlines for Evaluation and Conservative Treatment of Ano-recal dysfunktions) https://nekib.helsekompetanse.no/wp-content/uploads/2023/02/AI-retningslinjer-2019-pdf.

(S7) Changing paradigm of sacral neuromodulation and external anal sphincter repair for faecal incontinence in specialist centres. Ong K, Bordeianou L, Brunner M, **Buntzen S**, Collie MHS, Hanly A, Hunt CW, Matzel KE, O'Connell PR, **Rydningen M**, Savitt L, Totaro A, Vaizey CJ, Maeda Y. *Colorectal Dis.* 2021 Mar;23(3):710-715. doi: 10.1111/codi.15349. https://pubmed.ncbi.nlm.nih.gov/32894636/

(S8) A European snapshot of psychosocial characteristics and patients' perspectives of faecal incontinence-do they correlate with current scoring systems?
Creamer F, Orlando A, Brunner M, **Buntzen S**, Dennis A, Gómez-Fernández L, Handtrack C, Hanly A, Matzel KE, Duyos AM, Meurette G, O'Connell PR, Alonso CP, Ribas Y, **Rydningen M**, Wyart V, Vaizey CJ, Maeda Y.Int J Colorectal Dis. 2021 Jun;36(6):1175-1180. doi: 10.1007/s00384-021-03836-7.

(S9) Changing paradigm of sacral neuromodulation and external anal sphincter repair for faecal incontinence in specialist centres.

Ong K, Bordeianou L, Brunner M, **Buntzen S**, Collie MHS, Hanly A, Hunt CW, Matzel KE, O'Connell PR, **Rydningen M,** Savitt L, Totaro A, Vaizey CJ, Maeda Y.Colorectal Dis. 2021 Mar;23(3):710-715. doi: 10.1111/codi.15349.

(S10) Sacral Neuromodulation: Standardized Electrode Placement Technique.
Matzel KE, Chartier-Kastler E, **Knowles CH**, Lehur PA, Muñoz-Duyos A, Ratto C, **Rydningen MB**, Sørensen M, van Kerrebroeck P, de Wachter S.Neuromodulation. 2017 Dec;20(8):816-824. doi: 10.1111/ner.12695.

DepClinMed at UiT. Impact case number 2 "Towards precision medicine in inflammatory bowel disease"

Institution: UiT
Administrative unit: Department of Clinical Medicine
Title of case study: Towards precision medicine in inflammatory bowel disease
Period when the underpinning research was undertaken: 2012-present
Period when staff involved in the underpinning research were employed by the submitting institution: Jon Florholmen (1979-present (currently professor emeritus) Rasmus Goll (2000-present: 2000-2006 phd student, 2007-present associate professor, recently successfully evaluated for full professorship) Kay-Martin Johnsen (2015 – 2018 phd student, 2019-present researcher) Renate Rismo (2006-2008 phd student, 2009-2016 researcher) Trine Olsen (2006-2008 phd student, 2009-2015 researcher)
Period when the impact occurred: 2012-present

No. 1. Summary of the impact

Inflammatory bowel diseases (IBD) are chronic debilitating conditions affecting mostly young patients. In severe cases the use of biologic therapy can enable a more normal function in life and employment. However, these drugs are expensive and not without side effects, and the current international guidelines have no exit strategy for the therapy. The introduction of biologic drugs in IBD treatment were anti-TNF's and it was a natural development to focus on TNF as a central cytokine in IBD. Observational studies indicated that TNF gene expression in colon mucosa can serve as a biomarker to indicate the risk of disease relapse upon biologic drug withdrawal. This led to a patent application, and a Research Council of Norway (RCN) supported project for development of a commercial test-kit for TNF gene expression.

No. 2. Underpinning research

The underpinning research was conducted as part of several PhD projects at Department of Clinical Medicine UiT the Arctic University of Norway, the University Hospital of North Norway, and external partners in Germany (Novatec GmbH) facilitated by the tech-transfer company Norinnova in Tromsø who also handled the patenting process. The projects were supported by grants from Northern Norway Regional Health Authority for the PhD projects and RCN (BIOTEK and FORNY calls) for development of a commercial kit.

- Our first observation by Rismo et al (R1) indicated that a possible biomarker role of mucosal TNF gene expression was in Crohn's disease. The basis for the study was to treat patients with Crohn's disease with anti-TNF till endoscopic remission (no ulcers) followed by withdrawal of the drug. Rismo R et al observed that patients with normalized colon mucosal TNF gene expression (defined by the upper 95% CI limit of normal controls, detected by quantitative real-time PCR) had longer median time in remission compared to patients with higher that normal TNF gene expression. Time to relapse was 5 months for high TNF gene expression vs 17 months for normal TNF gene expression.
- Second, Olsen T et al (R2) underlined the first observation by making the same case in ulcerative colitis: When withdrawing biologic therapy for patients in endoscopic remission (Mayo endoscopic score 0-1), the time to relapse was significantly shorter if the patient had higher than normal TNF gene expression. For ulcerative colitis the median time to relapse was 5 months for high and 20 months for normal TNF gene expression.

- Unpublished prospective data on both diseases confirm these findings, with even longer remission time following more strict criteria for endoscopic remission: For ulcerative colitis, Mayo endoscopic score of 0 combined with a normalized TNF gene expression showed approximately 75% still in remission 40 months after withdrawal of biologic. Similarly for Crohn's disease, "no ulcer, no redness" combined with normalized TNF gene expression showed approximately 75% still in remission 30 months after withdrawal of biologic therapy.
- To our knowledge, the use of gene expression in clinical decisions is a novel idea. Our group started to work with the idea to use TNF gene expression as a biomarker in inflammatory bowel disease. A patent was filed in December 2013 and was granted in USA in 2018 (R3) and EU in 2022 (R4).

With financial support from RCN grants in the BIOTEK and FORNY calls we started a commercialization process with a medium sized biotech company in Germany, Novatec GmbH. The aim was to develop a commercial test kit for measurement of TNF gene expression in biopsies from colon mucosa. Unfortunately, Novatec was taken over by Gold Standard Diagnostics in 2022 and the new owners closed our common project after 6 months – before the kit was quite ready. With the support from Norinnova, the technology transfer company in North Norway, we now have contact with a Norwegian company who may want to take over the kit development and marketing.

In parallel with these pursuits, we have widened our knowledge base of the impact of TNF gene expression in the natural course of IBD.

- Johnsen K-M et al (R5) followed a cohort of patients with ulcerative colitis for 11 years using the algorithm with biologic withdrawal at endoscopic remission. High rates of success with re-treatment of patients who had a relapse could be demonstrated, and 41 % of the patients did not need re-start with biologics during the 11 years of observation. The formerly published data on longer remission time for patients with normalized TNF gene expression at biologic withdrawal could be confirmed in this separate cohort.
- Florholmen J et al (R6) published discovery and validation of a biomarker criterium for starting biologic therapy at debut of ulcerative colitis. The biomarker consists of a combination of TNF gene expression (higher cut-off than the stop criterium) combined with histologic score to determine if a patient belongs to the group with most severe disease who will need biologic treatment within the first year after debut of disease. With this biomarker positive, treatment can skip directly to the effective biologic therapy (so-called *top-down* treatment), avoiding several months of trial and error (the standard *step-up* ladder regimen).

No. 3. References to the research

R1: Rismo R, Olsen T, Cui G, Paulssen EJ, Christiansen I, Johnsen K, Florholmen J, Goll R. Normalization of mucosal cytokine gene expression levels predicts long-term remission after discontinuation of anti-TNF therapy in Crohn's disease. Scand J Gastroenterol 2013; 48 (3): 311-319. DOI: 10.3109/00365521.2012.758773

R2: Olsen T, Rismo R, Gundersen MD, Paulssen EJ, Johnsen K, Kvamme JM, Goll, R, Florholmen J. Normalization of mucosal tumor necrosis factor-α: A new criterion for discontinuing infliximab therapy in ulcerative colitis. Cytokine 2016; 79: 90-5. DOI: 10.1016/j.cyto.2015.12.021

R3: Patent in USA for using cytokine gene expression as biomarker in IBD US10012654B2

R4: Patent in EU for using cytokine gene expression as biomarker in IBD EP2936162B1

R5: Johnsen KM, Goll R, Hansen V, Olsen T, Rismo R, Heitmann R, Gundersen MD, Kvamme JM, Paulssen EJ, Kileng H, Johnsen K, Florholmen J. Repeated intensified infliximab induction – results from an 11-year prospective study of ulcerative colitis using a novel treatment algorithm. Eur J Gast Hep 2017; 29 (1): 98-104. DOI: 10.1097/MEG.0000000000000753

R6: Florholmen J, Johnsen KM, Meyer R, Olsen T, Moe ØK, Tandberg P, Gundersen MD, Kvamme JM, Johnsen K, Løitegård T, Raschpichler G, Vold C, Sørbye SW, Goll R. Discovery and validation of mucosal TNF expression combined with histological score - a biomarker for personalized treatment in ulcerative colitis. BMC Gastroenterol 2020; 20: 321 DOI: 10.1186/s12876-020-01447-0

No. 4. Details of the impact

The international clinical guidelines for treatment of inflammatory bowel disease have two major problems:

1. The criterium for starting biologic treatment is based on trial-and-error by testing the efficacy of conventional treatment first, and then move to biologics if the patient does not achieve remission, an algorithm termed *step-up*. This process may take months, and there are amounting indications that there is a window of opportunity where establishing early inflammation control and remission may help transform the disease towards milder phenotypes.
2. There is no advice if a patient can withdraw biologics. The clinical experience in general states that many patients will relapse soon after withdrawal. Consequentially, these expensive drugs are used without an exit strategy at high costs in healthcare expenditure and potential long term side effects.

Our group has developed two good candidate biomarkers for clinical decisions: when to start and when to stop biologic therapy in ulcerative colitis. Apart from aiding a better precision in decision making, the markers will likely reduce medicine expenditures. A possible further outcome from early adequate therapy may be to achieve a less aggressive phenotype of the disease, as indicated by a recent observation by Florholmen J et al https://doi.org/10.3389/fgstr.2023.1304944 However, our published results are based on observational studies stratifying the participants in follow-up studies. To achieve clinical impact in the treatment of inflammatory bowel disease, two factors are critical. 1: Our biomarker candidates must be evaluated in prospective randomized controlled trials, and 2: The commercial kit for measuring TNF gene expression must be marketed to make the biomarker evaluation easy to implement.

To address the first point, the use of biomarkers in both clinical decision nodes will be tested in planned RCT studies: The DUCT study will test the start criterium for selected top-down vs regular step-up treatment, and the SABAT study will test the stop criterium by test-driven stop of treatment vs stop of treatment without using the test. Both studies are backed by Northern Norway Regional Health Authority funding and will start inclusion during 2024.

To address the second point, we are currently in negotiation with a Norwegian company who may be interested to take over the commercialization process. To speed up this part of the project, we can provide all documentation and previous work generated by Novatec, which we got access to when Gold Standard Diagnostics closed the project. Norinnova is handling the tech transfer process.

Norway spends approximately NOK 2 bill. per year on biologics of which around NOK 600 mill. is used in IBD treatment. According to our estimates, the impact of a withdrawal biomarker will enable savings of approximately 30% of the costs on biologic medication for IBD. This includes costs for re-treatment for those who relapse.

The impact of a start criterion would be huge for those patients with most severe phenotypes, who will achieve remission much faster that with the standard step-up regimen in the current recommendations. Whether this can help change the individual disease phenotype towards a milder form remains to be determined from the prospective studies outlined above. If this is the case, the start criterion may also have a positive impact on overall medical expenses for the patient group.

The competing biomarkers like the PredictSURE IBD is based on measurement of the expression of 17 individual genes in blood samples. Though blood samples are more easily accessible than colon biopsies, the simplicity of measuring just one gene expression in the tissue that is target of the inflammation makes for a more robust test. Moreover, the same commercial test kit can be used for both *start* and *stop* with different cut-off levels: >18.000 copies/µg totalRNA for *start* and <7.500 copies/µg totalRNA for *stop* of biologic therapy.

No. 5. Sources to corroborate the impact

There is a great focus on biomarkers in IBD, and both American and European guidelines emphasize the importance of biomarkers in several aspects of IBD treatment:
AGA Clinical Practice Guideline on the Role of Biomarkers for the Management of Ulcerative Colitis DOI: 10.1053/j.gastro.2022.12.007
In the European Crohn's and Colitis Organization (ECCO) guidelines, the only established biomarkers in IBD are fecal calprotectin and CRP DOI: 10.1093/ecco-jcc/jjy113, but precision medicine is an area of high interest DOI: 10.1093/ecco-jcc/jjab050.
The most promising candidate for prediction of severe outcome is the PredictSURE-IBD assay (DOI: 10.1136/gutjnl-2019-318343). However, recently published data in Crohn's disease showed that the biomarker had no predictive value, but that a top-down approach yielded substantially better results for the patients DOI: 10.1016/S2468-1253(24)00034-7. This underlines the benefits of selective top-down treatment, but the question of patient selection for this treatment algorithm remains. Since a substantial part of IBD patients do not need biologic therapy, a general top-down strategy would lead to expensive over-treatment as well as increase the risk of severe side effects of these potent drugs.

DepClinMed at UiT. Impact case number 3 “Neonatal sepsis and antimicrobial stewardship strategies”

Institution: UiT
Administrative unit: Department of Clinical Medicine
Title of case study: Neonatal sepsis and antimicrobial stewardship strategies
Period when the underpinning research was undertaken: 2012 – present
Period when staff involved in the underpinning research were employed by the submitting institution: Claus Klingenberg (PhD 2003 - 2006, associate professor 2006 - 2012, professor I 2013 - present) Trond Flægstad (professor I from 1990 - 2022) Hildegunn Granslo (PhD 2009 - 2012, associate professor 2013 - present) Pauline Cavanagh (PhD 2009 - 2013, researcher 2013 – 2022, associate professor 2022 - present) Dagny Hemmingsen (PhD 2018 - present) Eirin Esaiassen (PhD 2014 - 2017, associate professor 2018 - present) Jon Fjalstad (PhD 2015 - 2018) Veronika Pettersen (Associate professor 2018 - present)
Period when the impact occurred: Progressively increasing from 2016

No. 1. Summary of the impact

Newborn infants are at high risk for severe infections. Many infants are therefore treated with antibiotics, but inappropriate antibiotic therapy has short- and long-term adverse effects. The comprehensive research led by Prof. Claus Klingenberg’s team in the Research Group for Child and Adolescent Health (RG-CAH) Infection subgroup has contributed with new knowledge on epidemiology of neonatal sepsis (**R1**), strengthened national and international collaboration in neonatal sepsis research (**R2, R3**), reported safety data on important and “ecologically friendly” antibiotics (**R4**) and evaluated new tools to improve antimicrobial stewardship (**R5, R6**). The research has paved the way for international studies and participation as partner in European research (**S1, S2, S3**). The research is also integrated in national and international neonatal sepsis guidelines (**S4, S5, S6**).

No. 2. Underpinning research

The RG-CAH, Infection subgroup, at DepClinMed, UiT has been active since late 1990s. Initially focus was on coagulase-negative staphylococci (CoNS), the most common cause of sepsis in preterm infants (**S7**). Prof Trond Flægstad was head of the RG until retirement and associate professor Pauline Cavanagh is leading experimental laboratory studies on CoNS with focus on molecular epidemiology and virulence (**S8**). The current underpinning research, led by prof. Claus Klingenberg, is conducted in collaboration with local (CANS, UiT), national (Norwegian Neonatal Network, Oslo and Stavanger University Hospital) and international (Lausanne University Hospital and Luzerner Kantonsspital in Switzerland, University Hospital of Würzburg, Germany and Rigshospitalet, Copenhagen, Denmark) partners. Focus is on improvements in therapy for severe infections (sepsis) in newborn infants.

Fjalstad (2016) (R1) published as PhD-student the first article with nationwide data from the Norwegian Neonatal Network (NNN). NNN contains granular data on all newborn infants admitted to all neonatal units in Norway. Here we showed that as many as 2.6% of all term infants in Norway were treated with antibiotics, but only 0.05% had a culture-proven sepsis, reflecting overtreatment. We found no difference in mortality with narrow- vs broad-spectrum regimens.

Subsequently **Esaiassen, Fjalstad at al. (2017) (R2)** systematically reviewed available evidence on harmful effects of antibiotics in newborn infants. We convincingly showed that prolonged antibiotic exposure in uninfected preterm infants was associated with an increased risk of necrotizing enterocolitis and/or death, and that broad-spectrum antibiotic exposure was associated with an increased risk of fungal infections.

As partner of the international neonatal sepsis trial network (**S3**), **Klingenberg and international colleagues (2019) (R3)** published a comprehensive systematic review on the use of the neonatal sepsis calculator. We showed that in neonatal units with a high use of antibiotics, implementation of this new tool was associated with a safe reduction of the antibiotic consumption by almost 50%.

Antimicrobial stewardship is not only about reduction of antibiotics, but also to use narrow-spectrum regimens and antibiotics with little adverse impact on the host gut microbiota (e.g. aminoglycosides). **Hemmingsen (2019) (R4)** published as PhD student a follow-up study on 219 school children treated with gentamicin in the neonatal period. This hitherto largest study with granular audiological evaluation of children exposed to gentamicin therapy in the neonatal period, did not show any sign of hearing impairment after exposure to a high-dose gentamicin regimen in the neonatal period.

Klingenberg co-supervised neonatologist Anlaug Vatne, Stavanger University Hospital, during her PhD. **Vatne** and **Klingenberg (2020) (R5)** demonstrated that by using structured "serial physical examination" of newborns infants who were admitted to the neonatal unit due to risk of infection, it was possible to reduce antibiotic consumption by almost 60%. This study was inspired by the work by Fjalstad (**R1**), in which Stavanger at that time used more antibiotics than other neonatal units in Norway.

Klingenberg and national collaborators initiated another national quality improvement (QI) project in three Norwegian neonatal units **(2020) (R6).** Here we evaluated whether a bundle of interventions (including an "automatic stop order" of antibiotic prescription after 48 hours) could reduce antibiotic treatment duration for suspected, sepsis. The "bundle" led to an overall reduction in antibiotic therapy and a reduction in the proportion of infants commenced on antibiotics. The three neonatal units participating in this QI-project had a significantly larger reduction in antibiotic use compared to all other Norwegian neonatal units.

This underpinning research took place in a period when there has been a growing recognition of the adverse effects of antibiotic overuse, in particular for newborn infants. Not only can the antibiotic overuse cause an increase in antimicrobial resistance. Antibiotic overuse in early life is also associated with severe short- and long-term adverse outcomes, the latter probably due to an antibiotic-induced disruption of the gut microbiota and a later skewed immunological responses.

No. 3. References to the research

(R1) **Fjalstad JW**, Stensvold HJ, Bergseng H, Simonsen GS, Rønnestad A, **Klingenberg C**. Early onset sepsis and antibiotic exposure in term infants: a nationwide population-based study in Norway. Pediatr Infect Dis J 2016; 35: 1-6. DOI: 10.1097/INF.0000000000000906

(R2) **Esaiassen E, Fjalstad JW**, Juvet LK, van den Anker J, **Klingenberg C**. Antibiotic exposure in neonates and early adverse outcomes - a Systematic Review and Meta-Analysis. J Antimicrob Chemotherapy 2017; 72: 1858-70. DOI: 10.1093/jac/dkx088

(R3) Achten NB, **Klingenberg C,** Benitz WE, Stocker M, Schlapbach LJ, Giannoni E, Bokelaar R, Driessen GJA, Brodin P, Uthaya S, van Rossum AMC, Plötz FB. Association of use of the early-onset sepsis calculator with reduction in antibiotic therapy and safety: A systematic review and meta-analysis. JAMA Pediatr 2019; 173: 1032-40. DOI: 10.1001/jamapediatrics.2019.2825

(R4) **Hemmingsen D**, Mikalsen C, Hansen AR, **Fjalstad JW**, Stenklev NC, **Klingenberg C**. Hearing assessment in schoolchildren after neonatal exposure to a high-dose gentamicin regimen. Pediatrics 2020; 145: e20192373. DOI: 10.1542/peds.2019-2373

(R5) Vatne A, **Klingenberg C**, Øymar K, Rønnestad A, Manzoni P, Rettedal S. Reduced antibiotic exposure by serial physical examinations in term neonates at risk of early-onset sepsis. Pediatr Infect Dis J 2020; 39: 438-43. DOI: 10.1097/INF.0000000000002590

(R6) Dretvik T, Solevåg AL, **Finvåg A**, Størdal EH, Størdal K, **Klingenberg C**. Active antibiotic discontinuation in suspected but not confirmed early-onset neonatal sepsis – a quality-improvement initiative. Acta Paediatr 2020; 109: 1125-30. DOI: 10.1111/apa.15202
Authors from the RG in Tromsø are highlighted in bold.

No. 4. Details of the impact

The research on neonatal sepsis and antibiotic use by the RG in Tromsø, with national and international collaborators, has contributed to new important knowledge in this field. It has also been important for shaping clinical practice and improving patient care both nationally and internationally, influencing guidelines, and fostering collaborative initiatives (**S1**).

The first nationwide study on neonatal sepsis and antibiotic use in Norway **(R1)** strongly contributed to focus on this topic in Norway, and it sparked several initiatives **(R5, R6)**. There has been a marked reduction in the overall antibiotic use in neonatal units in Norway since this paper **(R1)** was published. A beneficial side effect of this project **(R1)** was improvements in data quality in the NNN, and subsequently a number of new projects (**S7** and other not mentioned here) within this research field, led by the Klingenberg and the RG in Tromsø.

An impactful outcome of our research is also evident in national and international guidelines on neonatal sepsis. Our systematic review article on adverse outcomes of antibiotic use in neonates **(R2)** has been cited more than 150 times. This article **(R2)** strongly supports the importance of antimicrobial stewardship strategies and is also cited in the updated 2021 NICE guidelines for neonatal sepsis (**S6**). The important findings from our systematic review on the neonatal sepsis calculator **(R3),** published in a high-ranked journal, has also been frequently cited. Moreover, it is one of the key papers supporting this strategy in countries with an unnecessary high antibiotic use (e.g. USA, UK and Australia). The two papers, **R3** and **R5**, are among the central references for the European guidelines on "**Management of suspected early-onset neonatal sepsis" (S3). Finally, Klingenberg and national collaborators revised in 2023 the neonatal sepsis guidelines in Norway (S4). Evidence for these updated guidelines is to a large extent based on research from the RG in Tromsø and their collaborators. The article (R5) on "**Serial physical examination" is currently the favored approach in Norwegian neonatal units to maintain a prudent use of antibiotic therapy to neonates. In our setting, this approach can safely maintain a lower use of antibiotics than what can be achieved by using the sepsis calculator **(R3)**.

In Tromsø, the RG-CAH Infection subgroup is part of the Centre for New Antibacterial strategies (CANS; https://uit.no/research/cans). Optimizing use of existing antibiotics is one important strategy to combat antimicrobial resistance. In our project on gentamicin and hearing outcomes **(R4)** we investigated a local cohort of children who had been treated in the neonatal unit in Tromsø. All children were invited back for follow-up and examined with high-frequency audiometry (the most sensitive method to detect ototoxicity) at the clinical trial unit at the University Hospital North Norway. Safety data on long term outcomes are rare after antibiotic use

in neonates. We believe such data are very important, and the findings that gentamicin use in the neonatal period did not have persistent ototoxic effects, is an argument to maintain the use of this ecologically friendly antibiotic. This article was also published in one of the most prestigious pediatric journals.

Side effects of antibiotic overuse in neonates are partly secondary to microbiome disruption. The focus on antibiotics and the gut microbiota has sparked other "spin off" projects where the RG in Tromsø has central roles. The observational preterm infant gut (PINGU) study **(S9)** reported on potential beneficial effects of probiotic supplementation in preterm infants. The large randomized clinical trial (RCT), the ProRIDE study **(S10)**, was completed in 2023. Data from this RCT will lead to several publications. In 2024 a Tanzanian doctor will join the RG-CAH at DepClinMed on a PhD project at DepClinMed, based on the ProRIDE study, and funded by the Regional Health authorities of North Norway.

Prof. Klingenberg leading this underpinning research in Tromsø, will in 2024 lead a new module on Neonatal Infection, Inflammation, Immunology & Immunisation in the international Neonatal Online Training and Education Programme (NOTE) **(S11)**. The NOTE-programme is part of the European School of Neonatology, which represents the educational arm of the European Society for Paediatric Research (ESPR). The NOTE modules are integrated elements in the training to become certified subspecialists in neonatology for pediatricians, both in and outside Europe.

No. 5. Sources to corroborate the impact

(S1) Giannoni E, Dimopoulou V, **Klingenberg C**, et al. Analysis of Antibiotic Exposure and Early-Onset Neonatal Sepsis in Europe, North America, and Australia. JAMA Netw Open. 2022; 5: e2243691. DOI: 10.1001/jamanetworkopen.2022.43691

(S2) **Claus Klingenberg**, council member, Infection, Inflammation, Immunology and Immunisation section in European Society for Pediatric Research (ESPR), since 2023. https://www.espr.eu/sections/I4_section.php

(S3) Neonatal sepsis Trial Network. https://nest-net.org/members/

(S4) Stocker M, Buonocore G, Zimmermann LJI, Hellström-Westas L, Klingenberg C, Kornelisse R, Maier RF, Metsvaht T. **Management of suspected early-onset neonatal sepsis (2022). European Standards of care for newborn Health.** https://newborn-health-standards.org/standards/standards-english/medical-care-clinical-practice/management-of-suspected-early-onset-neonatal-sepsis-eons/

(S5) Neonatal sepsis (2023). Norsk veileder i nyfødtmedisin (Norwegian Guideline for neonatal care). Klingenberg C, Solevåg AL, Eriksen BH, Heggstad N, Ødegård SS, Vatne A og Brigtsen AK. https://www.helsebiblioteket.no/innhold/retningslinjer/pediatri/nyfodtmedisin-veiledende-prosedyrer-fra-norsk-barnelegeforening/4-infeksjoner/4.1-neonatal-sepsis

(S6) Neonatal infection: antibiotics for prevention and treatment (2021). NICE guideline [NG195]. https://www.nice.org.uk/guidance/ng195

(S7) Huncikova Z, Vatne A, Stensvold HJ, …… **Klingenberg C**. Late-onset sepsis in very preterm infants in Norway, 2009-2018. Arch Dis Child Fetal Neonatal Ed. 2023; 108:478-484. DOI: 10.1136/archdischild-2022-324977

(S8) Pain M, Hjerde E, **Klingenberg C**, Cavanagh JP. Comparative Genomic Analysis of *Staphylococcus haemolyticus* Reveals Keys to Hospital Adaptation and pathogenicity. Front Microbiol. 2019 Sep 10; 10:2096. DOI: 10.3389/fmicb.2019.02096

(S9) Bargheet A, **Klingenberg C,** Esaiassen E, Hjerde E, Cavanagh JP, Bengtsson-Palme J, Pettersen VK. Development of early life gut resistome and mobilome across gestational ages and microbiota-modifying treatments. eBioMedicine 2023; 92:104613.
DOI: 10.1016/j.ebiom.2023.104613

(S10) Kuwelker K, Langeland N, Löhr I, Gidion J, Manyahi J, Moyo S, Blomberg B, **Klingenberg C**. Use of Probiotics to Reduce Infections and Death and Prevent Colonization with Extended-spectrum beta-lactamase (ESBL) producing bacteria among newborn infants in Tanzania (ProRIDE Trial): study protocol for a randomized controlled clinical trial. Trials, 2021;22:312.
DOI: 10.1186/s13063-021-05251-3

(S11) New module on Neonatal Infection, Inflammation, Immunology & Immunisation in the Neonatal Online Training and Education Programme. https://www.espr.eu/activities-projects/note.php

DepClinMed at UiT. Impact case number 4 "Somatic morbidity and mortality in persons with severe mental illness"

Institution: UiT
Administrative unit: Department of Clinical Medicine
Title of case study: Somatic morbidity and mortality in persons with severe mental illness
Period when the underpinning research was undertaken: 2016 – present
Period when staff involved in the underpinning research were employed by the submitting institution*: Anne Høye (Ass. Prof. 2016 – 2021, Prof. 2021 - present) Ina Heiberg (PhD 2016 – 2019, postdoc and researcher 2019 - present) Ole Grønli (postdoc 30 % 2018 – 2021) Ingvild Myrbakk (PhD 2018 – 2022) Elisabeth Lund-Stenvold (PhD 50 % 2017 – present) Safak Caglayan (postdoc 2022 – present) *The main financing of the project was a joint venture between UiT, Northern Health Region and University Hospital of North Norway. All researchers are in the Psychiatry Research Group at DepClinMed.
Period when the impact occurred: Progressively starting from 2016

No. 1. Summary of the impact Through using national registry data and clinical data, the comprehensive research led by Prof. Anne Høye's team in the Psychiatry Research Group at the Department of Clinical Medicine has strongly contributed to new research on the extent and causes of increased morbidity and mortality in persons with severe mental illness, both nationally and internationally. The high-quality research has been crucial in increasing the focus on challenges related to somatic treatment of people with mental illness at all levels, including an impact on changes to Norwegian guidelines. It has also paved the way for further national and international research collaboration.
No. 2. Underpinning research The underpinning research conducted at DepClinMed in collaboration with regional *(University Hospital of North Norway, North Norway Health Region, Center of Clinical Documentation and Evaluation, Department of Community Medicine and Department of Psychology at UiT*), national (*National Institute of Public Health, University of Oslo, University of Bergen, The Norwegian University of Science and Technology, Vestfold Hospital trust, Akershus University hospital*) and international (*Karolinska Institute, Stockholm, ECNP Network*) partners has aimed at investigating mortality, morbidity, risk factors and clinical measures in persons with severe mental illness. The research has used data from linkages between several national registries, but also clinical cohorts and data from the longitudinal, population based Tromsø Study. Further research development has expanded with new linkages (e.g. with The Cancer Registry). The research has been conducted by a team consisting of researchers with diverse backgrounds and specializations, fostering a multidisciplinary approach to research. Names of the key researchers (with the positions they held at DepClinMed and the dates) are listed in the top of the document. Sources of the research included the following: North Norway Health Region, UiT The Arctic University of Norway, University Hospital of North Norway.

Anne Høye (MD PhD, Professor Psychiatry, Senior Consultant Psychiatry) has led the research. An integral part of the research was undertaken by **Ina Heiberg** (Cand. Polit. PhD) as part of her PhD. Ina Heiberg analysed data from linkages between The Norwegian Patient Registry (NPR), the Cause of Death Registry and the Norwegian reimbursement database, conducting the first nationwide study estimating standardised mortality ratios in patients with severe mental illness, including comorbidity with substance use (2018, R1), and underdiagnosing and undertreatment of cardiovascular diseases prior to cardiovascular death (including sex differences) (2019/2020, R2, R3). The registry linkage has in **Ina Heiberg's** postdoc project been expanded to include The Cancer Registry, investigating cancer screening and care in patients with mental illness.

Elisabeth Lund-Stenvold has used a clinical cohort in collaboration with national partners to investigate clinical management of cardiometabolic risk factors in patients with severe mental illness, the **Healthy Heart Project** (2022, R6, two more papers in progress). Through secondary research collaboration another PhD candidate, **Stine Larsen,** is participating in a national randomized controlled trial led by Torleif Ruud at Akershus University Hospital, investigating an evidence-based model for implementing treatment guidelines for physical health care in patients with severe mental illness (2022, two papers in progress). The collaboration with The National Institute of Public Health has also resulted in several papers on mortality (e.g. R4). **Ole Grønli** has investigated depression in the Tromsø Study (2022), underpinning research development in **Safak Caglayan's** postdoc project where the role of lifestyle and polygenic risk factors in cardiovascular comorbidity in mental illness (MentalCVD) is investigated (2023- present). This is a multidisciplinary approach in cooperation with NORMENT at UiO, aiming at studying CVD comorbidity in mental illness across an individual's life span. In collaboration with the Institute of Psychology at UiT, **Ingvild Myrbakk** has studied how to measure psychometric properties in patients admitted to elective coronary angiography (2022, R5).

No. 3. References to the research

1. Heiberg I, Jacobsen BK, Nesvåg R, Bramness J, Reichborn-Kjennerud T, Næss Ø, Ystrøm E, Hultman CM, Høye A (2018) Total and cause-specific standardized mortality ratios in patients with schizophrenia and/or substance use disorder. PlosOne 13(8) https://doi.org/10.1371/journal.pone.0202028

2. Heiberg IH, Jacobsen BK, Balteskard L, Bramness JG, Naess O, Ystrom E, Reichborn-Kjennerud T, Hultman CM, Nesvag R, Høye A (2019) Undiagnosed cardiovascular disease prior to cardiovascular death in individuals with severe mental illness. Acta Psychiatr Scand, 139(6):558-571; https://doi.org/10.1111/acps.13017

3. Heiberg I, Jacobsen BK, Balteskard L, Bramness J, Næss Ø, Ystrøm E, Reichborn-Kjennerud T, Hultman CM, Nesvåg, R, Høye A (2020) Diagnostic tests and treatment procedures prior to cardiovascular death in individuals with severe mental illness. Acta Psychiatr Scand https://doi.org/10.1111/acps.13157

4. Høye A, Jacobsen BK, Bramness JG, Nesvåg R, Reichborn-Kjennerud T (2021) Total and cause-specific mortality in patients with personality disorders: the association with comorbid severe mental illness and substance use disorders. Soc Psychiatry Psychiatr Epidemiol https://doi.org/10.1007/s00127-021-02055-3

5. Myrbakk I, Friborg O, Høye A, Steigen T, Bergvik S (2022) Psychometric evaluation of the Coronary Revascularisation Outcome Questionnaire (CROQ) in Norwegian patients admitted

to elective coronary angiography and possible percutaneous coronary intervention. Health Qual Life Outcomes Feb 5;20(1):21. https://doi.org/10.1186/s12955-022-01927-9

6. Ringen PA, Lund-Stenvold E, Andreassen OA, Gaarden TL, Hartberg CB, Johnsen E, Myklatun S, Osnes M, Sørensen K, Vaaler A, Tonstad S, Engh JA, Høye A (2022) Quality of clinical management of cardiometabolic risk factors in patients with severe mental illness in a specialist mental health care setting. Nord J Psychiatry. Feb 24;1-8 https://doi.org/10.1080/08039488.2022.2039288

No. 4. Details of the impact

The research took place on the background of an internationally growing recognition of the highly increased burden of physical morbidity and mortality in persons with severe mental illness, and has strongly contributed to the national and international knowledge on prevention and treatment strategies in this vulnerable group of patients. The findings have been far-reaching, and have contributed to changing clinical practice. The findings and dissemination of results have also influenced clinical guidelines and promoted new, collaborative research initiatives.

Project leader Anne Høye has presented the subject on numerous national conferences on mental health and addiction (2016, 2017, 2018, 2019, 2021). Preliminary findings have been presented to the public through numerous interviews (e.g. **S1**), to health politicians in different meetings/settings and to health care administrative organs such as the Norwegian Directorate of Health (2017 - 2019), influencing the implementation of new guidelines highlighting a much higher focus on screening and treatment of physical diseases in patients with mental illness than previously (**S2**). An example of this is the inclusion of the "Healthy Heart Tool", which has been used in some of the research projects, in the guidelines. This tool is the Norwegian adaption of the UK "Lester Tool" and the Australian Positive Cardiometabolic Health resource, and it has been administered by Oslo University Hospital throughout the collaborative research network and is implemented both within research and clinical practice in addition to the national guidelines (**S2**). Findings were also presented for The Norwegian Medical Health Association (2019), directly influencing a state-of-the-art report published in 2023 (**S8**). The findings were also a main inspiration for a report from The Norwegian Healthcare Investigation Board in 2023 (**S9**). In addition, the national/international collaboration has influenced the innovative development of the first fidelity scale for physical health care (2020, **S3**). Further, the findings are displayed to health care workers through teaching courses for physicians, psychologists and nurses, and in book chapters used in education of health care workers (exemplified **S6, S7**). Findings have also been presented at international conferences, both by Anne Høye and by the PhD candidates/postdocs. The findings have also been disseminated in clinical contexts through teaching of specialist candidates, nurses and ward personnel within psychiatric health care, to GP's and to outpatient clinics. The findings have also been included in the teaching of medical doctors at several universities in Norway during the project period and afterwards.

In clinical practice, the results and the dissemination of these have had a strong influence on highlighting the importance of including preventive measures and follow-up for somatic diseases in persons with severe mental illness. An example of this is the development and implementation of group-based smoking cessation in persons with mental illness (2022 – present). As part of WP 3 in CVD-MENT (described below), a pilot study took place at the University Hospital of North Norway and at Vestfold Hospital Trust in 2022. This smoking cessation initiative has later been expanded to The Norwegian University of Science and Technology, Akershus University hospital and Haukeland Hospital in Bergen, aiming at implementing group-based smoking cessation as part of the clinical approach to reduce smoking in this patient group (2024). This tool has been widely disseminated at several Norwegian hospitals throughout Norway, in line with the results from our

research and the national collaboration within this field. Collaboration with users and patients has all the way been an important part of the development of clinically relevant research projects.

The research has expanded to further collaboration, e.g. collaboration with researchers at The National Institute of Public Health (**S5**) and the national multi-centre study CVD-MENT (*Preventing cardiovascular comorbidity in severe mental disorders with a multidisciplinary approach*), financed by the Norwegian Research Council, where Anne Høye leads WP3; aiming at investigating group-based smoking cessation in persons with severe mental illness. Internationally, the membership in the European College of Neuropsychopharmacology (ECNP) Thematic Working Group "*Physical and Mental Health – PAN-Health*" has resulted in several high-impact publications (e.g. **S4, S10**). Further collaboration includes projects using a combination of health data and newly genotyped data in the Tromsø study, as exemplified through Safak Caglayan's project under 2. *Underpinning research*.
Ongoing impacts continue to shape clinical and research practices, contributing to a sustained and evolving legacy. The establishment and progression of such collaborative studies serve as tangible indicators of the research's influence, showcasing its role as a foundational element in ongoing investigations.

No. 5. Sources to corroborate the impact

(S1) Storvik A.G. (Interview **A Høye and I. Heiberg**, Dagens Medisin 28.08.2018): Norsk studie: Schizofreni og alvorlig ruslidelse gir høy risiko for tidlig død https://www.dagensmedisin.no/psykisk-helse/norsk-studie-schizofreni-og-alvorlig-ruslidelse-gir-hoy-risiko-for-tidlig-dod/312324

(**S2**) National guidelines for somatic health in patients with severe mental illness (2018) https://www.helsedirektoratet.no/nasjonale-forlop/somatisk-helse-og-levevaner-ved-psykiske-lidelser-og-eller-rusmiddelproblemer

(S3) Ruud T, Sørensen Høifødt T, **Høye A** et al. The Physical Health Care Fidelity Scale: Psychometric properties. Adm Policy Men Health 2020: https://doi.org/10.1007/s10488-020-01019-0

(**S4**) Solmi M, Fiedorowicz JG, Poddighe L, Delogu M, Alessandro M, **Høye A, Heiberg IH** et al. Disparities in screening, and treatment of cardiovascular diseases in patients with mental disorders across the world: systematic review and meta-analysis of 46 observational studies. Am J Psychiatry 2021 Sep 1;178(9):793-803; https://doi.org/10.1176/appi.ajp.2021.21010031

(S5) Tesli M, Degerud E, Plana-Ripoll O,…, **Høye A** et al. Educational attainment and mortality in schizophrenia. Acta Psychiatr Scand. 2022 Feb 13. https://doi.org/10.1111/acps.13407

(S6) Høye A, Lien L (2022). Somatisk sykdom og levevaner. In: Lien L, Lie TW (red). Sammensatte problemer, sammenvevde tiltak. Integrert behandling av rus og psykiske lidelser (s. 134 – 144). Oslo: Fagbokforlaget. https://www.fagbokforlaget.no/Sammensatte-problemer,-sammenvevde-tiltak/I9788245035599

(S7) Høye A (2023): Risiko for somatisk sykdom og tidlig død blant mennesker som har alvorlig psykisk lidelse. In: Fause Å, Rolland EG, Sebergsen K (red). Klar for praksisstudier i psykiske helsetjenester (s 67-80). Oslo: Fagbokforlaget.
https://issuu.com/fagbokforlaget/docs/klar_for_praksisstudier_i_psykiske_helsetjenester_?fr=sNmQ4MDY1NTEwOTE

(S8) Den Norske legeforening rapport 2023: Bedre helse og lengre liv for personer med alvorlig psykisk lidelse eller rus- og avhengighetslidelse
https://www.legeforeningen.no/contentassets/415f122144e24a9e9bc86ecda6c89aff/bedre-helse-lengre-liv-2023.pdf

(S9) UKOM rapport 2023: Somatisk helse hos pasienter med alvorlig psykisk lidelse
https://ukom.no/rapporter/somatisk-helse-hos-pasienter-med-alvorlig-psykisk-lidelse/sammendrag

(S10) Fabiano N, Gupta A, Wong S, Tran J,…, **Høye A** et al: Physical activity, suicidal ideation, suicide attempt and death among individuals with mental or other medical disorders: a systematic review of observational studies. Neuroscience and Biobehavioral Reviews Jan 2024; https://doi.org/10.1016/j.neubiorev.2024.105547

DepClinMed at UiT. Impact case number 5 “Stroke: clinical and epidemiological perspectives”

Institution: UiT
Administrative unit: Department of Clinical Medicine
Title of case study: Stroke: clinical and epidemiological perspectives
Period when the underpinning research was undertaken: 2012 - present
Period when staff involved in the underpinning research were employed by the submitting institution: Ellisiv B Mathiesen: from onset to present date Tor Ingebrigtsen: from onset to present date Agnethe Eltoft: 2015-2017 (PhD-affiliation), 2020 - present Anne Merete Vangen-Lønne: 2012-2017 Maria Carlsson: 2013-2017, 2022 - present Jørgen Isaksen: 2014 – present Melinda Roaldsen: 2022 – present Stein Harald Johnsen: from onset to present date Anne Merete Vangen-Lønne, PhD affiliation 2012-2017 Marit Herder, PhD affiliation 2008-2013 Mary Helen Søyland, PhD affiliation 2020- present Torbjørn Øygard Skodvin, PhD affiliation 2017-2018
Period when the impact occurred: 2012-2022

No. 1. Summary of the impact

The stroke research has led to important insight in trends in incidence and current risk factor for ischemic stroke, intracerebral hemorrhagic stroke (ICH) and subarachnoid hemorrhage (SAH). The longitudinal population-based design with repeated cross-sectional surveys over five decades in a geographically defined area has provided a unique possibility to study time trends in risk factors and incidence of stroke subtypes, case-fatality and long-term mortality. The research is internationally recognized and has informed guidelines. Results from repeated large-scale ultrasound assessments surveys of carotid atherosclerosis as a risk factor for ischemic stroke and cardiovascular disease in the general population as well as our participation in large international collaborations within his field have challenged current views on the role of ultrasound markers of atherosclerosis in risk prediction and influenced guidelines. We have led an international multicenter randomized controlled trial on treatment with tenecteplase in ischemic wake-up stroke patients, which is the largest RCT on thrombolysis in wake-up stroke to date. Results from the trial have influenced clinical guidelines and been included in systematic reviews, meta-analyses, and current status updates.

No. 2. Underpinning research

The underpinning research on stroke epidemiology and carotid atherosclerosis has focused on time trends in incidence and risk factors of the three main stroke types, including comprehensive research on the occurrence, progression and risk factors for carotid atherosclerosis as well as the impact of carotid atherosclerosis on stroke and other cardiovascular diseases (CVD).

The research has been conducted by several researchers from the Brain and Circulation Research Group, IKM, mainly as a part of PhD and postdoc projects. Prof. Ellisiv B. Mathiesen has led and supervised several of the projects.

In her PhD project (2012-2017), Anne Merete Vangen-Lønne found that the overall age- and sex adjusted incidence of ischemic stroke in persons aged ≥30 years declined with 27% from 1995–2012. Overall, the combined changes in seven cardiovascular risk factors, the systolic blood

pressure, total cholesterol, HDL- cholesterol, daily smoking, physical activity, diabetes and body mass index accounted for 57% (95% CI 28–100) of the decrease in incidence from 1995 through 2012, with decreasing blood pressure and decline in smoking prevalence as the most important contributors. The increasing diabetes prevalence contributed negatively, as did the change in body mass index, although not significant (**R1**).
Maria Carlsson studied incidence, risk factors and long-term mortality of intracerebral hemorrhage (ICH) in her PhD-project (2016-2021). Incidence rates of ICH remained stable in the overall population during the period 1995-2013. Incidence rates in women tended to decrease, driven by a 74% decrease in non-lobar ICH, whereas incidence rates in men were stable (**R2**). Lower blood pressure levels, and a steeper decrease in blood pressure in women may have contributed to the difference between sexes.
Mary-Helen Søyland has in her ongoing PhD-project studied the occurrence, risk factors and characteristics of ischemic and hemorrhagic stroke wake-up stroke, known-onset stroke, and stroke of unknown onset other than wake-up, based on data from 60,320 patients included the national Norwegian Stroke registry from 2012 through 2019. The study was to our knowledge the first nationwide study on the occurrence and characteristics of both acute ischemic and hemorrhagic wake-up stroke and unknown-onset stroke.
Ellisiv B. Mathiesen has for approximately 25 years been responsible for the Carotid Ultrasound Examination of the Carotid Arteries Study, a longitudinal study with repeated cross-sectional surveys over 20 years with of carotid atherosclerosis. Marit Herder showed in her PhD-project (2008-2013) that found that age, male sex, total cholesterol, systolic blood pressure and smoking were associated with progression of total plaque area (TPA), whereas male sex, total cholesterol, and systolic blood pressure (inverse) were predictors of progression of intima-media thickness (IMT). To our knowledge, this was the first paper that presented data on progression of TPA and IMT in the same individuals (**R3**). We have taken part in international collaborations on carotid atherosclerosis in risk prediction, such as the PROG-IMT collaboration (https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(12)60441-3/fulltext), the USE-CIMT study (https://juliuscentrum.umcutrecht.nl/en/studies-en-cohorten/cohort-use-imt and on asymptomatic carotid stenosis.

Prof. Tor Ingebrigtsen has led and supervised clinical and epidemiological studies on subarachnoid hemorrhage (SAH) and unruptured intracranial aneurysms (uIA). He was among the first to show that bifurcation geometry is associated with the presence of uIA. Jørgen Gjernes Isaksen explored this concept further in his PhD-project and showed that computational fluid dynamics can be used to study hemodynamic stresses related to aneurysm formation and rupture risk, and thus has a potential for use in individualized risk assessment. This has inspired comprehensive research efforts worldwide. Isaksen (assoc. prof. from 2014) and Ingebrigtsen supervised Torbjørn Øygard Skodvin's PhD study (2017-2018) on the use of hemodynamic and morphological parameters to predict rupture risk. In a unique longitudinal case study of patients diagnosed with an asymptomatic uIA that later ruptured, he showed that rupture changes the morphology so much that cross-sectional comparison of ruptured and unruptured aneurysm is an inadequate design in studies of risk factors for rupture (**R4**).
The team has conducted a population-based MR angiography study of 1870 adults aged 40–84 years. The study showed that the prevalence is significantly higher than previously assumed (**R5**). This means that the rupture rate is lower than assumed, and that the risk-balance between haemorrhage-preventive invasive treatment (microsurgery or neurovascular intervention) and watchful waiting favours the latter more than previously assumed.

Jørgen Isaksen took the initiative to include a module for registration of subarachnoid hemorrhage in the Norwegian Stroke Registry (NSR). He has led a national working group of neurosurgeons who have taken part in the development together with researchers and staff at

the registry. The module is now operative from Jan 1, 2024. Isaksen has together with researchers at the NTNU, Norway, a leading role in register- and population study-based research on unruptured intracranial aneurysms (UIA) and aSAH in Norway.
Ellisiv Mathiesen (PI), Melinda Roaldsen (PhD-student and trial manager) and Agnethe Eltoft (trial officer, postdoc.student/assoc. prof.) co-ordinated the Tenecteplase in Ischaemic Wake-up Stroke trial (TWIST), an investigator-initiated international, multi-centre, prospective, randomised-controlled, open-label blinded end-point trial of tenecteplase vs standard care in patients with acute ischemic wake-up stroke selected by plain CT. The inclusion of patients took place in 2017-2021 in 77 hospitals and 10 countries. It is the largest published randomized controlled trial on thrombolysis in patients with ischemic wake-up stroke to date. Treatment with tenecteplase was not associated with better functional outcome for the primary outcome assessed as a shift in the score on the modified Rankin scale (mRS) at 90 days. The proportion with an excellent clinical outcome, defined as mRS score 0 or 1, was 45% in the tenecteplase group and 38% in the control group. There was no significant difference between treatment groups in risk of symptomatic intracranial hemorrhage or risk of death at 90 days (**R6**).

No. 3. References to the research

R1: Vangen-Lønne AM, Wilsgaard T, Johnsen SH, Løchen ML, Njølstad I, Mathiesen EB. Declining incidence of ischemic stroke: What is the impact of changing risk factors? The Tromsø study 1995–2010. Stroke. 2017;48: 544–550.

R2: Carlsson M, Wilsgaard T, Johnsen SH, Vangen-Lønne AM, Løchen ML, Njølstad I, Mathiesen EB. Temporal trends in incidence and case fatality of intracerebral hemorrhage: the Tromsø Study 1995-2012. *Cerebrovasc Dis Extra*. 2016;6(2):40-9. doi: 10.1159/000447719.

R3: Herder M, Johnsen SH, Arntzen KA, Mathiesen EB. Risk factors for progression of carotid intima-media thickness and total plaque area. A 13-year follow-up study. The Tromsø Study. *Stroke* 2012;43:1818-1823

R4: Skodvin TØ, Evju Ø, Sorteberg A, Isaksen JG. Prerupture intracranial aneurysm morphology in predicting risk of rupture: a matched case-control study. *Neurosurgery* 2019;84:132-140 doi: 10.1093/neuros/nyy010, https://munin.uit.no/handle/10037/13590

R5: Johnsen LH, Vangberg T, Herder M, Ingebrigtsen T, Mathiesen EB. Prevalence of unruptured intracranial aneurysms: impact of different definitions. The Tromsø Study. *J Neurol Neurosurg Psychiatry*. 2022;93:902-907. doi: 10.1136/jnnp-2022-329270.
https://hdl.handle.net/10037/28767

R6: Roaldsen MB, Eltoft A, Wilsgaard T, Christensen H, Engelter ST, Indredavik B, Jatužis D, Karelis G, Kõrv J, Lundström E, Petersson J, Putaala J, Søyland MH, Tveiten A, Bivard A, Johnsen SH, Mazya M, Werring DJ, Wu TY, De Marchis GM, Robinson TG, Mathiesen EB. Safety and efficacy of tenecteplase in patients with wake-up stroke assessed by non-contrast CT (TWIST): a multicentre, open-label, randomised controlled trial. *Lancet Neurol.* 2023;22:117-126. doi: 10.1016/S1474-4422(22)00484-7, *https://hdl.handle.net/10037/32746*

No. 4. Details of the impact

The stroke epidemiology research has contributed to new and updated knowledge on the incidence, risk factors and prognosis of each of three stroke types. The Tromsø Study is one of very few epidemiological studies which has been carried out over several decades in a geographically defined area. Insights from stroke risk over time that can be compared directly to

those arising in the contemporary population are important to understand the shifting factors that influence stroke risk.
We have found that changes in cardiovascular risk factors accounted for 57% (95% CI, 28%–100%) of the decrease in ischemic stroke incidence in people ≥30 years of age for the time period of 1995 to 2012. This result is referred to in the annual Heart Disease and Stroke Statistics reports from the American Heart Association (the latest version being from 2022, **S1**). Our finding on time trends in incidence and case fatality of hemorrhagic stroke has been included in a systematic review on this topic (**S2**).
Our findings on risk factors for SAH have been used to inform the work of the NINDS Unruptured Intracranial Aneurysms (UIA) and Subarachnoid Hemorrhage (SAH) and Subject Characteristics Working Group (WG), whose task it was to identify, define, and classify Common Data Elements (CDEs) describing the characteristics of patients diagnosed with UIA and SAH (**S3**).
Our research on uIA prevalence was highlighted at the 2022 EANS Congress, the Vascular section of the European Association of Neurosurgical Societies, where the paper was designated as one of four articles published in 2022 that should impact clinical practice (oral presentation by prof. Andreas Raabe). The article was rated as "Very influential" in the Peers-for-peers organisation, as one of 78 of 11,617 rated publications (**S4**). In addition, our findings regarding risk factors for rupture has improved the prediction of rupture risk in individual patients. Altogether, this has contributed to increased restraint with preventive treatment, and reduced resource use and disease burden related to complications from preventive treatment.
Jørgen Isaksen took the initiative to include a module for registration of subarachnoid hemorrhage in the Norwegian Stroke Registry (NSR), and plans for implementing this were developed in 2021-2022 **(S5)**. He has led a national working group of neurosurgeons who have taken part in the development together with researchers and staff at the registry. The module is now operative from Jan 1, 2024.
Carotid atherosclerosis and stenosis are important risk factors for ischemic stroke. We have conducted a longitudinal study with repeated cross-sectional surveys over 20 years with assessment of carotid atherosclerosis and stenosis. Our results on risk factors for progression of atherosclerosis has informed recommendations included in the 2017 Clinical Practice Guidelines of the European Society for Vascular Surgery on Management of atherosclerotic carotid and vertebral artery disease (**S6**). We showed that assessment of plaque burden is a better predictor of stroke than intima-media thickness and have advocated the use of plaque burden in risk prediction, which is now included in international guidelines (**S7**).
The results from the TWIST trial were presented at the European Stroke Organsation's (ESO) Conference on May 6, 2022 and was published online in Lancet Neurology on Dec. 19, 2022. The results have influenced ESO's expedited guideline on thrombolytic treatment with tenecteplase in ischemic stroke (**S8**) and have been included in systematic reviews, meta-analyses and current status updates. Due to the results been published quite late in the reporting period, the first documentation of the impact is from March 2023 (**S8**). In 2022, Melinda Roaldsen was appointed Chief Operations Officer for the Stroke Action Plan for Europe, a pan-European project which in collaboration with ESO and the patient organization Stroke Alliance for Europe sets targets for the implementation of evidence-based preventive actions and stroke services in Europe until 2030 (**S9**).

No. 5. Sources to corroborate the impact

S1: Tsao CW, Aday AW, Almarzooq ZI, et al. on behalf of the American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics—2022 Update: A Report From the American Heart Association. *Circulation.* 2022;145:e153-e639, https://doi.org/10.1161/CIR.0000000000001052

S2: Li X, Zhang L, Wolfe CDA, Wang Y. Incidence and Long-Term Survival of Spontaneous Intracerebral Hemorrhage Over Time: A Systematic Review and Meta-Analysis. *Front Neurol*.

2022;13:819737. doi:10.3389/fneur.2022.819737, https://www.frontiersin.org/journals/neurology/articles/10.3389/fneur.2022.819737/full

S3: Bijlenga P, Morita A, Ko NU, Mocco J, Morel S, Murayama Y, Wermer MJH, Brown RD Jr, on behalf of the Unruptured Cerebral Aneurysms and SAH CDE Project Investigators. Common Data Elements for Subarachnoid Hemorrhage and Unruptured Intracranial Aneurysms: Recommendations from the Working Group on Subject Characteristics. *Neurocrit Care*. 2019;30:S20-S27, https://link.springer.com/article/10.1007/s12028-019-00724-5, https://link-springer-com.mime.uit.no/content/pdf/10.1007/s12028-019-00724-5.pdf
S4: peersforpeers.com: https://app.peersforpeers-neurosurgery.org/app/main/articles/5b9f94d2876cf1070cf90b32
S5: Årsrapport Norsk hjerneslagsregister 2021 (page 121) https://www.stolav.no/fag-og-forskning/medisinske-kvalitetsregistre/norsk-hjerneslagregister/rapporter/#arsrapporter
S6: Naylor AR, Ricco JB, de Borst GJ, Debus S, de Haro J, Halliday A, Hamilton G, Kakisis J, Kakkos S, Lepidi S, Markus HS, McCabe DJ, Roy J, Sillesen H, van den Berg JC, Vermassen F, Esvs Guidelines Committee, Kolh P, Chakfe N, Hinchliffe RJ, Koncar I, Lindholt JS, Vega de Ceniga M, Verzini F, Esvs Guideline Reviewers, Archie J, Bellmunt S, Chaudhuri A, Koelemay M, Lindahl AK, Padberg F, Venermo M. Editor's Choice - Management of Atherosclerotic Carotid and Vertebral Artery Disease: 2017 Clinical Practice Guidelines of the European Society for Vascular Surgery (ESVS). *Eur J Vasc Endovasc Surg*. 2018;55:3-81. doi: 10.1016/j.ejvs.2017.06.021, https://www.ejves.com/article/S1078-5884(17)30395-7/fulltext
S7: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J.* 2016;37:2315-2381, doi: 10.1093/eurheartj/ehz455, https://academic.oup.com/eurheartj/article/41/1/111/5556353?login=false
S8: Alamowitch S, Turc G, Palaiodimou L, Bivard A, Cameron A, De Marchis GM, Fromm A, Kõrv J, Roaldsen MB, Katsanos AH, Tsivgoulis G. European Stroke Organisation (ESO) expedited recommendation on tenecteplase for acute ischaemic stroke. *Eur Stroke J.* 2023;8(1):8-54. doi: 10.1177/23969873221150022, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10069183/
S9: https://actionplan.eso-stroke.org/; https://actionplan.eso-stroke.org/about-sap-e/steering-committee

Impact case guidelines

Each case study should include sufficiently clear and detailed information to enable the evaluation committee to make judgements based on the information it contains, without making inferences, gathering additional material, following up references or relying on members' prior knowledge. References to other sources of information will be used for verification purposes only, not as a means for the evaluation committee to gather further information to inform judgements.

In this evaluation, impact is defined as an effect on, change or benefit to the economy, society, culture, public policy or services, health, the environment or quality of life, beyond academia.

Timeframes

- The impact must have occurred between 2012 and 2022
- Some of the underpinning research should have been published in 2012 or later
- The administrative units are encouraged to prioritise recent cases

Page limit

Each completed case study template will be limited to **five pages** in length. Within the annotated template below, indicative guidance is provided about the expected maximum length limit of each section, but institutions will have flexibility to exceed these so long as the case study as a whole remains no longer than **five pages** (font Calibri, font size 11). Please write the text into the framed template under the sections 1–5 below. The guiding text that stands there now, can be deleted.

Maximum number of cases permitted per administrative unit

For up to 10 researchers: one case; for 10 to 30 researchers: two cases; for 30-50 researchers: three cases; for 50-100 researchers: four cases, and up to five cases for units exceeding 100 researchers.

Naming and numbering of cases

Please use the standardised short name for the administrative unit, and the case number for the unit (1,2,3, etc) in the headline of the case. Each case should be stored as a separate PDF-document with the file name: [Name of the institution and name of the administrative unit] [case number]

Publication of cases

RCN plans to publish all impact cases in a separate evaluation report. By submitting the case the head of the administrative units consents to the publication of the case. Please indicate below if a case may not be made public for reasons of confidentiality.

If relevant, describe any reason to keep this case confidential:

Please write the text here

[Department of Clinical Dentistry (IKO), UiT] [case number 1]

Institution: UiT The Arctic University of Norway
Administrative unit: Department of Clinical Dentistry
Title of case study: Oral health psychology
Period when the underpinning research was undertaken: 2013-2024
Period when staff involved in the underpinning research were employed by the submitting institution: 2013-2024
Period when the impact occurred: 2015-2022

1. Summary of the impact (indicative maximum 100 words)
This section should briefly state what specific impact is being described in the case study.

Contributions towards the emerging field of oral health psychology, both at national and international levels.

2. Underpinning research (indicative maximum 500 words)

The application of psychological theory to the realm of dentistry has been of key interest to researchers at IKO, UiT. The research has highlighted the importance of psychological knowledge and theory with oral health practice and research. A substantial part of this activity has investigated the phenomenon of dental anxiety: This includes expanding the understanding of development and maintenance of dental anxiety (research item V), as well as inspecting dental anxiety through the lens of psychological trauma (research item IV). Also, the research has pinpointed that psychological phenomena among dental health professionals are related to their clinical practice and life in general, for instance how psychological capacities/tendencies of dentists and dental students impact their perception of clinical encounters and their quality of life (research items III, VI) and how dental professionals are regarded in society more in general (research item I). Such findings make it relevant to implement psychological theory into training and teaching of oral health professionals, and to provide tools to improve challenging patient encounters, e.g., emotional competence training (research item II) and awareness of how emotional states and arousal could impact clinical practice, both for students and oral health practitioners. More recent developments not included in the research items list have been studies into the psychological foundations of delay of dental care and investigations of the role of cognitive processes in oral hygiene behaviours.

The work within this field has taken place mainly between 2013-2023, and has also included work related to two Phd-projects (Linda Stein 2013-2015 and Hege Nermo 2015-2021). The research activities are closely tied to the strategic plans of the department of clinical dentistry.

Key researchers:

A. Jan Bergdahl; Prof.; retired from IKO in 2016.
B. Jan-Are K. Johnsen; Associate Prof. IKO 2013-2024
C. Hege Nermo; phd-candidate (2015-2021); Associate Prof. from 2022.

The focus on patient centred care and behavioural aspects of dentistry were given considerable attention when planning and developing the dental education at UiT; see:

Eriksen HM, Bergdahl J, Bergdahl M. A patient-centred approach to teaching and learning in dental student clinical practice. Eur J Dent Educ. 2008;12(3):170-175. doi:10.1111/j.1600-0579.2008.00518.x.

Prof. Bergdahl played a key role in strategically establishing this research environment in the years preceeding this case study. Furthermore, the PhD-project of Hege Nermo was funded by the Norwegian Directorate for Health, through Troms fylkeskommune, as part of the TOO-programme (TOO: Tilrettelagt tannhelsetilbud til tortur- og overgrepsutsatte og personer med sterk angst for tannbehandling (odontofobi)).

3. References to the research (indicative maximum of six references)

I. Johnsen, J.-A. K., Eggesvik, T. B., Rørvik, T. H., Hansen, M. W., Wynn, R., & Kummervold, P. E. (2019). Differences in emotional and pain-related language in tweets about dentists and medical doctors: Text analysis of Twitter content. *JMIR Public Health and Surveillance, 5*(1), 1 - 9. doi: 10.2196/10432.

II. Johnsen, J.-A. K., Borit, M., & Stangvaltaite-Mouhat, L. (2022). Using storytelling in undergraduate dental education: Students' experiences of Emotional Competence training. *European Journal of Dental Education*. doi: 10.1111/eje.12868

III. Larsen, M., Holde, G. E., & Johnsen, J.-A. K. (2022). Challenging encounters in clinical dentistry: a qualitative study investigating online reviews of patient satisfaction with Norwegian dentists. *Acta Odontologica Scandinavica, 80*(5), 328-337. doi: 10.1080/00016357.2021.2009909

IV. Nermo, H., Willumsen, T., Rognmo, K., Thimm, J., Wang, C. E. A., & Johnsen, J.-A. K. (2021). Dental anxiety and potentially traumatic events: a cross-sectional study based on the Tromsø Study—Tromsø 7. *BMC Oral Health, 21*, 600. doi:10.1186/s12903-021-01968-4

V. Nermo, H., Willumsen, T., & Johnsen, J.-A. K. (2019). Changes in dental anxiety among 15- to 21-year-olds. A 2-year longitudinal analysis based on the Tromsø study: Fit futures. *Community Dentistry and Oral Epidemiology, 47*, 127 - 133. doi: 10.1111/cdoe.12434.

VI. Storjord, H. P., Teodorsen, M. M., Bergdahl, J., Wynn, R., & Johnsen, J.-A. K. (2014). Dental anxiety: A comparison of students of dentistry, biology and psychology. *Journal of Multidisciplinary Healthcare, 7*, 413 - 418. doi: 10.2147/JMDH.S69178

4. Details of the impact (indicative maximum 750 words)
We have identified the impact of the research activities as follows:

Key research topics were chosen to be included in two text-books (Norwegian and English language) aimed at students within oral health, as well as oral health practitioners (see 5. for references). This includes application of basic and overarching psychological concepts into the field of oral health (e.g. chapters such as "Basic Oral Health Psychology"), but also specific psychological ideas related to behaviour change, impacts of orthognathic surgery om psychosocial functioning, and health literacy. Also, the focus on communication skills and therapeutic competence in patient encounters within dentistry and oral health helped develop the "Teravri"-project in 2019, of which key researchers have been part of the creation and application process as well as the development of key contents and teaching materials. Here the focus is on developing technological tools that can serve as a supplement to, or intensify, traditional methods of teaching therapeutic competence. The pedagogical activities that will spawn from "Teravri" are not limited to oral health, but constitute multidisciplinary and cross-departmental initiatives which are currently being implemented at UiT.

While public health initiative such as the Norwegian TOO-programme draws heavily on insights into psychological trauma and oral health psychology, its inception was prior to the period included in this impact study (2011). However, it still is an important contextual element which formed the backdrop for some of the included research items. Indeed, the clinical guidelines and practice documents for TOO are dynamic documents that are being revised yearly based on feedback from clinicians and researchers. Also, we see the implementation of oral health psychology within the courses offered by the Norwegian Dental Association as part of the systematic post-graduate education mandatory for all dentists. E.g., TSE Module 8 has "patient communication with specific focus on anxious and traumatized patients" as one of its key topics. Furthermore, the recent guidelines issued by the Norwegian Directorate of Health with regards to oral health reflect an increased focus on communication and psychological elements as part of responsible clinical practice. This highlights that the impacts of oral health psychology spans beyond pure research activities/academia, and that these principles and ideas have migrated into clinical practice and public health policy.

The relevance of oral health to health in general has been strengthened by the research and activities within the field, and as a result new, cross-disciplinary collaborations have materialized that should benefit research and patients (e.g., research group for "Clinical Psychology" at Department of Psychology, UiT; see Thim et al., 2023; as well as the research group for "Health Art & Society" at the Faculty of Humanities, Social Sciences and Education, UiT). Finally, oral health psychology is given substantial attention in projects such as "#<3Care4YoungTeeth" (2021) where the aim is to improve oral health among adolescents, including development and collaborative design of technological tools. Other institutions with dental education have asked for input from IKO, UiT on topics from oral health psychology when redesigning or restructuring their oral health educations and/or curriculums, e.g. the University of Malmö (seminar between IKO, UiT and UoM held May 19th 2021; key researcher B presented contents related to research item II).

The impacts described herein has been made in collaboration with several other institutions; most notably the Dental Public Health Competence Center for Northern Norway (TkNN), Sintef and the University of Oslo (UiO). TkNN has been a close collaborating partner through their hosting of the TOO-programme which included funding the phd-project of one of the key researchers. Also, we should acknowledge that the Faculty of Dentistry at UiO has played an important role in helping develop the oral health psychology research area both domestically and abroad, as well as helping disseminate the findings. Prof. Tiril Willumsen at UiO has been instrumental in this work, both within and outside Norway (also central to the teaching in TSE Module 8, see above).

5. Sources to corroborate the impact (indicative maximum of ten references)

Link to the Norwegian Directorate of Health; guidelines for oral health (adults): https://www.helsedirektoratet.no/faglige-rad/helsefremmende-og-forebyggende-tannhelsetiltak-for-voksne-over-20-ar

Link to the Norwegian Dental Association TSE course modules: https://www.tannlegeforeningen.no/kurs-og-etterutdanning/tse.html

Link to the "Teravri"-project website: https://uit.no/project/teravri

Cross-departmental collaboration paper; Department of Psychology, UiT: Thimm, J. C., Rognmo, K., Nermo, H., Johnsen, J.-A. K., Skre, I., & Wang, C. E. A. (2023). Associations between stressful life events in childhood/adolescence and adulthood: Results from the 7th Tromsø survey. European Journal of Psychotraumatology, 14(2), 2237360. doi:10.1080/20008066.2023.2237360

Link to the Directorate of Health website for TOO:
https://www.helsedirektoratet.no/tema/tannhelse/tilrettelagt-tannhelsetilbud--too

Link to the publically available website for TOO: https://www.tooinfo.no/

English language text-book: Willumsen, T., Lein, J. P. Å, Gorter, R., & Myran, L. (eds.) 2022. Oral health psychology: Psychological aspects related to dentistry. Cham, Switzerland: Springer.
https://link.springer.com/book/10.1007/978-3-031-04248-5

Norwegian language text-book: Willumsen, T., Myran, L., & Lein, J. P. Å (eds.). Odontologisk psykologi. Oslo: Gyldendal.
https://www.gyldendal.no/faglitteratur/psykologi/generell/odontologisk-psykologi/p-10022786-no/

Link to the website for the project "#<3Care4YoungTeeth":
https://www.sintef.no/en/projects/2021/care4youngteeth3/

[Department of Clinical Dentistry (IKO), UiT] [case number 2]

Institution: UiT The Arctic University of Norway
Administrative unit: Department of Clinical Dentistry
Title of case study: Oral ecology/oral microbiology
Period when the underpinning research was undertaken: 2013-2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2014-2024
Period when the impact occurred: 2016-2022

1. Summary of the impact (indicative maximum 100 words)

Contributions towards the field of antibiotic resistance research, the importance of monitoring antibiotic consumption by dental health professionals and advocating for rational use of antibiotic when they are needed. Promote the use of the narrow spectrum antibiotic phenoxymethylpenicillin instead of the broad-spectrum amoxicillin in treating dento-alveolar infections.

2. Underpinning research (indicative maximum 500 words)

The frequency of antimicrobial drug resistance in the community is raising and many scientific reports informed of the increasing in resistance profile of oral bacteria. Not so clear is the level of resistance among oral bacteria in different communities with different prescription practices in dentistry. The research conducted at department of clinical dentistry seek to investigate the emergence of antibiotic resistance among oral bacteria and the role of dental health professional to halt the problem form two aspects. The first aspect is attitude, knowledge, and tendencies to antibiotic prescription and actual contribution of dental prescription to the total antibiotic prescription in the community. The second aspect is about resistance determinants in oral bacterial and the role of horizontal gene transfer (HGT) in dissemination of resistance among bacterial population. This line of research started long time ago by Professor Mohammed Al-Haroni and continued after he joined the department of clinical dentistry in 2014.

The work within this field has taken place at the department of clinical dentistry mainly between 2014-2022 and it is included work related to one PhD-projects (Tracy Lunde; 2016-2022) and one postdoc project (Supathep Tansirichaiya; 2018-2021), collaboration projects with colleagues from Norway, England, Scotland and Sweden.

The research work in this field is still ongoing and the recent publication in 2023 highlighted an increase of antibiotic prescription patern among dentists in Norway from 2018 to 2022, especially during the Covid-19 pandemic. This latest publication about Covid-19 and prescription of antibiotic by dentists in Norway has resulted in establishment of new contact with the Antibiotic Centre for Primary Care in Norway (https://www.med.uio.no/helsam/english/research/groups/general-practice-medicine/asp/) to formulate an action plan to tackle the increasing trend in antibiotic presecrption in dental health professionals in Norway, especially for these who graduated from outside Scandinavian countries.

- Key researchers from the department of clinical dentistry:
    1. Mohammed Al-Haroni; Professor; IKO from 2014-2024.
    2. Rania Al-Mahdi; Associate professor; IKO from 2019-2024
    3. Tracy Lunde; PhD-candidate (2016-2022); postdoc from 2022-2024.
    4. Supathep Tansirichaiya; Postdoc (2018-2021).

3. References to the research (indicative maximum of six references)

1. Smith A, Al-Mahdi R**,** Palmer N, Dahlen G and Al-Haroni M (Corresponding author). Comparison of antimicrobial prescribing for dental and oral infections in England and Scotland with Norway and Sweden 2010-2016. BMC Oral Health. **2020**Jun 16;20(1):172. doi: 10.1186/s12903-020-01163-x

2. Supathep Tansirichaiya, Sabrina John Moyo, Mohammed Al-Haroni, Adam P. Robert. Capture of a Novel, Antibiotic Resistance Encoding, Mobile Genetic Element from Escherichia coli Using a New Entrapment Vector. J Appl Microbiol. 2021 Mar;130(3):832-842. doi: 10.1111/jam.14837. Epub 2020 Sep 1

3. Lunde T, Hjerde E and Al-Haroni M (Corresponding author). Prevalence, diversityand transferability of Tn916-Tn1545 family ICE in oral streptococci. J Oral Microbiol. 2021 Mar 15;13(1):1896874. doi: 10.1080/20002297.2021.1896874

4. J. Wigand, S. Tansirichaiya, E. Winje, M. Al-Haroni (Corresponding author). Functional screening of a human saliva metagenomic DNA reveal novel resistance genes against sodium hypochlorite and chlorhexidine, BMC Oral Health 21(1) (2021) 632

5. Tansirichaiya S, Winje E, Wigand J, Al-Haroni M. Inverse PCR-based detection reveal novel mobile genetic elements and their associated genes in the human oral metagenome. BMC Oral Health. 2022;22(1):210

1. F. Tousi, M Al-Haroni, S.A Lie, B Lunde. Antibiotic prescriptions among dentists across Norway and the impact of COVID-29 pandemic. BMC Oral Health 23 (2023)

4. Details of the impact

- Research findings are implemented in the teaching curriculum for dental students in their 3rd year taking the oral ecology course at the department of clinical dentistry.
- Collaboration with Professor Andrew Smith from University of Glasgow, Scotland have resulted into the change of clinical guidelines of antibiotic prescription in Scotland in 2021 and adoption of the Norwegian prescription practices of using the narrow spectrum phenoxymethylpenicillin when treating dento-alveolar infections instead of broad spectrum antibiotics.
- Research findings has been used as a material to inform the public and advocate for the rational use of antimicrobials.

5. Sources to corroborate the impact

https://www.sdcep.org.uk/media/ckgfnx3w/sdcep-drug-prescribing-ed-3-update-june-2021.pdf

https://www.forskning.no/bakterier-tenner/du-har-seks-milliarder-bakterier-i-munnen-flere-av-dem-er-resistente-mot-vanlige-bakteriedrepende-midler/2057787

UiT The Arctic University of Norway, Department of Community Medicine (ISM), Impact case 1

Institution: UiT- The Arctic University of Norway
Administrative unit: Department of Community Medicine (ISM)
Title of case study: Disease prevention through surveillance and analyses of non-communicable diseases and modifiable risk factors in population-based cohorts
Period when the underpinning research was undertaken: 2012-present
Period when staff involved in the underpinning research were employed by the submitting institution: Ola Løvsletten (chief engineer 2018-19, researcher 2019-present) Sameline Grimsgaard (phd 1993-2001, assoc prof 2013-2015, prof 2018-present) Charlotta Rylander (phd 2010, postdoc 2011-16, assoc prof 2016-21, prof 2021-present) Tom Wilsgaard (phd 1998-2002, post doc 2002-05, assoc prof 2005-12, prof 2012-present) Magritt Brustad (phd 2000-04, postdoc 2004-07, researcher 2004-10, prof 2010-present) Kristin B. Borch (phd 2009-13, postdoc 2013-15, researcher 2015-16, assoc prof 2017-present) Laila A. Hopstock (phd 2007-12, researcher 2012-15, assoc prof 2015-18, researcher 2018-22, prof 2022) Marie W. Lundblad (phd 2017-21, researcher 2021-22, postdoc 2022-present) Marisa da Silva (phd 2015-20) Bjarne K. Jacobsen (phd 1985-87, assoc prof 1988, senior researcher 1989-91, prof 1992-present) Anne Elise Eggen (1993–prof present) Guri Skeie (phd 2003-09, postdoc 2009-14, assoc prof 2014-18, prof 2018-present) Inger Torhild Gram (assoc prof 1992-99, prof 1999-present) Inger Njølstad (phd 1990-93, researcher 1993-99, postdoc 1999-2001, prof 2002-23, prof emerita present)
Period when the impact occurred: 2012 - 2022

1. Summary of the impact

Our research on non-communicable diseases (NCDs) and modifiable risk factors, derived from extensive population-based cohorts, informs stakeholders and shapes public health policies, national guidelines, and public resources. This work not only enhances public health but also fortifies the national understanding of NCDs and their preventable risks.

2. Underpinning research

We provide examples of the underpinning research that target NCD risk reduction conducted at the Department of Community Medicine (ISM) in collaboration with national and international partners, drawing primarily on data from the Tromsø Study and the Norwegian Women and Cancer (NOWAC) Study. We've categorized key modifiable risk factors following the Norwegian Institute of Public Health's guidelines. This research, part of diverse ISM projects, including postdoctoral and PhD work, has notably influenced public health policies on tobacco use, diet, blood pressure, and overall NCD risk management. We've detailed the contributions of principal researchers, their ISM tenure, and roles above.

Physical activity: ISM has conducted significant research on physical activity, utilizing data from the Tromsø Study and the NOWAC study. Data from NOWAC contributed to the EPIC study, revealing that leisure-time physical activity is associated with reduced risks across 26 cancer types (Moore et al, 2016, **R1**). In Tromsø, there's been a positive trend in regular leisure-time exercise over the past 30 years. Yet, there's also been a rise in sedentary behavior at work during this period (Morseth et al, 2020, **R2**).

Tobacco: Results from extensive research on tobacco use and control, has been initiated, conducted, and disseminated nationally and internationally from ISM. ISM has published on the effects of smoking in different cohorts (Parajuli, 2013, **R3**) as well as "snuff" use, showing that snuff use may prevent successful smoking cessation. Further, one of the world's largest randomized controlled trials (RCT)'s on smoking cessation is conducted from ISM, where results showed found that smoking cessation interventions may be equally good when delivered by a mobile app or email at a population level.

Diet with emphasize on Vitamin D: ISM plays a significant role in both national and international nutrition research. Notably, ISM has provided critical expertise in the areas of Vitamin D, fiber, and cereals, contributing to the creation of systematic reviews for the 2012 Nordic Nutrition Recommendations (NNR) (Lamberg-Allardt et al, 2013, **R4**). Additionally, ISM was involved in updating these guidelines for the 2023 edition, with work having commenced in 2020. The Norwegian arm of the EPIC study is led from our department (Skeie G) from where numerous articles on nutrition and cancer are published. Data from the Tromsø Study indicate that while the population generally adheres to the 2012 Nordic Nutrition Recommendations (NNR2012), there is a notable discrepancy with many individuals consuming more saturated fat and less fiber and vitamin D than advised. (Lundblad, 2019, **R5**).

Blood pressure: Longitudinal data from the Tromsø Study have shown both time and cohort effects in systolic blood pressure, where systolic blood pressure increased with age in women and men born 1920 to 1949, whereas a decrease or flattening trend was observed in the younger birth cohorts (Hopstock LA et al, 2015, **R6**).

Overweight and obesity: With longitudinal data from the Tromsø Study it is observed that overweight and obesity, measured as body mass index (BMI), waist circumference or body fat have increased in both women and men, with a higher increase in the younger generations (i.e. Ola Løvsletten et al, 2020, **R7**, and other publications). In the NOWAC study it has been demonstrated how the short-term adult weight change increases the risk for obesity-related cancers, and especially pancreatic cancer (da Silva M, 2018, **R8**).

NCD risk factors combined and other related research: From 2007-08 (Tromsø6) until 2015-16 (Tromsø7) there had been an improvement in cardiovascular disease (CVD) risk factors during 8 years in individuals with high risk for CVD, although the guideline-based treatment target achievement was low for all risk factors despite smoking (Hagen AN et al, 2022, **R9**). Several other publications from the Tromsø Study show how singular or multiple risk factors for CVD has changed over time (i.e. Hopstock LA et al, 2017, **R10**). Further, ISM has successfully developed and piloted a smartphone-based information communication technology solution for collecting data on the four modifiable risk factors for the four main NCDs (Gram IT et al, 2022, **R11**). This has been further developed as one of three pillars of the funded EU Study "Watching the risk factors: Artificial intelligence (AI) and the personalized prevention and management of chronic conditions" (WARIFA) (2021-2024) where several researchers from our department are involved (Gram IT, Skeie G and more).

The department contributes with both data and manpower to international projects on NCD risk factor prevention. Examples of such international collaborations are the NCD-RisC (The NonCommunicable Diseases Risk Factor Collaboration), which focuses on global trends and health effects of cardiometabolic risk factors (Wilsgaard T et al**,** the Tromsø Study), and the EPIC study (Skeie G et al., NOWAC), leading to major impact in cancer research, and further to prevention, and treatment.

3. References to the research

R1. Moore, Steven C., I-Min Lee, Weiderpass E, Campbell PT, Sampson JN, Kitahara CM, Keadle SK, Arem H, de Gonzalez AB, Hartge P, Adami HO, Blair CK, **Borch KB**, Boyd E, Check DP, Fournier A, Freedman ND, Gunter M, Johannson M, Khaw KT, Linet MS, Orsini N, Park Y, Riboli E, Robien K, Schairer C, Sesso H, Spriggs M, Dusen RV, Wolk A, Matthews CE, and Patel AV. Association of Leisure-Time Physical Activity with Risk of 26 Types of Cancer in 1.44 Million Adults. JAMA Intern. Med. 176, no. 6 (2016): 816-25. DOI: 10.1001/jamainternmed.2016.1548 .

R2. Morseth B, **Hopstock LA**. Time trends in physical activity in the Tromsø study: An update. PLoS One. 2020;15(4):e0231581. DOI: 10.1371/journal.pone.0231581.

R3. Parajuli R, Bjerkaas E, Tverdal A, Selmer R, Le Marchand L, Weiderpass E, and **Gram IT**. The Increased Risk of Colon Cancer Due to Cigarette Smoking May Be Greater in Women Than Men. Cancer Epidemiol Biomarkers Prev. 22, no. 5 (May 2013): 862-71. DOI: 10.1158/1055-9965.Epi-12-1351.

R4. Lamberg-Allardt C, **Brustad M**, Meyer HE, Steingrimsdottir L. Vitamin D - a systematic literature review for the 5th edition of the Nordic Nutrition Recommendations. Food Nutr Res. 2013;57. DOI: 10.3402/fnr.v57i0.22671

R5. **Lundblad MW**, Andersen LF, **Jacobsen BK**, Carlsen MH, Hjartåker A, **Grimsgaard S**, and **Hopstock LA**. Energy and nutrient intakes in relation to National Nutrition Recommendations in a Norwegian population-based sample: the Tromsø Study 2015–16. Food Nutr Res. 2019. DOI: 10.29219/fnr.v63.3616.

R6. **Hopstock LA**, Bønaa KH, **Eggen AE**, **Grimsgaard S**, **Jacobsen BK**, Løchen M-L, Mathiesen EB, **Njølstad I**, and **Wilsgaard T**. Longitudinal and Secular Trends in Blood Pressure Among Women and Men in Birth Cohorts Born Between 1905 and 1977. Hypertension. 2015;66(3):496-501. DOI: 10.1161/HYPERTENSIONAHA.115.05925.

R7. **Løvsletten O**, **Jacobsen BK**, **Grimsgaard S**, **Njølstad I**, **Wilsgaard T**, Løchen M-L, **Eggen AE**, and **Hopstock LA**. Prevalence of general and abdominal obesity in 2015–2016 and 8-year longitudinal weight and waist circumference changes in adults and elderly: the Tromsø Study. BMJ Open. 2020;10(11):e038465. DOI: 10.1136/bmjopen-2020-038465.

R8. **da Silva M**, Weiderpass E, Licaj I, Lissner L, **Rylander C**. Excess body weight, weight gain and obesity-related cancer risk in women in Norway: the Norwegian Women and Cancer study. Br J Cancer. 2018;119(5):646-56. DOI: 10.1038/s41416-018-0240-5.

R9. Hagen AN, Ariansen I, Hanssen TA, Lappegård KT, **Eggen AE**, Løchen ML, **Njølstad I**, **Wilsgaard T**, **Hopstock LA**. Achievements of primary prevention targets in individuals with high risk of cardiovascular disease: an 8-year follow-up of the Tromsø study. Eur Heart J Open. 2022;2(5):oeac061. DOI: 10.1093/ehjopen/oeac061.

R10. **Hopstock LA**, Bønaa KH, **Eggen AE**, **Grimsgaard S**, **Jacobsen BK**, Løchen ML, Mathiesen EB, **Njølstad I**, and **Wilsgaard T**. Longitudinal and secular trends in total cholesterol levels and impact of lipid-lowering drug use among Norwegian women and men born in 1905-1977 in the population-based Tromsø Study 1979-2016. BMJ Open. 2017;7(8):e015001. DOI: 10.1136/bmjopen-2016-015001.

R11. **Gram IT**, **Skeie G**, Oyeyemi SO, **Borch KB**, **Hopstock LA**, and **Løchen M-L**. A smartphone-based information communication technology solution for primary modifiable risk factors for

noncommunicable diseases: Pilot and feasibility study in Norway. JMIR Form Res. 2022;6(2):e33636. DOI: 10.2196/33636.

4. Details of the impact

The department's comprehensive research into NCDs and associated risk factors has yielded insights into incidence, trends, and the combined impact of modifiable risk factors on NCDs, highlighting opportunities for prevention. Leveraging the extensive longitudinal population-based studies at our department, our research has informed public health through accessible science communication, shaping guidelines and recommendations, influencing public health policy, driving technological innovation such as the development of self-help and monitoring applications, and contributing to expert panels at both national and international levels.

The Tromsø Study, alongside the cited researchers and others, provides critical data to the Norwegian Institute of Public Health (NIPH) for tracking population trends in diet (including salt, saturated fat, and fruit and vegetable intake), blood pressure, obesity, and cholesterol levels. This information is accessible on the NIPH website, serving both the public and policymakers in devising recommendations and preventive measures for the Norwegian populace (**S1**). With expertise in cardiovascular disease (CVD) and its risk factors, the Tromsø Study and researchers have played a pivotal role in an expert panel that formulated the Norwegian guidelines for CVD risk assessment and management (Njølstad I, **S2**). Findings on physical activity from the NOWAC and Tromsø Study are regularly shared with the public and policymakers, highlighting the significance of an active lifestyle (**S3**). The Tromsø Study's insights are particularly influential in governmental strategies, such as the "Action Plan for Physical Activity 2020-2029" (**S4**), which aims to enhance public health by improving access to outdoor spaces and implementing other initiatives to boost activity levels among the population. Additionally, research on weight change and obesity, including the adverse effects of weight gain on cancer risk, is disseminated to the public, further informing health interventions and planning (**S5**).

ISM has for many years contributed into expert groups related to tobacco legalizations as well as communicated results from collaborative research to the national and international public, and directly to the Norwegian Directorate of Health, for them to exploit. The large RCT lead from the ISM on smoking cessation further led to the creation of the motivation app “slutta.no” which can be used by the public and health care professionals (Gram IT, **S6**). Results regarding the effects on smoking on cancer (in different sites) are disseminated in national and international platforms, informing the public on the harmful effects of smoking (Gram IT, **S7**).

The department's role in shaping dietary recommendations and disseminating research findings, particularly concerning Vitamin D, is substantial at both national (**S8**) and international levels. Our experts, including Brustad M and Skeie G, have made significant contributions to the National Council of Nutrition, an esteemed group established by The Norwegian Directorate of Health to enhance nutritional focus in public and healthcare settings. Additionally, ISM experts are integral to the development of chapters and review papers for the Nordic Nutrition Recommendations (NNR), contributing to both the 2012 edition and the 2023 guidelines. The department's input into the NNR is vital for public health and policymakers, as it forms the foundation for national dietary guidelines for the public (**S9**). Moreover, ISM is represented in the Norwegian Scientific Committee for Food and Environment by Skeie G, serving from 2019 to 2023.

ISM actively participates in public discourse on NCD risk factors, including a notable instance in 2020 when we contributed to an appeal urging the government to prioritize actions to mitigate NCDs (**S10**). The department's extensive international networks, data sharing, and collaborative efforts in research on cardiovascular disease (CVD) and cancer, reinforce the international evidence base for prevention of NCDs, informing health policies and interventions at both national and international levels. The Tromsø Study, with abovementioned researchers, contributes with

data on, among other, blood pressure into the NCD Risk Factor Collaboration presenting global trends (**S11**).

5. Sources to corroborate the impact

S1. Norwegian Institute of Public Health. Indicators for non-communicable diseases connected to the national and global strategy for non-communicable diseases [Indikatorer for ikke-smittsomme sykdommer knyttet til den nasjonale og globale NCD-strategien]. Norwegian Institute of Public Health; 2023. Available from: https://www.fhi.no/en/nc/Indicators-for-NCD/?term=

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S10. Organizations, institutions and professionals. Folkehelseopprop til regjeringen [Public health appeal to the government], Folkehelseforeningen; 2020 [updated 18.12.2020]. Available from: https://folkehelseforeningen.no/folkehelseopprop-til-regjeringen/.

S11. Norsk Helseinformatikk (Marthe Lein). Nordmenns blodtrykk er blitt markant forbedret [Norwegians' blood pressure has markedly improved], 2017 [updated 24. 01. 2017]. Available from: https://nhi.no/livsstil/egenomsorg/nordmenns-blodtrykk-er-blitt-markant-forbedret.

UiT The Arctic University of Norway, Department of Community Medicine (ISM), Impact case 2

Institution: UiT The Arctic University of Norway (UiT)
Administrative unit: Department of Community Medicine (ISM)
Title of case study: Unravelling atrial fibrillation: Sex-specific insights and proactive prevention strategies from the Tromsø Study
Period when the underpinning research was undertaken: 2012 – present
Period when staff involved in the underpinning research were employed by the submitting institution: Maja-Lisa Løchen (1986-2022) Ekaterina Sharashova (phd 2012-2017, researcher 2017-2019, assoc prof 2019-present) Sweta Tiwari (phd student, post doc and researcher 2013-2023) Bente Morseth (phd 2008-2011, post doc 2013-2019) Audhild Nyrnes (phd 2008-2013, researcher 2019-2022) Hilde Espnes (phd 2019 – present) Tom Wilsgaard (phd 1998-2002, post doc 2002-2005, assoc prof 2005-2012, prof 2012-present)
Period when the impact occurred: progressively starting from 2016

1. Summary of the impact

The comprehensive research led by Prof. Maja-Lisa Løchen's team in the Epidemiology of Chronic Diseases research group has transformed our understanding of atrial fibrillation (AF). Analysing Tromsø Study data, the team identified sex-specific AF risk factors, emphasizing blood pressure in women and body mass index (BMI) in men. These findings challenge current treatment norms and drive personalized prevention strategies. Internationally recognized, the research sparks discussions on sex-specific blood pressure targets, influencing clinical guidelines. Crucially, it paves the way for ongoing AF intervention trials (e.g., NEXAF) and collaborative projects in screening (e.g., AFFECT-EU) and genetics (GENAF), shaping the trajectory of AF research and clinical approaches.

2. Underpinning research

The underpinning research conducted at ISM in collaboration with local *(Department of Clinical Medicine, School of Sport Sciences, and Department of Psychology at UiT)*, national *(University of Bergen, University of Oslo, and Baerum Hospital)* and international partners *(Monash University, Australia; Sahlgrenska Academy - University of Gothenburg, Sweden; University of Groningen, Netherlands; University Heart and Vascular Centre Hamburg, Germany)* focused on unravelling the natural history of AF through extensive analysis of the large population based longitudinal Tromsø Study data. Spanning several years, this research sought to comprehensively investigate AF incidence trends, risk factors including genetic risk factors, and their impact on the population's health focusing on sex differences and AF subtypes.

The research has been conducted by several researchers from the Epidemiology of Chronic Diseases research group, ISM as a part of several smaller projects including PhD and postdoctoral projects. **Maja-Lisa Løchen** (MD, DrMed, Professor Preventive Medicine, Senior Consultant Cardiology) and later also **Ekaterina Sharashova** (MD, MPD, PhD, Associate professor) played a pivotal role in leading the AF research team and contributing their expertise in the field. The team consisted of researchers with diverse backgrounds and specializations, fostering a multidisciplinary approach to AF research. Names of the key researchers (with the positions they held at ISM and

the dates) are also listed in the top of the document. Sources of funding included the following: UiT The Arctic University of Norway, Helse Nord, The National Association for Public Health (Nasjonalforeningen for folkehelsen), Norwegian EXTRA Foundation for Health and Rehabilitation through EXTRA FUNDS, the Norwegian Heart and Lung Patient Organization, EU.

An integral component of this research was undertaken by **Audhild Nyrnes (MD, PhD)** as part of her doctoral project. **Audhild Nyrnes** in collaboration with **Maja-Lisa Løchen** validated AF outcomes for the Tromsø Study participants, establishing the foundational groundwork for all subsequent AF research endeavours. **Audhild Nyrnes et al** further discovered that inflammatory biomarkers **(2012)** were independently associated with AF risk in men but not in women, while palpitations **(2013**) and uric acid **(2014)** were associated with increased risk of AF in both women and men.

Bente Morseth et al (2016) (R1) in her post doc project demonstrated that leisure time physical activity was associated with AF in a U-shaped pattern. Moderate physical activity was associated with a reduced risk of AF, whereas higher activity levels attenuated the benefits of moderate activity. This has led to the hypothesis that the mechanisms underlying an increased risk of AF with intensive exercise are different from those underlying a reduced risk with moderate physical activity. **Sweta Tiwari et al (2015) (R2)** demonstrated that enlarged left atrium is a significant risk factor for AF in both sexes, and adding measures of abnormal diastolic flow increased the predictive ability significantly. Later **Kim Arne Heitmann et al (2022)** confirmed that left atrial enlargement increased AF risk, however physical activity attenuated the increased risk of AF with left atrial enlargement in both women and men and in all age groups suggesting that the protective effect of moderate physical activity outweighs the potential risk of AF with left atrial enlargement.

Sweta Tiwari et al (2017) further demonstrated that in stroke-free participants AF was independently associated with cognitive decline as measured with the tapping test. Later, as a part of the AF-SCREEN International Collaboration **Maja-Lisa Løchen (2022) (S4)** contributed to the report on AF and dementia that summarized evidence linking AF to cognitive impairment and dementia, offering guidance on investigating and managing dementia in AF patients, while also addressing potential pathophysiologic mechanisms and highlighting knowledge gaps for future research.

Maja-Lisa Løchen (2017-2018) also collaborated with Icelandic researchers and contributed our data and expertise to several articles on genetic risk factors for AF published in high-ranking journals.

Ekaterina Sharashova et al (2020) (R3) uncovered sex-specific patterns in AF risk factors, particularly emphasizing the differential impact of blood pressure in women and men. The study reviled stronger associations of elevated systolic and diastolic blood pressure with future AF risk in women compared to men despite generally favourable cardiovascular risk profile in women. Moreover, having elevated blood pressure over longer time increased AF risk gradually, especially in women. Further, **Hilde Espnes et al (2021) (R4)** found that increasing systolic blood pressure was associated with an increased risk of both paroxysmal/persistent AF and permanent AF in women, but only paroxysmal/persistent AF in men. While blood pressure was a stronger AF risk factor in women compared to men, higher BMI had a greater influence on future AF development in men than in women **(Jocasta Ball et al, 2017) (R5)**. Consequently, **Ekaterina Sharashova et al (2022) (R6)** demonstrated that from 1994 to 2016 AF incidence rates decreased in women, while the rates increased following a reverse J-shape in men. Reduction in blood pressure in women, and increase in BMI in men had the largest contribution to the AF incidence trends. Altogether these findings highlight the importance of sex-specific risk stratification and optimizing blood pressure management as well as interventions to decrease BMI for the prevention of AF and AF

subtypes in clinical practice. Even modest reductions in population blood pressure and BMI are likely to have a significant effect on the public health burden of AF.

Later, in collaboration with MORGAM consortium and through our participation in several EU projects, such as AFFECT-EU **Bente Morseth et al (2021) (R7)** have confirmed that risk of AF was largely attributed to BMI, high alcohol consumption and a history of myocardial infarction or stroke from middle age in a large European cohort.

The research took place against the backdrop of a growing recognition of the global burden of AF and a heightened focus on preventive strategies. The Tromsø Study, being one of the largest longitudinal population-based studies and having validated follow-up data on AF, provided a robust platform for collecting and analysing data, ensuring the generalizability and reliability of the findings.

3. References to the research

(R1) **Morseth B**, Graff-Iversen S, Jacobsen BK, Jørgensen L, Nyrnes A, Thelle DS, Vestergaard P, **Løchen ML**. Physical activity, resting heart rate, and atrial fibrillation: the Tromsø Study. *Eur Heart J 2016* Aug 1;37(29):2307-13. DOI:10.1093/eurheartj/ehw059

(R2) **Tiwari S**, Schirmer H, Jacobsen BK, Hopstock LA, **Nyrnes A**, Heggelund G, **Njølstad I**, Mathiesen EB, **Løchen ML**. Association between diastolic dysfunction and future atrial fibrillation in the Tromsø Study from 1994 to 2010. *Heart 2015* Aug;101(16):1302-8. DOI:10.1136/heartjnl-2015-307438

(R3) **Sharashova E**, **Wilsgaard T**, Ball J, **Morseth B**, Gerdts E, Hopstock LA, Mathiesen EB, Schirmer H, **Løchen ML**. Long-term blood pressure trajectories and incident atrial fibrillation in women and men: the Tromsø Study. *Eur Heart J 2020* Apr 21;41(16):1554-1562. DOI:10.1093/eurheartj/ehz234

(R4) **Espnes H**, Ball J, **Løchen ML**, **Wilsgaard T**, **Njølstad I**, Mathiesen EB, Gerdts E, **Sharashova E**. Sex-Specific Associations between Blood Pressure and Risk of Atrial Fibrillation Subtypes in the Tromsø Study. *J Clin Med 2021* Apr 5;10(7):1514. DOI:10.3390/jcm10071514

(R5) Ball J, **Løchen ML**, **Wilsgaard T**, Schirmer H, Hopstock L, **Morseth B**, Mathiesen EB, **Njølstad I**, **Tiwari S**, **Sharashova E**. Sex Differences in the Impact of Body Mass Index on the Risk of Future Atrial Fibrillation: Insights From the Longitudinal Population-Based Tromsø Study. *J Am Heart Assoc 2018* Apr 19;7(9):e008414. DOI:10.1161/JAHA.117.008414

(R6) **Sharashova E**, Gerdts E, Ball J, **Espnes H**, Jacobsen BK, Kildal S, Mathiesen EB, **Njølstad I**, Rosengren A, Schirmer H, **Wilsgaard T**, **Løchen ML**. Sex-specific time trends in incident atrial fibrillation and the contribution of risk factors: the Tromsø Study 1994-2016. *Eur J Prev Cardiol 2023* 11;30(1):72-81. Published: 14 October 2022. DOI:10.1093/eurjpc/zwac234

(R7) **Morseth B**, Geelhoed B, Linneberg A, Johansson L, Kuulasmaa K, Salomaa V, Iacoviello L, Costanzo S, Söderberg S, Niiranen TJ, Vishram-Nielsen JKK, **Njølstad I**, **Wilsgaard T**, Mathiesen EB, **Løchen ML**, Zeller T, Blankenberg S, Ojeda FM, Schnabel RB; MORGAM consortium. Age-specific atrial fibrillation incidence, attributable risk factors and risk of stroke and mortality: results from the MORGAM Consortium. Open Heart 2021 Jul;8(2):e001624. DOI:10.1136/openhrt-2021-001624

4. Details of the impact

The epidemiological research on AF in the Tromsø Study has contributed to new knowledge regarding AF incidence, risk factors and AF subtypes in women and men **(S1)** contributing to our understanding of AF natural history, pathophysiology and risk stratification. The findings have been far-reaching, shaping clinical practice and improving patient care both nationally and internationally, influencing guidelines, and fostering collaborative initiatives.

An impactful outcome of our research was evident in the 2016 European Guidelines on cardiovascular disease prevention in clinical practice **(S2)**, where prof. Maja-Lisa Løchen was

invited to provide insights on AF. Subsequently, we have contributed to other guidelines and position papers addressing AF prevention **(S3, S4)**. This engagement reflects the recognition of our expertise in the field, solidifying our research's influence on shaping international guidelines.

Furthermore, our contributions extend to the realm of women's health, notably in the book on Women's Hearts (Kvinnehjerter: en medisinsk fagbok om vanlige hjertesykdommer) written by Maja-Lisa Løchen and Eva Gerdts **(S5)**, where substantial content delves into AF. Additionally, Maja-Lisa´s expertise in sex differences in AF and heart disease led to an invitation to the Government's Women's Health Committee (Utvalg om kvinners helse og helse i et kjønnsperspektiv) **(S6)**, showcasing the real-world application of our research in shaping health policy and fostering gender-specific considerations in the prevention and management of heart-related conditions.

A study on the interplay of blood pressure burden over time and sex **(R3)** has had an impact on clinical practice and personalized sex-specific prevention strategies both nationally and internationally. Importance of the findings has been highlighted by Shah DC in the editorial of the European Heart Journal: “The stronger associations of elevated blood pressure with future AF risk in women in this study despite lower blood pressure, lower prevalence of hypertension, lower lipid levels, and lower BMI (compared to the men) should open debate about gender-specific optimal BP targets or treatment thresholds. Current guidelines rightly emphasize more aggressive, rapid, and sustained control of BP values than before, and while we await confirmatory data of reduced future AF risk in longitudinal studies, cross-sectional studies of atrial substrate evaluation, e.g. by magnetic resonance imaging correlated with BP burden over time, may provide supportive evidence over a shorter time frame.” **(S7)** The ongoing discussions and debates in the scientific community, as highlighted in editorials and conferences, serve as indirect indicators of the research's impact on shaping opinions and influencing clinical guidelines. The paper also received the "Article of the Year 2019" award from the Norwegian Epidemiological Association (NOFE), underscoring its quality and impact within the academic community **(S8)**.

High quality and up-to-date information on AF epidemiology is constantly disseminated to the public, patients, healthcare professionals, and researchers. We are a part of the Norwegian Atrial Fibrillation Research Network (afib.no) **(S9)**, present and discuss our findings on scientific cardiological conferences (ESC Congress, ESC Preventive Cardiology Congress), conduct seminars for researchers and clinicians, disseminate findings to patients (Troms County Branch in The National Association for Public Health/ Troms fylkeslag i Nasjonalforeningen for folkehelsen), and to the public**.** The research has impacted the general population by raising awareness of sex-specific risk factors for AF. Public lectures, media engagements, and information dissemination have empowered individuals to make informed choices regarding their cardiovascular health, contributing to primary prevention efforts.

Prof. Maja-Lisa Løchen who led this research over many years was recently awarded the Norwegian Cardiological Society's Research Prize for 2023 **(S10)**. “Through her work as a professor and senior consultant, she has influenced primary and secondary prevention of cardiovascular disease over several decades," states the jury's rationale. It is awarded to individuals who have made a significant contribution to highlighting cardiovascular research both nationally and internationally, with a scientific output of international standards that has directly or indirectly influenced the treatment of patients with heart and vascular diseases.

The impact unfolded progressively over the years, with key milestones such as contribution to the European guidelines **(S2, S3, S4)**, or the publication long-term blood pressure trajectories and risk of AF **(R3)** serving as significant catalysts for broader recognition and influence. Ongoing impacts continue to shape clinical and research practices, contributing to a sustained and evolving legacy. The establishment and progression of collaborative studies (NEXAF, AFFECT-EU, GENAF) serve as

tangible indicators of the research's influence, showcasing its role as a foundational element in ongoing investigations.

5. Sources to corroborate the impact

(S1) **Løchen ML**, **Tiwari S**. Epidemiologisk atrieflimmerforskning i tromsøundersøkelsen. Hva har vi lært? Hjerteforum 2019 2(32): 35-44. https://www.legeforeningen.no/contentassets/bb474a6452f94094a39ba73342453a5d/hjforum-2.2019-web-9-epidemiologisk-atrieflimmerforskning-i-tromsoundersokelsen.-hva-har-vi-lart.pdf

(S2) Piepoli MF, Hoes AW, Agewall S, …, **Løchen ML** et al; ESC Scientific Document Group. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Practice Guideline. *Eur Heart J 2016* Aug 1;37(29):2315-2381. DOI: 10.1093/eurheartj/ehw106

(S3) Gorenek B, Pelliccia A, Benjamin EJ, …, **Løchen ML** et al. European Heart Rhythm Association (EHRA)/European Association of Cardiovascular Prevention and Rehabilitation (EACPR) position paper on how to prevent atrial fibrillation endorsed by the Heart Rhythm Society (HRS) and Asia Pacific Heart Rhythm Society (APHRS). Eur J Prev Cardiol. 2017 Jan;24(1):4-40. Epub 2016 Nov 4. PMID: 27815538; PMCID: PMC5427484. DOI: 10.1177/2047487316676037

(S4) Rivard L, Friberg L, Conen D, …, **Løchen ML** et al. Atrial Fibrillation and Dementia: A Report From the AF-SCREEN International Collaboration. *Circulation 2022* Feb;145(5):392-409. DOI: 10.1161/CIRCULATIONAHA.121.055018

(S5) **Løchen ML**, Gerdts E. Kvinnehjerter (E-bok - tilsvarer 1. trykte utgave fra 2015). En medisinsk fagbok om vanlige hjertesykdommer. GYLDENDAL 2022. https://www.gyldendal.no/faglitteratur/e-boeker/medisin/kvinnehjerter-e-bok/p-10032332-no/

(S6) Utvalg om kvinners helse og helse i et kjønnsperspektiv https://www.regjeringen.no/no/dep/hod/org/styrer-rad-og-utvalg/tidligere-styrer-rad-og-utvalg/utvalg-om-kvinners-helse-og-helse-i-et-kjonnsperspektiv/id2870286/

(S7) Shah DC. Longitudinal, long-term evaluation of new-onset atrial fibrillation: the interplay of blood pressure burden over time and gender. *Eur Heart J (EDITIRIAL) 2020* Apr 21;41(16): 1563–1564. DOI: 10.1093/eurheartj/ehz374

(S8) Norwegian Epidemiological Association's (NOFE's) "Paper of the year" prize 2019. Assessment criteria were: outstanding scientific quality and integrity in a) methodologic robustness, b) presentation, and c) contribution to the field. https://nofe.no/arets-artikkel/

(S9) Notes from the afib.no 7th annual meeting at Lysebu; September 2023. https://afib.no/2023/10/17/3351/

(S10) Hjertespesialist og IKMs instituttleder Maja-Lisa Løchen ble nylig tildelt Norsk kardiologisk selskaps forskningspris for 2023. https://uit.no/nyheter/artikkel/kortnytt?p_document_id=829840

UiT The Arctic University of Norway, Department of Community Medicine (ISM), Impact case 3

Institution: UiT The Arctic University of Norway
Administrative unit: Department of Community Medicine (ISM)
Title of case study: Measuring health outcomes for priority setting decisions
Period when the underpinning research was undertaken: 2012-22
Period when staff involved in the underpinning research were employed by the submitting institution: PI, since 1999, PhD students 2013-17
Period when the impact occurred: 2013-23

1. Summary of the impact

Decisions on healthcare resources allocation and priority setting are increasingly being based on cost-effectiveness analysis, whereby effectiveness is measured in terms of gained QALYs (quality-adjusted life years). However, immense challenges are involved in this generic health measure. Our research has made important methodological impacts on measuring health-related quality of life, and how to account for equity. This research has impacted Norwegian guidelines for priority setting and health technology assessment, as well as the use of patient-reported measures in clinical quality registries and clinical trials. By including quality of life in population health studies, we provide new insights on health inequalities.

2. Underpinning research

In collaboration with the Knowledge Center (now part of the Norwegian Institute of Public Health) we initiated a comprehensive review on how QALYs had been measured in all cost-effectiveness analyses published in 2010 (Wisløff et al 2012). We identified six generic health state utility (HSU) instruments, with EQ-5D holding a strongly dominant position. Following this work, and in his role as adjunct professor at Monash University, Australia, Olsen had a pivotal role in designing the largest ever research project on comparing these generic HSU-instruments and their relationships with some widely used disease specific instruments. The PI was professor Jeff Richardson, with whom Olsen had collaborated since 1998. This Multi-Instrument-Comparison project ('MIC-Study') had surveys in six countries on a total of 8,000 subjects (mostly people living with prevalent chronic conditions).

Data collection in the Norwegian study arm was funded by ISM. Olsen then won a grant from NRC (#221452) to undertake a range of analyses. Thanks to additional financial support from ISM, two PhD-students were employed. The MIC-Study gained immense interest in the international research community, with data made available open-access.

The key insights from the MIC-Study that have important impacts was the development of 'exchange rates', or mapping functions: i) across the value sets ('currencies') of different HSU-instruments; and, ii) from disease specific instruments to a HSU-based value set, so that QALYs can be calculated. Without such mapping functions, it was impossible to know if QALY-gains calculated on the basis of one HSU-instrument would be identical in magnitude had a different HSU been applied. Thus, the key impact for decision makers is that – even if different instruments have been used, be that a HSU-instrument or a disease specific instrument – QALY-gains can be made commensurable, and results from different cost-effectiveness analyses can be compared.

The close collaboration with the Australian team led to further research, motivated by a common critique of the EQ-5D that it is negligent to psychosocial health domains. After a conceptual paper (Olsen and Misajon 2020), we investigated empirically the relative importance of four additional

psychosocial dimensions, as compared to the five core dimensions in the EQ-5D (Chen and Olsen, 2021, 2022). Our work has impacted the EuroQol Group and its Research Foundation to support more research on 'bolt-on' dimensions. A further impact was that Olsen became member of the EuroQol Group, and was asked to join their descriptive system working group (DSWG) to contribute to this work on potential extensions of the instrument.

In addition to health technology assessments, the EQ-5D is increasingly being used in population health surveys and clinical quality registries. We had the EQ-5D included in the Norwegian Registry for Spine Surgery, as well as in the latest wave of The Tromsø Study. Based on the latter, we have provided new insights on Norwegian gender-specific gradients in health, measured along each of three socioeconomic indicators: education, occupation and income. Lastly, in the absence of a Norwegian value set, we developed a hybrid value set that may operate as an interim in western countries that have yet to develop their own national tariff.

- Names of the key researchers and what positions they held at the administrative unit at the time of the research (where researchers joined or left the administrative unit during this time, these dates must also be stated).

Faculty members

Jan Abel Olsen, professor of health economics and health services research, ISM, since 1999
Hans Olav Melberg, professor of health economics and health services research, ISM, since 2021

PhD students

Thor Gamst-Klaussen, 2013-2017
Admassu N. Lamu, 2014-2017

Affiliated partner funded by the NRC-grants in 20% position

Gang Chen, 2014-2022, associate professor of health economics, Monash University, Australia

Relevance: The Norwegian Decision Forum; priority setting guidelines; clinical quality registries; consistent methodologies in cost-effectiveness analyses; measuring population health

3. References to the research

1. Chen G, Olsen JA: *Extending the EQ-5D: The case for a complementary set of 4 psycho-social dimensions.* Quality of Life Research, 2022. DOI: 10.1007/s11136-022-03243-7
2. Olsen JA, Misajon R: *A conceptual map of health-related quality of life dimensions: Key lessons for a new instrument.* Quality of Life Research. DOI: 10.1007/s11136-019-02341-3
3. Olsen JA, Lindberg MH, Lamu AN: *Health and wellbeing in Norway: Population norms and the social gradient*. Social Science and Medicine 2020. DOI: 10.1016/j.socscimed.2020.113155
4. Olsen JA, Lamu A, Cairns J: *In search of a common currency: A comparison of seven EQ-5D-5L value sets*. Health Economics, 2017. DOI: 10.1002/hec.3606
5. Gamst-Klaussen T, Lamu AN, Chen G, Olsen JA: *Assessment of outcome measures for cost-utility analysis in depression: mapping depression scales onto the EQ-5D-5L*. BJPsych Open, 4(4), 160-166. DOI: 10.1192/bjo.2018.21
6. Lamu AN, Gamst-Klaussen T, Olsen JA: *Preference Weighting of Health State Values: What Difference Does it Make, and Why?* Value in Health, 2016. DOI: 10.1016/j.jval.2016.10.002

4. Details of the impact

The extensive work in this case study has been motivated by the need for a generic measure of health-related quality of life, that is methodologically convincing and relevant across different settings, be that health technology assessments (HTA), clinical quality registries or population health surveys.

For healthcare decisions on resource allocation and priority setting, there is a pressing need for applying a commensurable measure of health outcomes. Given the principal health policy objective of maximizing health for all, decision makers must be able to compare competing technologies in terms of how much health improvement each programme claim to produce. For example; how much QALY-gains can be expected by increasing the capacity in low back surgery, as compared to spending the same slice of the budget to increase the capacity to treat depression? In Norway, decisions made by The Decision Forum on whether to prescribe new medical products are based on HTAs, in which the estimation of QALY-gains is a most challenging variable.

The abovementioned research has come to influence health policies in various ways, as signified by the researchers' involvement in several expert committees, including advisory boards with NoMA. Olsen and Melberg (then employed at UiO, from 2021 at UiT) were members of the priority setting commission (https://www.regjeringen.no/no/dokumenter/NOU-2014-12/id2076730/). We contributed significantly to the development of what later became the official Norwegian priority setting criteria. Following the publication of the commission report, we were involved in extensive outreach and dissemination activities.

In addition to influencing guidelines on cost-effectiveness analyses and priority setting, our work on measuring and valuing health-related quality of life has impacted the use of EQ-5D in clinical quality registries and clinical trials, such as Norwegian Registry for Spine Surgery (https://www.kvalitetsregistre.no/register/muskel-og-skjelett/nasjonalt-kvalitetsregister-ryggkirurgi, and a much cited RCT on telemedicine (Buvik et al 2019).

As for methodological contributions to measuring health inequalities, we have shown how inequalities can be measured, not only in terms of differences in *quantity* of health (life years), but also in terms of differences in *quality* of life. By use of data from population health surveys we have provided new insights on inequalities in health-related quality of life by use of HRQoL measures (EQ-5D-5L, and EQ-VAS) as well as subjective wellbeing. Furthermore, we have shown how *quantity and quality* of life can be combined into quality adjusted life expectancies, by combining data from registries and population health surveys (Gutacker et al 2023).

As for contributing to a more relevant descriptive system for health and wellbeing, we have developed a set of psychosocial bolt-ons, intended to supplement the widely used EQ-5D-5L instrument. The motivation is to make measures of health outcomes applicable and relevant in new and expanding user groups, such as elderly care, and people suffering from lack of energy, mental health, and social isolation. Our conceptual work was awarded *best published paper of the year*, in QURE (Olsen and Misajon, 2020).

A key to applying preference-based measures of health, is to develop country-specific value sets. This is a very resource intensive endeavour. In the absence of a value set for Norway, we investigated the extent to which some general preference patterns could be identified in other western countries, that could be used to develop a hybrid value set (Olsen et al 2018). This work gained much interest in the EuroQol Group, leading to a revised hybrid value set (Roudijk et al 2022) in response to more country-specific value sets being published.

This research has been accompanied with extensive international collaborations og outreach activities. The key partner institutions involved are: Centre for Health Economics, Monash

University, Australia (Jeff Richardson and Gang Chen); Syddansk Universitet (Dorte Gyrd-Hansen and Trine Kjær); London School of Hygiene and Tropical Medicine (John Cairns); University of York (Nils Gutacker).

Outreach activities include teaching at several universities and speciality courses for hospital doctors, invited speaker to conferences and seminars. Furthermore, we are involved in a wide range of peer reviewing and assessment committees on the abovementioned topics.

5. Sources to corroborate the impact

1. NOU 2014-12 Åpent og rettferdig: Prioritering i helsetjenesten [Open and Fair: Prioritization in Healthcare Services] https://www.regjeringen.no/no/dokumenter/NOU-2014-12/id2076730/
2. Gutacker N, Kinge JM, Olsen JA: *Inequality in quality-adjusted life expectancy by educational attainment in Norway: An observational study*, BMC Public Health, 2023. DOI: 10.1186/s12889-023-15663-2
3. Roudijk B, Janssen B, Olsen JA: *How do EQ-5D-5L value sets differ*? in Devlin N et al: *Value sets for EQ-5D-5L*, Springer Open Access, 2022. DOI: 10.1007/978-3-030-89289-0_6
4. Chen G, Olsen JA: *Filling the psycho-social gap in the EQ-5D: the empirical support for four bolt-on dimensions.* Quality of Life Research 2020. DOI: 10.1007/s11136-020-02576-5
5. Rudolfsen JH, Solberg T, Ingebrigtsen T, Olsen JA: *Associations between utilization rates and patients' health: A study of spine surgery and patient-reported outcomes (EQ-5D and ODI)* BMC Health Services Research 2020. DOI: 10.1186/s12913-020-4968-2
6. Buvik A, Bergmo TS, Bugge E, Småbrekke A, Wilsgaard T, Olsen JA. *Cost-effectiveness of Telemedicine in Remote Orthopedic Consultations: Randomised Controlled Trial*. Journal of Medical internet Research, 2019. DOI: 10.2196/11330
7. Lamu AN, Olsen JA: *Yes, health is important, but as much for its importance via social life: The direct and indirect effects of health on subjective well-being in chronically ill individuals*, Health Economics, 2017. DOI: 10.1002/hec.3536
8. Lamu, AN, Olsen JA: *The relative importance of health, income and social relations for subjective well-being: An integrative analysis*, Social Science & Medicine, March 2016, 176–185. DOI: 10.1016/j.socscimed.2016.01.046
9. Gamst-Klaussen T, Chen G, Lamu AN, Olsen JA: *Health state utility instruments compared: inquiring into nonlinearity across EQ-5D-5L, SF-6D, HUI-3 and 15D*. Quality of Life Research, 2016. DOI: 10.1007/s11136-015-1212-3
10. Wisløff T, Hagen G, Hamidi V, Movik E, Klemp M, Olsen JA: *Estimating QALY gains in applied studies: A review of cost-effectiveness analyses published in 2010 that expressed health gains in terms of quality-adjusted-life-years.* PharmacoEconomics 2013. DOI: 10.1007/s40273-014-0136-z

UiT the Arctic University of Norway (UiT), the Department of Community Medicine (ISM), Impact case 4

Institution: UiT the Arctic University of Norway (UiT)
Administrative unit: Department of community medicine (ISM)
Title of case study: Improving maternal and child health in Georgia through health registries and surveillance
Period when the underpinning research was undertaken: 2014 - 2022
Period when staff involved in the underpinning research were employed by the submitting institution: - *Ingvild Hersoug Nedberg* (PhD student 2016 – 2022, associate professor 2022- present) - *Tormod Brenn* (scientific assistant 1980-1986, research fellow 1986-1989, researcher 1989-2000, associate professor 2000-2019, professor 2019-2023, professor emeritus 2023-present). - *Finn-Egil Skjeldestad* (professor 2008-2020) - *Charlotta Rylander* (PhD student 2006-2010, researcher 2010-2011, post doc 2011-2016, associate professor 2016-2021, professor 2021-present) - *Erik Eik Anda* (PhD student 2004 – 2009, post doc and researcher 2009-2014, associate professor 2014 – 2022, professor 2022- present)
Period when the impact occurred: 2016 - present

1. Summary of the impact

The Department of Community Medicine (ISM) collaborated with the United Nations International Children's Emergency Fund (UNICEF) to design and implement the Georgian Birth Registry (GBR) in 2016, becoming the nation's exclusive source of official birth data. Since it's initiation, ISM has been involved in quality control of the registry, research projects addressing maternal and child health, and supervision of local PhD students utilizing the registry. This has significantly enhanced Georgia's epidemiological competence, leading to local research addressing high caesarean section rates and revealing system-related shortcomings. The GBR not only offers legal identity documentation from birth but also facilitates public health initiatives and disease tracking. The registry's integration into a broader digital health platform fosters synergy with initiatives such as hepatitis C, COVID registries and lead surveillance, promoting comprehensive healthcare efforts in Georgia.

In 2021, ISM, together with UNICEF and the National Center for Disease Control & Public Health Georgia (NCDC) designed and started implementing a national surveillance system for lead in children in Georgia using a novel method for measuring lead in microvolume blood samples developed by our Canadian partner Institut national de santé publique du Québec (INSPQ). This is the first time this method has been implemented in a large-scale surveillance system, and it implies that children no longer need to go through invasive venous blood sampling for estimating exposure to lead and other toxic metals.

2. Underpinning research

Historically, several important associations between exposures and outcomes that might affect pregnancy and childbirth have been established through systematic and meticulous analyses of medical birth registry data. For example, associations between advanced maternal age and birth defects, spinal birth defects and vitamin use and the importance of adequate and timely antenatal care to avoid adverse outcomes. To combat seemingly high perinatal mortality, inflated caesarean section rates and frequent maternal morbidity, Georgia decided to create their own birth registry. In September 2014, the Department of community medicine (ISM) was contacted by UNICEF with a request to plan, create and implement a national digital

birth registry for the republic of Georgia. Initially, this was commissioned research where one researcher from ISM (Anda) was hired to complete the assignment in 24 months. Thirteen months of planning and creating the electronic modules, 4-5 months of implementation and 6-7 months of quality assurance and quality control. Besides ISM and UNICEF, NCDC helped facilitate the process and would eventually become responsible for collecting, storing, and using the data. A local IT company (CiTi) wrote the codes for the electronic modules. The GBR was launched in January 2016 **(R1)** and is today the sole provider of official birth registry data with over 300 000 deliveries recorded to date. In 2018, the multiple indicator cluster survey (MICS) revealed alarmingly high lead levels in children in Georgia, especially in the western part of the country. Research shows that there is no effective medical treatment for high blood lead levels, thus the only feasible solution is prevention. To ascertain whether prevention measures work, a surveillance system is needed. Designing a national surveillance system for lead was commissioned through a tender competition by UNICEF in 2022 and ISM won the bid.

Combined activities, insights, efforts and impacts that have come from the initial implementation of the GBR and the lead surveillance system include:

i) *Improved epidemiological competence in Georgia.* Competence to analyse and interpret the large quantity of data collected in Georgia was primarily missing and needed to be created. We have initiated projects **(R2)** and trained PhD students locally. (2016 – 2022, Anda, Brenn, Rylander, Skjeldestad).

ii) *Conduct research that could be directly applicable locally.* Georgia has been struggling with very high caesarean section numbers. A Norwegian-based PhD project has uncovered several of the mechanisms responsible for the high rates and suggestions how to reduce them **(R3, R4)**. (2017 – 2022, Nedberg, Anda, Skjeldestad, Rylander)

iii) *Uncover shortcomings that are linked either to the system or to the service providers.* Any time a new system of registration is introduced, changes in reported health indicators occur. Specific examples include quality of gestational age data, missing data on important maternal conditions during pregnancy and misclassification between stillbirths and early neonatal mortalities **(R5)**. (2016 – 2022, Anda, Rylander, Skjeldestad)

iv) *New research findings that might have external applicability.* Overuse of antenatal care (ANC) services – there has been an increase in pregnant women ending up in an intensive care unit (ICU), but there has been no decrease in adverse outcomes. In 2016, to reduce maternal and perinatal mortalities, the WHO increased the recommended number of antenatal visits in developing countries from 4 to 8. While this initiative is meant to reduce mortality, it may not be applicable for all countries that were defined as low or middle income (LMIC). Even though the number of recommended visits increased from 4 to 8 in Georgia, there has been no significant reduction in the use of ICU, neonatal intensive care units (NICU), maternal mortality or perinatal mortality **(R6)**. Caesarean sections (CS) are not elective in Georgia, yet the total proportion is close to 50%. Thus, many of the reasons for CS registered in the GBR are typical misclassifications that may also be present in other countries that are in a similar situation **(R3)**. (2017 – 2022, Rylander, Skjeldestad, Anda)

v) *Local impacts.* The GBR provides individuals with legal proof of identity from the moment of birth, including the acquisition of citizenship and access to basic rights and services. It enables the collection of stratified vital statistics, which are crucial for demographic analysis and long-term planning **(R7)**. The registry aids in monitoring and responding to public health issues by providing accurate population data and facilitates maternal and child health initiatives, and disease tracking. (2016 – 2022, Anda, Brenn, Rylander, Nedberg.).

vi) *Expand and utilize synergy effects to connect different activities in the region.* The GBR is part of a larger digital health platform that includes among others, registries on hepatitis C

(HCV), COVID, cancer, hospitalizations and mortalities. The advantages from combining such registry information are well known in the Nordic countries. We have started similar efforts in Georgia, for example links between COVID-related hospitalizations and HCV status. We have also initiated projects that combine local blood lead level measurement programmes with the GBR. In fact, we have recently designed a brand-new national surveillance system for lead detection **(R8)** in Georgian children that can be linked to the GBR and the mothers. (2016 – 2022, Rylander & Anda).

3. References to the research

(R1) Implementing a birth registry in a developing country - experiences from Georgia. Anda EE, Nedberg IH, Rylander C, Gamkrelidze A, Turdziladze A, Skjeldestad FE, Ugulava T, Brenn T. Tidsskr Nor Laegeforen. 2017 Dec 20;138(2). DOI: 10.4045/tidsskr.17.0553. Available from: https://tidsskriftet.no/en/2017/12/originalartikkel/implementing-birth-registry-developing-country-experiences-georgia

(R2) Perinatal mortality and its association with antenatal care utilization in the Republic of Georgia. Tinatin Manjavidze. 2020. https://munin.uit.no/handle/10037/19910

(R3) Factors Associated with Cesarean Section among Primiparous Women in Georgia: A Registry-based Study. Nedberg IH, Rylander C, Skjeldestad FE, Blix E, Ugulava T, Anda EE. J Epidemiol Glob Health. 2020 Dec;10(4):337- 343. Epub 2020 Aug 21. DOI: 10.2991/jegh.k.200813.001

(*R4) Changes in cesarean section rates after introduction of a punitive financial policy in Georgia: A population-based registry study 2017-2019*. Nedberg IH, Manjavidze T, Rylander C, Blix E, Skjeldestad FE, Anda EE. PLoS One. 2022 Jul 19;17(7):e0271491. eCollection 2022. DOI: 10.1371/journal.pone.0271491

(R5) Incidence and Causes of Perinatal Mortality in Georgia. Manjavidze T, Rylander C, Skjeldestad FE, Kazakhashvili N, Anda EE. J Epidemiol Glob Health. 2019 Sep;9(3):163-168. DOI: 10.2991/jegh.k.190818.001

(R6) The impact of antenatal care utilization on admissions to neonatal intensive care units and perinatal mortality in Georgia. Manjavidze T, Rylander C, Skjeldestad FE, Kazakhashvili N, Anda EE. PLoS One. 2020 Dec 2;15(12):e0242991. eCollection 2020. DOI: 10.1371/journal.pone.0242991

(R7) Vital statistics report in Georgia. National statistics office of Georgia. 2021. Available from: https://www.geostat.ge/media/48502/2021-VS-Report-%28eng%29.pdf

(R8) *The Georgian Lead Surveillance System (G-LESS).* A final report to the United Nations Children's Fund Georgia. 2022. Rylander C and Anda EE. Available from: https://uit.no/Content/832176/cache=20232911095513/G-LESS_UNICEF_UiT_report.pdf

4. Details of the impact

i) The former Minister of Health and former Director of the NCDC Amiran Gamkrelidze has been involved in these projects and it was made clear that competence building in epidemiology and statistics was crucial for Georgia to handle all the new collected digital data. The first project to accommodate this was the Georgian Norwegian Collaborative in Public Health, funded by The Norwegian Directorate for Higher Education and Skills (HKDir) (2015-2019), it encompassed both Master **(S1)** and PhD levels **(S2)**. Besides the competence building, it was important to keep the activities and students in Georgia to avoid brain drain. Today, two of the PhD students are employed both at NCDC and the

University of Georgia, three more are currently employed as 4-year PhD students with 25% time at NCDC. The end goal is that all stay on to contribute locally.

ii) Caesarean section (CS) rates have been increasing steadily in Georgia finally reaching a point where it has become a national priority to reduce them. Research from Norway has shown that there is not much to gain in terms of maternal and child health when CS rates exceed 20%. Yet, they are close to 50% in Georgia. Punitive efforts had a temporary effect **(R3, S3),** but in the end several clinics sued the government for "unlawful fining" and won. CS rates started increasing again shortly after. One of the explanations we found for excess CS rates were that hospitals were reimbursed more money from the government for performing a CS as opposed to a vaginal delivery. During 2022 a new order was created that ensures equal payment for both types of delivery. **(S4)**

iii) Changes in the way that an outcome (e.g a disease or condition) is measured or defined may change over time. When a completely new system for registering for example disease, such as a birth registry, is introduced, changes can be many and substantial. These changes are usually linked to the quality of the reported data, missing data or misclassification of data. Previously, gestational age (GA) was registered at birth and estimated by a doctor. Today, they can calculate the intervals between early ultrasounds and the actual birth dates, giving more accurate personal and population estimates. In fact, the average GA in Georgia is only 38 weeks, considerably shorter than the biological 40 week- duration of a pregnancy. This may be attributed to the high number of CS since other types of induction of labour are rare and as mentioned above, they are trying to reduce CS. Another example is the underreporting of maternal diseases during pregnancy. A former PhD student at UiT (Tinatin Manjavidze), now a postdoc, initiated (2022) a WHO project that addresses this issue with the aim to have a more complete registration of these events **(S5)**. These discrepancies would never have been discovered without the GBR and the efforts to rectify them can be measured, in turn, by analysing future GBR data.

iv) Before Georgia integrated the GBR with its national e-health platform, parents had to visit the capital to register their newborns, a step necessary for citizenship recognition, ID number allocation, and government reimbursements. Now, the process is fully automated from birth **(S6).** Additionally, the Ministry of Health has issued directives to enhance maternal and child health based on GBR insights **(S7).** With GBR's integration into the social services agency's digital systems, the cumbersome back-and-forth for ANC financing is eliminated, and medical records are now digitally stored for easy access. Changing ANC providers, once a formal process, is now straightforward and swift.

v) One of the more profound impacts from the GBR-involvement has been synergy effects and initiation of other projects in the region. There are serious problems with lead exposure in Georgia, especially in the western part of the country. Since our group was familiar with surveillance and have expertise in environmental exposures to contaminants, we were asked by UNICEF to create a national surveillance system for lead in children (and later pregnant women) in Georgia **(R8).** This new system was ordered implemented in 2022.

vi) Finding sources of lead exposure and reduce the lead levels in Georgian children is a priority for the government in Georgia and ISM has played an important role on the way to reaching this goal through designing the national lead surveillance system, implementing the system and plan further activities **(S8 and S9).** The surveillance system is officially financed through the national budget of Georgia. By implementing the use of accurate lead measurements in microvolume blood samples, the children no longer must be exposed to painful venous blood sampling. The actual samples are easier to transport (no need for ice) and store (are stable in room temperature for months). The laboratory analyses are price competitive and because of the low testing volumes, the equipment used in the laboratories need cleaning far less often than before. Finally, through these efforts, ISM has been instrumental in building and implementing local laboratory capacity

at NCDC. Georgia now has their own ability to process and analyse these microsamples **(S10)**.

5. Sources to corroborate the impact

(S1) Georgian-Norwegian Master Program in Public Health at Tbilisi State University: Students' Nato Pitkshelauri, George Lobzhanidze, Nino Chikhladze. https://tcm.tsu.ge/index.php/TCM-GMJ/article/view/312

(S2) Perinatal mortality and its association with antenatal care utilization in the Republic of Georgia. Tinatin Manjavidze. https://munin.uit.no/handle/10037/19910

(S3) Clinics were fined for caesarean sections. Radiotavesupleba. https://www.radiotavisupleba.ge/a/საკეისრო-კვეთისთვის-კლინიკები-დაჯარიმდნენ/29376119.html

(S4) Health Ministry to offer full financing of childbirth, caesarean section. Agenda.ge. https://agenda.ge/en/news/2023/4538

(S5) Evaluating the continuity of information for maternal care after the implementation of the digital Georgian Birth Registry. https://ahpsr.who.int/newsroom/news/item/04-07-2023-decoding-digital-health-understanding-how-digital-innovations-are-strengthening-health-systems

(S6) "On the manner of production and delivery of medical statistical information"- translated from Georgian. The original order was written in 2016. https://matsne.gov.ge/ka/document/view/4509878?publication=0

(S7) "Regarding the approval of the 2017-2030 national strategy for the promotion of maternal and newborn health of Georgia and the 2017-2019 action plan for its implementation." translated from Georgian. The original order was written in 2017. https://matsne.gov.ge/ka/document/view/3825285?publication=0

(S8) Ending childhood lead poisoning in Georgia. Progress and lessons learned between 2017 and 2023. https://www.unicef.org/documents/ending-childhood-lead-poisoning-georgia#:~:text=The%20Government%20of%20Georgia%20and,blood%20lead%20levels%20(BLLs(

(S9) PM: Georgia committed to addressing lead poisoning "comprehensively", achieving "greater results" with "united global community". https://agenda.ge/en/news/2024/147

(S10) Microsampling Devices Used to Monitor Lead Levels in Georgia. https://www.neoteryx.com/microsampling-news/microsampling-devices-used-to-monitor-lead-levels-in-georgia

UiT The Arctic University of Norway, Department of Community Medicine (ISM), Impact case 5

Institution: UiT The Arctic University of Norway
Administrative unit: Department of Community Medicine (ISM)
Title of case study: Investigations of human exposure to environmental contaminants
Period when the underpinning research was undertaken: 2012-present
Period when staff involved in the underpinning research were employed by the submitting institution: Torkjel M Sandanger (PhD 2003, postdoc 2003-2005, assoc prof 2012-2018, prof 2017-present) Charlotta Rylander (PhD 2010, postdoc 2011-16, assoc prof 2016-21, prof 2021-present) Therese Haugdahl Nøst (PhD 2014, postdocs 2014-20, researcher 2020-24, assoc prof 2024-present) Vivian Berg (PhD 2015, postdoc 2016-2018, assoc prof 2018-present) Dolley Charles (PhD 2023, researcher 2023-present) Lara Cioni (PhD candidate 2020-2023) Ana Carolina Miranda Coelho (PhD candidate 2020-present)
Period when the impact occurred: 2012-2022

1. Summary of the impact (indicative maximum 100 words)

Our research in the field of human biomonitoring of POPs using novel designs and unique samples from our Department's cohorts has been used to shape international regulations of contaminants and evaluate food safety. We have also co-authored reports through the Arctic Monitoring and Assessment Programme, which supports regulatory bodies. We have contributed to efforts to protect human and environmental health by demonstrating the dynamic nature of human exposure to POPs, demonstrated exposures of emerging concern and the effectiveness of regulatory measures in reducing this exposure. Finally, we have been used as experts in several national media with large audiences.

2. Underpinning research (indicative maximum 500 words)

We provide examples of the underpinning research on environmental contaminants conducted at the Department of Community Medicine (ISM) in collaboration with national and international partners, drawing primarily on data from the Tromsø Study, the Norwegian Women and Cancer (NOWAC) Study and the MISA study. Our research has focused on assessing emerging pollutants including non-persistent compounds in humans and describing changes in human exposure to persistent organic pollutants (POPs) over time. The work was initiated by professor Torkjel M. Sandanger (associate professor at the time) and performed by PhD students and postdoctoral fellows under his supervision. These projects represent a collaboration between the Department of Community Medicine and the Norwegian Institute for Air Research (NILU), the Fram Centre, Tromsø, Norway, but has also involved the University Hospital of Northern Norway, Tromsø, Norway, University of Laval, Quebec, Canada, Institut national de santé publique du Québec (INSPQ), Quebec, Canada and the Arctic Monitoring and Assessment Programme (AMAP).

Investigating exposure to non-persistent and emerging contaminants

In 2011, we showed as strong association between women's self-reported use of cosmetic products, especially skin lotion, and the concentrations of parabens in their blood using samples

from 350 Norwegian women (Sandanger et al., 2011; **R1**). Among heavy users of skin care products, the level of parabens in the blood was higher than levels of all other potential environmental pollutants surveyed, and this was one of the first larger epidemiological studies assessing paraben exposure in the general population.

In recent years, PhD students Lara Cioni and Ana Carolina Coelho has developed new analytical methods for determining oxidisable PFAS precursors in blood, enabling us to describe exposure to PFAS through the breakdown of precursor compounds (Cioni et al., 2022; **R2**). In this effort we revealed that almost all samples investigated from the Norwegian Women and Cancer postgenome cohort had detectable PFAS precursors and results suggested that human exposure to PFAS is underestimated when only long chain PFAS are analysed (Coêlho et al., 2023; **R3**).

Time trends of POPs in blood

A longitudinal examination of POPs based on repeated blood samples from the Tromsø Study collected during 1979 to 2007 revealed changing patterns of exposure in Northern Norwegian men. The observed trends demonstrated a general decline in concentrations of polychlorinated biphenyls (PCBs) and pesticides (OCPs) from 1979 to 2007 (Nøst et al., 2013; **R4**). Further, certain perfluorinated substances (PFAS) initially rose before declining while others showed a steady increase (Nøst et al., 2014; **R5**). We also studied how PFAS time-trends changed relatively fast in pregnant women (Berg et al., 2014; **R6**). Our results demonstrated the impact of regulatory actions, such as bans and restrictions on POP production and use, in reducing human POP exposure (Nøst et al., 2017; **R7**). The studies also indicated that observed trends aligned more with historical emissions than with the age of individuals. Despite the general understanding that these compounds accumulate with age, we showed that if we successfully reduce emissions substantially, concentrations will decline even when you age. The latter was supported by results using a mechanistic exposure model based on emission estimates to predict PCB concentrations based on personal characteristics and lifestyle factors (Nøst et al., 2016; **R8**). This model could predict time-varying concentrations in individuals, offering alternative exposure metrics, which have been used in our research focusing on POPs and diabetes (Rylander et al., 2015; **R9**). Subsequent research expanded the longitudinal POP data and compared 30-year-olds across time points for POPs (Nøst et al., 2019; **R10**) and PFAS (Berg et al., 2021; **R11**). This way we could evaluate how time trends were influenced by the chosen design of the study. The main conclusions were the same, but the time trends were more pronounced in the older men.

3. References to the research (indicative maximum of six references)

R1: Sandanger TM, Huber S, Moe MK, Braathen T, Leknes H, Lund E. Plasma concentrations of parabens in postmenopausal women and self-reported use of personal care products: the NOWAC postgenome study. J Expo Sci Environ Epidemiol. 2011;21(6):595-600. DOI: 10.1038/jes.2011.22.

R2: Cioni L, Nikiforov V, Coêlho ACMF, Sandanger TM, Herzke D. Total oxidizable precursors assay for PFAS in human serum. Environ Int. 2022;170:107656. DOI: 10.1016/j.envint.2022.107656.

R3: Coêlho ACMF, Cioni L, Van Dreunen W, Berg V, Rylander C, Urbarova I, Herzke D, Sandanger TM. Legacy perfluoroalkyl acids and their oxidizable precursors in plasma samples of Norwegian women. Environ Int. 2023;178:108026. DOI: 10.1016/j.envint.2023.108026.

R4: Nøst TH, Breivik K, Fuskevåg OM, Nieboer E, Odland JØ, Sandanger TM. Persistent organic pollutants in Norwegian men from 1979 to 2007: intraindividual changes, age-period-cohort effects, and model predictions. Environ Health Perspect. 2013;121(11-12):1292-8. DOI: 10.1289/ehp.1206317.

R5: Nøst TH, Vestergren R, Berg V, Nieboer E, Odland JØ, Sandanger TM. Repeated measurements of per- and polyfluoroalkyl substances (PFASs) from 1979 to 2007 in males from Northern Norway: assessing time trends, compound correlations and relations to age/birth cohort. Environ Int. 2014;67:43-53. DOI: 10.1016/j.envint.2014.02.011.

R6: Berg V, Nøst TH, Huber S, Rylander C, Hansen S, Veyhe AS, Fuskevåg OM, Odland JØ, Sandanger TM. Maternal serum concentrations of per- and polyfluoroalkyl substances and their predictors in years with reduced production and use. Environ Int. 2014;69:58-66. DOI: 10.1016/j.envint.2014.04.010.

R7: Nøst TH, Sandanger TM, Nieboer E, Odland JØ, Breivik K. The impacts of emission trends of POPs on human concentration dynamics: Lessons learned from a longitudinal study in Norway (1979-2007). Int J Hyg Environ Health. 2017 Jun;220(4):776-781. DOI: 10.1016/j.ijheh.2017.01.015.

R8: Nøst TH, Breivik K, Wania F, Rylander C, Odland JØ, Sandanger TM. Estimating Time-Varying PCB Exposures Using Person-Specific Predictions to Supplement Measured Values: A Comparison of Observed and Predicted Values in Two Cohorts of Norwegian Women. Environ Health Perspect. 2016;124(3):299-305. DOI: 10.1289/ehp.1409191.

R9: Rylander C, Sandanger TM, Nøst TH, Breivik K, Lund E. Combining plasma measurements and mechanistic modeling to explore the effect of POPs on type 2 diabetes mellitus in Norwegian women. Environ Res. 2015;142:365-73. DOI: 10.1016/j.envres.2015.07.002.

R10: Nøst TH, Berg V, Hanssen L, Rylander C, Gaudreau E, Dumas P, Breivik K, Sandanger TM. Time trends of persistent organic pollutants in 30-year-olds sampled in 1986, 1994, 2001 and 2007 in Northern Norway: Measurements, mechanistic modeling and a comparison of study designs. Environ Res. 2019;172:684-692. DOI: 10.1016/j.envres.2019.02.047.

R11: Berg V, Sandanger TM, Hanssen L, Rylander C, Nøst TH. Time trends of perfluoroalkyl substances in blood in 30-year old Norwegian men and women in the period 1986-2007. Environ Sci Pollut Res Int. 2021;28(32):43897-43907. DOI: 10.1007/s11356-021-13809-6.

4. Details of the impact (indicative maximum 750 words)

Investigating emerging or recent exposure to contaminants

The extensive use of parabens in cosmetic products has been massively debated because of their endocrine disrupting properties. Of major concern has been exposure of newborns and babies below the age of six months. The number of epidemiological studies assessing human exposure to parabens have been limited and our study was one of the first larger studies from a general population. Our study was important when assessing likely exposure scenarios on humans, and because of this it was extensively referenced in the first assessment of the overall risk for all parabens and later in the assessment of propylparabens. Our research (**R1**) has contributed to establishing new guidelines for several parabens in consumer products **(S1-S3)**. In the same period, we were actively involved in public dissemination of our results in several media, also national television **(S4).** More recently, the studies of precursor compounds to PFAS exposures **(R2-R3)** have represented a similar potential future impact parallel to the past efforts on parabens. The results are so far communicated from the EU project in a podcast series, also including our researchers **(S5)**.

Time trends of POPs in blood

Our studies of time trends of POPs **(R4-R11, especially R4-R5)** were also been cited by regulatory bodies. Specifically, our work was referred to by the European Chemical Agency (ECHA) suggesting regulating the use of the emerging PFAS, PFHxS, in the EU **(S6)**, by the European Food Safety Authority **(S7)** for state of the art for human biomonitoring**,** the Norwegian Scientific Committee for Food and Environment (**S8**) when presenting their benefit-risk assessment of fish and fish products in the Norwegian diet. Our work has further been extensively used by the Arctic Monitoring and Assessment Program (AMAP) **(e.g. S9-S10)**. AMAP is a working group of the Arctic Council, which is a high-level intergovernmental forum that promotes cooperation among the Arctic States and indigenous communities on common Arctic issues, particularly sustainable development and environmental protection. AMAP is an important part of the Arctic Council. Because of our extensive work on contaminants in humans with a focus on Arctic populations and our participation in the AMAP human Health Expert group, both Torkjel M Sandanger **(S9)** and Therese H Nøst **(S9-10)** have co-authored several chapters in several AMAP reports which are important guidance documents for the Arctic Council in their efforts to describe the effects of human exposure to POPs in the Arctic. These studies have received considerable attention in several media contributing to public awareness of environmental contaminants with many national and international news articles, blog entries from non-governmental organizations, etc., but one example is our participation in a well-known national television program (**S11**). Prof. Sandanger was awarded UiT's dissemination prize **(S12)** for his active involvement in public information in 2015.

5. Sources to corroborate the impact

Below are examples of the impact of our research beyond academia.

S1: European Commission Scientific Committee on Consumer Safety (SCCS), Clarification on Opinion SCCS/1348/10 in the light of the Danish clause of safeguard banning the use of parabens in cosmetic products intended for children under three years of age; 2011. Available from: https://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_069.pdf

S2: European Commission Scientific Committee on Consumer Safety (SCCS), Opinion on Propylparaben (SCCS/1623/20), final version of 30-31 March 2021. Available from: https://health.ec.europa.eu/system/files/2022-08/sccs_o_243.pdf

S3: The Fram Centre. Stricter EU rules on parabens; 2012. Available from: partner.sciencenorway.no/cosmetics-eu-forskningno/stricter-eu-rules-on-parabens/1373719

S4: Prof. Sandanger participated in "Forbrukerinspektørene" in 2015 - a Norwegian TV program that investigates consumer issues, tests products, and provides viewers with practical advice on consumer rights, helping them make informed decisions and avoid scams or poor purchases. The show often features expert commentary and aims to protect consumer interests. Available from: Vår kjemiske hverdag – 3. Gift i kosmetikk (Sesong 1) – NRK TV

S5: PFASology, March 2022. A podcast about PFAS in our blood from the PERFORCE 3 project. Available from: open.spotify.com/episode/2P6nWiGzidlkddpCu1hS4x **PFAS**ology is a science podcast covering the different disciplines of PFAS research. It is created by the 15 early-stage researchers (ESRs) within PERFORCE3. Over the course of the series, the ESRs will discuss the challenges and solutions associated with the global occurrence of PFAS.

S6: European Chemicals Agency (ECHA) ANNEX XV RESTRICTION REPORT PROPOSAL FOR A RESTRICTION SUBSTANCE NAME(S): Perfluorohexane sulfonic acid (PFHxS), its salts and PFHxS-related substances; 2019. Available from: echa.europa.eu/documents/10162/a22da803-0749-81d8-bc6d-ef551fc24e19

S7: European Food Safety Authority (EFSA) supporting publication, EXTERNAL SCIENTIFIC REPORT, Review of the state of the art of human biomonitoring for chemical substances and its application to human exposure assessment for food safety; 2015. Available from: efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/sp.efsa.2015.EN-724

S8: Norwegian Scientific Committee for Food and Environment (2014). Benefit-risk assessment of fish and fish products in the Norwegian diet – an update. Scientific Opinion of the Scientific Steering Committee. VKM Report 15 [293 pp], ISBN: 978-82-8259-159-1, Oslo, Norway. Available from: nmbu.brage.unit.no/nmbu-xmlui/bitstream/handle/11250/2472616/Skåre_2014_Ben.pdf?sequence=1

S9: AMAP Assessment 2015: Human Health in the Arctic. Arctic Monitoring and Assessment Programme (AMAP), Oslo, Norway. vii + 165 pp. Available from: 01885-AMAP-Human-Health-Assessment-Report-Book-v2.indb

S10: AMAP, 2021. AMAP Assessment 2021: Human Health in the Arctic. Arctic Monitoring and Assessment Programme (AMAP), Tromsø, Norway. x+240pp. Available from: www.amap.no/documents/doc/amap-assessment-2021-human-health-in-the-arctic/3593

S11: Therese H Nøst and Torkjel Sandanger participated in "Schrödingers cat" in 2015, a Norwegian TV program that explores a wide range of topics in science and technology. The show aims to make complex scientific ideas accessible to the general public, featuring experiments, interviews with experts, and reports on the latest research and discoveries in various fields such as physics, biology, and environmental science. We presented the results from the first POP time trend studies and human biomonitoring in general. Available from: tv.nrk.no/serie/schrodingers-katt/2015/DMPV73000815/avspiller

S12: Prof Sandanger was awarded UiT's public dissemination prices in 2015: Available from: en.uit.no/news/article?p_document_id=423850

IC 1: SAMI NURSING- A BACHELOR PROGRAMME

[IHO- University of Tromsø-] [IC 1 RRNH]

Institution: University of Tromsø
Administrative unit: IHO, Department of Health and Care Sciences
Title of case study: Sami Nursing
Period when the underpinning research was undertaken: 2016-2021
Period when staff involved in the underpinning research were employed by the submitting institution: 2016- ongoing
Period when the impact occurred: 2021

1. Summary of the impact (indicative maximum 100 words)

The creation of a Bachelor's program in Sámi Nursing holds significant importance not only for the Sámi community but also for the broader population. This program emphasizes the Northern Sámi language, Sámi cultural studies, contemporary Sámi issues, and the concept of cultural safety within the nursing profession. The availability of nurses fluent in Sámi is crucial for patient care in the North and serves as a valuable measure of quality in the provision of healthcare services.

2. Underpinning research (indicative maximum 500 words)

The initial study within the project highlighted a deficiency in learning outcomes, focus areas, and literature pertaining to Sámi culture and health in Norway's Bachelor of Nursing programs. This study gathered data from 25 of the 26 universities and colleges that offer nursing education.

The second study yielded two articles that describe and discuss patients' and their relatives' experiences when interacting with healthcare providers. These articles detailed how and why these individuals felt culturally unsafe and identified key factors in effective communication with Sámi patients.

The third segment of the project examined the experiences of Norwegian and Sámi nurses when caring for Sámi patients. Conducted by a PhD researcher, the studies uncovered a neglect in the use of interpreters, as Norwegian nurses often assumed that "patients spoke sufficiently good Norwegian." Additionally, nurses from both groups reported instances of both culturally safe and culturally unsafe care.

Armed with insights from the lack of Sámi perspectives in Norwegian nursing curricula, the narratives of patients and nurses, we aimed to enhance our curricula. Our goals included re-establishing collaboration with the Sámi College and attempting to reinstate a Sámi program in Kautokeino, which had not been pursued since 1998, prior to the merger of UiT and Finnmark University College. The Sámi Parliament politicians had already laid substantial groundwork. The initiative was warmly received by the Sámi community, both locally and nationally.

As a result of these efforts, we now have national guidelines for a Sámi Bachelor's program in nursing, established in 2021.

- Dr. Mehus,Head of RG-RRNH at IHO,UiT. 2016-2021.
- Dr. Liss Eriksen, member of the RG-RRNH,UiT,IHO. 2016-2022.Retired 2023
- Dr. Bongo, lecturer and researche , member of the RRNH,IHO,UiT. Retired 2017
- PhD candidate Engenes, member of the RG-RNNH. 2016- 2022. Ongoing position.
- Dr.Sivertsen, Flinders university Adelaid, Au,/IHO,UiT 20% position since 2016-ongoing.
- Dr. Moffitt. Head of Research at Aurora College,Yellowknife,NWT,CA. Partner in the project Sami Nursing.

This research commenced with an exploration of the learning outcomes and literature concerning Sámi issues, culture, and knowledge within Norway's Bachelor of Nursing programs. The findings

were disappointing. Concurrently, the Ministry of Education and Research initiated the RETHOS process, which aimed to integrate learning outcomes related to Sámi knowledge across all Bachelor programs in healthcare education.

3. References to the research (indicative maximum of six references)

1. **Mehus,G.,**Hætta Klemetsen, A.B., **Emaus,N.,Okstad,L.** (2022) The history of Sámi nursing education and the path towards regulations on a national guideline for Sámi nursing education in Norway. ***AlterNative*** *https://doi.org/10.1177/11771801231168762*
2. **Engnes Isaksen, Janne**; **Sivertsen, Nina; Bongo, Berit Andersdatter; Mehus, Grete.** Sámi and Norwegian nurses' perspectives on nursing care of Sámi patients: a focus group study on culturally safe nursing. *International Journal of Circumpolar Health* vol.80 https://doi.org/10.1080/22423982.2021.1948246
3. **Engnes, Janne Isaksen**; Sivertsen, Nina; Bongo, **Berit Andersdatter; Mehus, Grete.** Sámi language in Norwegian healthcare: "He speaks good enough Norwegian, I don't see why he needs an interpreter". *Scandinavian Journal of Caring Sciences* 2021. https://doi.org/10.1111/scs.12986
4. **Mehus,G.,Bongo,B.A,Engnes,J.I** & Moffitt,P.Exploring why and how encounters with the Norwegian health-care system can be considered culturally unsafe by North Sami-speaking patients and relatives: A qualitative study based on 11 interviews. *International journal of circumpolar heal*th . 2019;78(1):1612703 doi: 10.1080/22423982.2019.1612703.
5. **Mehus,G.,Bongo A.,Berit**. & Moffitt,P. Important Factors When Communicating with Sami Patients. *Nordisk sygeplejeforskning. 2018; 8(4);288-301. DOI:10.1826/isnn l 1982-2686-2018-04-04* https://munin.uit.no/handle/10037/14292
6. **Eriksen,L.,Bongo,B.A. & Mehus,G.** Urfolksperspektiv i utdanning.Sykepleierutdanningen i Norge uten urfolkskunnskap? *Tidskriftet Nordisk Sygeplejeforskning/Nordic Nursing Research.2017; 7(4)*

4. Details of the impact (indicative maximum 750 words)

The rationale for UiT's continued commitment to this critical work is built on former Finnmark University Colleges previous effort over several decades and stems from the provisions of the International Labour Organization Convention (ILO No. 169, 1989). This implies that the Sámi, as an indigenous people, have the right to health services based on their language and cultural background. These are considerations that the conventional nursing education does not sufficiently address (Eriksen et al., 2017). UiT, as the sole higher education institution, has taken these issues seriously and early on identified them as an area within healthcare that requires strengthening and through the education programme acted accordingly. Therefore, the work to establish a Sámi nursing education in collaboration with SA in Kautokeino has been of great importance both for the Sámi community and for UiT as an educational institution (Mehus et al., 2023; Okstad et al., 2021).

In December 2018, UiT was awarded 25 fully funded study places in the revised national budget based on the existing national guidelines for a bachelor's degree in nursing (Okstad et al., 2021). In the same allocation, Sámi allaskuvla received funds to establish a project position to support the development of a Sámi nursing education program. The collaboration between the two educational institutions thus became part of the funding for the study places (Hofstad, 2018).
In January 2019, the working group tasked with developing the study program was established.

The work continued until spring 2020. The accreditation of the program was carried out by UiT The Arctic University of Norway's University Board in June 2020 (Mehus & Okstad, 2020).
The announcement of the program was underway, and the first intake of students was conducted in December 2020, with the start of the cohort in January 2021. Later that winter, the RETHOS group for Sámi guidelines was established, with representatives from both UiT and Sámi allaskuvla (Ministry of Education and Research, 2020; Mehus et al., 2023). The work on the guidelines took place throughout 2021 and was approved and implemented from January 1, 2022 (Ministry of Education and Research, 2022; Mehus et al., 2023).

In summary, our assertion is that UiT has taken international and national conventions, laws, and regulations seriously on behalf of the Sámi people in the effort to advocate for a Sámi nursing program and, importantly, to establish and implement the study program. The establishment of this program is of great significance for users, patients, and relatives who interact with the healthcare system at various levels.

Additional references:

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Forskrift om nasjonal retningslinje for samisk sykepleierutdanning, (2022). https://lovdata.no/dokument/LTI/forskrift/2021-10-26-3096

Mehus, G., Hætta, A. B. K., Emaus, N., & Okstad, L. (2023). The history of Sámi nursing education and the path towards regulations on a national guideline for Sámi nursing education in Norway. AlterNative: An International Journal of Indigenous Peoples

Mehus, G., & Okstad, L. (2020). Akkreditering Samisk sykepleierutdanning. Universitetsstyret UiT Norges arktiske universitet.

Okstad, L., Emaus, N., Hætta, A. B. K., & Mehus, G. (2021). Samisk sykepleierutdanning: Målet er å utdanne kulturelt trygge sykepleiere. Sykepleien(82754), e-82754. https://doi.org/10.4220/Sykepleiens.2021.82754

Lov 02. juli 1999 om pasient- og brukerrettigheter (1999). https://lovdata.no/dokument/NL/lov/1999-07-02-63

Lov om Sametinget og andre samiske rettsforhold (1987).

5. Sources to corroborate the impact (indicative maximum of ten references)

– Slik utdanner vi bedre sykepleiere for samiske pasienter - regjeringen.no
https://sykepleien.no/meninger/2021/02/et-studium-i-samisk-sykepleie-har-vaert-etterlengtet
https://sykepleien.no/2021/11/vil-bedre-helsetjenesten-samiske-pasienter
https://www.regjeringen.no/contentassets/3ff0fbf202244ee19abdf8968e8745d6/forslag-til-forskrift-om-nasjonal-retningslinje-for-samisk-sykepleierutdanning.pdf
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Forskrift om nasjonal retningslinje for samisk sykepleierutdanning - Lovdata
Reindriftssamer kan ha pleie- og omsorgsbehov i to kommuner - Nasjonalt senter for aldring og helse

Impact case 2-RRNH- Community-based injury prevention in relation to youths and risk taking in snowmobiling in West-Finnmark.

[UiT] [IHO]

Institution: UiT
Administrative unit: IHO
Title of case study: Community-based injury prevention in relation to youths and risk taking in snowmobiling in West Finnmark.
Period when the underpinning research was undertaken: 2007-2012
Period when staff involved in the underpinning research were employed by the submitting institution: IHO, UiT
Period when the impact occurred:2012-2019 annual events from March until May.

1. **Summary of the impact** (indicative maximum 100 words): Snowmobiling in the north is a popular activity which also lead to injuries and fatalities. Our intervention is based on an incident in 2011 where three boys froze to death. A parent who lost his child and I were cooperating in a community-based intervention, using the story from this incident and my PhD work from youths risk taking in snowmobiling to illustrate attitudes towards risk-taking and giving advises to snowmobilers what to do, and not to do to avoid accidents. A quantitative study from 2019 (Rønninget al.) shows a decrease in fatalities among the young in this area and there were an overall decrease in injuries in West-Finnmark. The local engagement and discourse that has taken place, involving the snowmobile association, parents, youth, and researchers, may have had an impact on awareness regarding driving behavior and thus influenced the occurrence of accidents. Preventive work is nevertheless difficult to measure.

2. **Underpinning research** (indicative maximum 500 words

Youth in the north use nature and snowmobiles for socializing and are riding together in the rural, outback areas. The activity contributes to social interaction in nature, and they describe the feeling when riding as “a connection between them, the vehicle and the terrain”. Injury reporting is based on retrospective, trauma data collected from hospitals in Northern Norway, emergency clinics, and police where All Terrain Vehicles are involved in 2013-2014. Studies indicate that there have been many accidents and fatalities over the years (Hortemo et.al., 1990; Jeppesen & Wisborg, 2005; Rønning, 2019). On average, the few studies available have recorded between 1-3 deaths each year. Men are overrepresented in both fatal and non-fatal accidents, but the context of the accidents is sparsely described Rønning et.al. (2019).

In my qualitative research from my article based doctoral thesis, the goal was to examine how youth thought about snowmobiling in general as an activity, the contexts of accidents, risk-taking, and their attitudes towards taking risks (Mehus, 2012). The findings are based on 17 focus group interviews in gender-segregated groups with 81 youths, showing that the youths' motivation to ride was the sense of freedom in the mountains, the companionship with each other, and a physical feeling of being connected to the nature and terrain. Many also said that being well-dressed and prepared for bad weather was important for them to enjoy and have fun when riding (Mehus et al., 2010). Risk-seeking behavior such as driving hard and fast, enjoying alcohol while driving, riding without a helmet, and driving outside legal trails was tempting for many. However, some said they always adhered to laws and regulations and was protective of the very expensive vehicle (Mehus et al., 2011).
Interventions and countermeasures to prevent accidents are described based on youths’ narratives about what activities that could and have led to accidents, with- and without human injuries (Mehus et al., 2016). Based on these studies, the recommendation was to work

preventively at the individual, group, and organizational levels. This also including discussing with parents their ability to mobilizing interventions regarding their child's driving behavior. The municipal infrastructure, such as the trail network and planning and maintenance of these, is also important on the intervention side to prevent accidents. Such as risk assessment and improvement of the trail routes described in a report of us which we were called to do for Kvalsund municipality, where the fatal incident occurred (Mehus & Mehus, 2012).
Rønning et al. (2019) show that men continue to top the injury- and death statistics, and there is no report of fatalities in the 16–20-year age group for 2013-2014. However, there is a call for more detailed and continuous registrations related to this kind of trauma (Rønning et .al. 2019)

Professor Grete Mehus, IHO-Hammerfest,UiT have done focus 17 group interviews in Finnmark, North Troms and at Svalbard(2008-2009). Intervention in the community was annual, in the spring;March- May from 2102-2019.

- Medical students (IKM-UiT) and doctors working in Finnmark and Troms have focus on retrospective studies from snowmobile accidents mm.

3.References to the research

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Mehus, A. G., & **Mehus, G.** (2012). *Prosjektrapport med forslag til tiltak for å forbedre merking, standard og infrastruktur i snøscooter løyenettet ,Kvalsund kommune* (Project report with proposed measures to improve marking, standards, and infrastructure in the snowmobile trail network, Kvalsund Municipality.
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Mehus, G., Germeten, S., & Henriksen, N. (2011). How young people communicate risks of snowmobiling in Northern Norway:a focus group study. *International Journal of Circumpolar Health*, *70*(2), 9. How young people communicate risks of snowmobiling in northern Norway: a focus group study: International Journal of Circumpolar Health: Vol 70, No 2 (tandfonline.com)

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Rønning, T. H., Grov, E. K., & Wisborg, T. (2019). Fatalities and personal injuries from the use of ATVs and snowmobiles in Northern Norway in 2013-14. *Tidsskr Nor Laegeforen*, *139*(7).

https://doi.org/10.4045/tidsskr.18.0966 (Dødsfall og personskader ved bruk av ATV og snøscooter i Nord-Norge i 2013–14.)

4. Details of the impact (indicative maximum 750 words)

The RG have been engaged in a cooperation with the local snowmobile association regarding accident- and injury prevention in the local community from 2012-2019. This both because of my doctoral research, my membership in the local association of snowmobiling, and as a parent of youths snowmobiling in rural areas. My thesis explores young people's attitudes towards risk-taking and snowmobiling from a health promotion and injury prevention perspective (Mehus, 2012; Mehus et al., 2010, 2011; Mehus & Henriksen, 2011; Mehus et al., 2016).

The background of the intervention was that on the 3rd and 4th of March in 2011 nine youths from Hammerfest was in Kvalsund and headed to the mountain on snowmobiles without paying attention to the weather forecast. Then, a terrible storm hit the with hurricane-force winds. This group of was caught out there, without no preparations and plans, poorly dressed. Only six of them returned alive a day later (Vatn, 2011).

Following the conclusion of the memorial services and the passage of several months, a convocation was held within the local snowmobile association. The consensus reached was unequivocal: such tragedies must be averted in the future. Consequently, a dedicated committee was formed with the purpose of devising strategies for the prevention of accidents and injuries, drawing upon the insights gleaned from the unfortunate event and incorporating my scholarly contributions derived from research conducted in Finnmark, Northern Troms, and Svalbard (Mehus, 2012; Mehus et al., 2016).

One of the parents, who had lost his son, and I initiated an innovation project in the junior high schools of Hammerfest and Kvalsund as an annual event which also was supported by the Norwegian Public Roads Administration, The Norwegian Council of Road Safety (funders) and the local snowmobile association of Hammerfest and Kvalsund we started planning for interventions regarding risk taking in snowmobiling.

The goal of this collaboration was to make young people aware of the risks in snowmobiling and enable them to assess these risks based on the fatal incident in the local community in 2011. We got access to schools and talked about how fatal mistakes and poor preparation lead to significant danger. In these meetings, the father deceased openly reflected on what he believed had caused his son's death, how bad equipped they were for the mountain trip, what disastrous choices were made, and how all of this contributed to their deaths on the mountain that day. In addition, all the grief it has caused for the family and friends. Additionally, I shared my findings from my research from Northern Norway and Svalbard, which were based on interviews with 81 youths aged 16–24 years, about how these youths described their driving patterns, how injuries and accidents occurs and the risks they expose themselves to. Findings from my studies was in line with some of the unlucky assessments done by the youths in the incident. After the meeting with the pupils, they got a plastic, pocket-card with SAFETYRULES of countermeasures and assessments according to planning a trip. This was based on findings from national and international studies reporting snowmobile accidents and recommendations to avoid them:

- **S**afety equipment**:** first aid kit, mobile phone/satellite phone, compass, search bar, mountain -blanket and spade.
- **A**lcohol is not allowed when snowmobiling.
- **F**ollow the trails for your own safety.
- **E**verybody has to wear helmets and well-insulated clothes.
- **T**ry to avoid night driving, mountain climbing and showing off.
- **Y**oung boys are in the risk zone for accidents - be aware.
- **R**ules are made four your own safety.
- **U**nfamiliar areas demand extra attention.

- **L**et someone know where you are going and when you will return.
- **E**ven short trips can be long - be prepared.
- **S**mall children are not allowed to drive.

By this reminder they could discover whether they were breaking recommended safety rules or contributing to safe rides.
In addition, we arranged a small, anonymous survey regarding if they have learned something from meeting us? Yes, the most reported that they have got good advice. This results, were summed up and reported The Norwegian Council of Road Safety. Based on this community-based intervention the snowmobile association got the award of road safety in 2016.
We also invited parents to separate meetings to discuss how they intervened regarding rules and control of the youth's activity. Parents, on their part and with these rules as a basis, we think were better equipped to set demands on the snowmobiling behavior of the youth.

I was called to be a co-partner in another project in the municipality of Kvalsund aimed to improve and set standard plans on the infrastructure for the snowmobile trails (Mehus & Mehus, 2012). In addition, I was invited by the The Norwegian Council of Road Safety to present my research and our community-based work at a conference in Halifax, Nova Scotia, Canada in 2018.

Based on all this, as an academic and a snowmobiler, I think and hope that our interventions have been succeeded but, the result of an intervention is difficult to measure. One study on retrospective data from registered deaths and injuries on ATV`s, including snowmobiles during 2013-2014 in Northern Norway revealed 7 deaths and 87 injured. This study did not discuss whether there was an ongoing, community-based intervention at the time of their study in Finnmark. On the other hand, they reported no fatalities under the age of 20 years from the findings from Northern Norway in 2013-2014 (Rønning et al., 2019). More consecutive and detailed registrations are required.

Bakke, H. K., Dehli, T., & Wisborg, T. (2014). Fatal injury caused by low-energy trauma - a 10-year rural cohort. *Acta Anaesthesiol Scand*, *58*(6), 726-732. https://doi.org/10.1111/aas.12330

Hortemo, G. S., Brattebo, G., & Hellesnes, S. (1990). [The snowmobile--only for fun? Registration of snowmobile accidents in Western Finnmark 1988-89].[see comment]. *Tidsskrift for Den Norske Laegeforening*, *110*(10), 1196-1198.

Jeppesen,E. & wisborg,T. (2005) Skader fra bruk av snøscooter i Vest-Finnmark. [Injuries from snowmobile accidents in West Finnmark]Tidsskr Nor Lægeforen 125:3248-51

Mehus, A. G., & Mehus, G. (2012). *Prosjektrapport med forslag til tiltak for å forbedre merking, standard og infrastruktur i snøscooter løyenettet ,Kvalsund kommune* (Project report with proposed measures to improve signage, standards, and infrastructure in the snowmobile trail network, Kvalsund Municipality., Issue.

Mehus, G. (2012). *Ungdom, risiko og snøscooterkjøring. En studie av ungdoms forhold til snøscooterkjøring , risikotaking ,ulykker og uhell med foreslåtte forebyggingsstrategier.* [Articles, University of Tromsø]. Universitetet i Tromsø, Munin. http://munin.uit.no/handle/10037/4735

Mehus, G., Germeten, S., & Henriksen, N. (2010). Snøscooterkjøring og scooterfeelingen [Youth, Snowmobiling and the "Snowmobile Feeling"] [referee]. *Tidsskrift for Ungdomsforskning*, *10*(2), 17.

Mehus, G., Germeten, S., & Henriksen, N. (2011). How young people communicate risks of snowmobiling in Northern Norway:a focus group study. *International Journal of Circumpolar Health*, *70*(2), 9.

Mehus, G., & Henriksen, N. (2011). Ungdom og snøscooterkjøring:kjørevaner,risikovurdering og ulykker [Nye tall om ungdom]. *Tidskrift for ungdomsforskning*, *11*(1), 9.

Mehus, G., Mehus, A. G., Germeten, S., & Henriksen, N. (2016). Young people and snowmobiling in northern Norway: accidents, injury prevention and safety strategies. *Rural Remote Health*, *16*(4), 3713.

Rønning, T. H., Grov, E. K., & Wisborg, T. (2019). Fatalities and personal injuries from the use of ATVs and snowmobiles in Northern Norway in 2013-14. *Tidsskr Nor Laegeforen*, *139*(7). https://doi.org/10.4045/tidsskr.18.0966 (Dødsfall og personskader ved bruk av ATV og snøscooter i Nord-Norge i 2013–14.)

Vatn, P. (2011, 7.mars). Ni ungdommer savnet på fjell i Porsanger -Full storm og dårlig sikt i leiteområdet *Finnmark Dagblad*. http://www.finnmarkdagblad.no/nyheter/article5514287.ece

5. Sources to corroborate the impact (indicative maximum of ten references)

Mehus, A. G., & **Mehus, G.** (2012). *Prosjektrapport med forslag til tiltak for å forbedre merking, standard og infrastruktur i snøscooter løyenettet ,Kvalsund kommune* (Project report with proposed measures to improve signage, standards, and infrastructure in the snowmobile trail network, Kvalsund Municipality.
Prosjektrapport+med+forslag+til+tiltak+for+å+forbedre+Scooterløyper.pdf (custompublish.com)

Seks nominerte til trafikksikkerhetspris - Radio Nordkapp

Nyheter | Her er utstyret du trenger for å ferdes trygt på fjellet (ifinnmark.no)

Norwegian Council for Road Safety, Head of department in Finnmark: Knut Larsen, cellphone: 93207641 (retired 2023).

The Norwegian Public Road Administration-Finnmark: Kristian Øvernes cellphone: 900 99 150

The head of the snowmobile association in Hammerfest og Kvalsund: Tom Roger Larsen cellphone 48049751

Impact case - number 3

Institution: UiT, The Artic University of Norway
Administrative unit: Department of Health and Care Sciences
Title of case study: Implementation of the PED-t intervention to a routine clinical context.
Period when the underpinning research was undertaken: 2014-2018
Period when staff involved in the underpinning research were employed by the submitting institution: 2014
Period when the impact occurred: 2021- dd

1. Summary of the impact (indicative maximum 100 words)
This section should briefly state what specific impact is being described in the case study.

The impact of a novel therapy for patients with eating disorders (PED-t)

- The new therapy has now been delivered in a primary care setting ("Frisklivssentral")
- (N= 16 patients fulfilled the treatment)
- Therapists in 10 HLC appointed by the authorities as research centers, were invited to be trained on ED literacy and to run PED-t. (N= 9 completed)
- Two qualitative studies exploring expectations and experiences with the new treatment in a new arena (one published, one in review)
- Seminars
- Public dissemination (media)
- The treatment PED-t is now implemented as a permanent offer in Fredrikstad at the "Frisklivssentralen"

2. Underpinning research (indicative maximum 500 words)

The randomized controlled study consists of two ph.d project

1) **A randomized controlled trial of physical exercise- and dietary therapy versus cognitive behavior therapy: Treatment effects for women with bulimia nervosa or binge eating disorder. https://doi.org/10.1002/eat.23228**

The aim was to test the efficacy of a new treatment for eating disorder (bulimia nervosa and binge eating disorder) consisting of physical exercise and dietary counselling (PED-t). This testing used aa randomized controlled design comparing the PED-t against the best evidenced treatment (i.e., cognitive- behavioral therapy- CBT), and a waiting list control group, respectively. Both the PED-t and the CBT proved effective in alleviating eating disorder symptoms as well as improving overall quality of life at post-test and after a 24-month follow-up. The findings make a strong case for highlighting the PED-t as an alternative treatment for bulimia and binge eating disorders.
This argument and conclusion is further strengthened by feasibility and acceptability studies where participants and therapists were interviewed as well as participants who dropped out of treatment.
https://doi.org/10.1136/bmjopen-2018-025344
https://doi.org/10.1136/bmjopen-2017-019386
https://doi.org/10.1080/17482631.2020.1731994

Overall, patients found the treatment beneficial, but reasons for patients' drop-out were a reliable source of information to further refine the treatment manual. Moreover, to further examine the

status of the PED-t as an appropriate alternative to established treatments, further replications with other patients and in non-controlled clinical contexts settings are needed.

https://nih.brage.unit.no/nih-xmlui/handle/11250/2562679
https://tfmathisen.no/forskning/fakt-studien-behandling-av-spiseforstyrrelser/

2) Patients' and therapists' experiences with a new treatment for eating disorders, combining physical exercise and dietary therapy. An interview study.

In the effectiveness study of the PED-t https://doi.org/10.1002/eat.24020
was further explored interviewing patients' and therapists' experiences where the PED-t was implemented in a non-controlled clinical setting, i.e. a Healthy Life Center ("Frisklivssentral").

Names of the key researchers and what positions they held at the administrative unit at the time of the research (where researchers joined or left the administrative unit during this time, these dates must also be stated).

Gunn Pettersen, professor, Department of health and care sciences, UiT, The Artic University of Norway was the main link to the PI (ass prof Mathisen, Østfold University College), and served as the expert on qualitative designs and analyses (Main supervisor in a ph.d project in the RCT and co-author in both publications related to the RCT and the implementation study).

3. References to the research (indicative maximum of six references)

1. Mathisen TF, Rosenvinge JH, **Pettersen G**, Friborg O, Vrabel K-A, Bratland-Sanda S, Svendsen M, Stensrud T, Bakland M, Wynn R & Sundgot-Borgen J, (2017). The PED-t trial protocol: The effect of physical exercise –and dietary therapy compared with cognitive behavior therapy in treatment of bulimia nervosa and binge eating disorder. Study protocol of a randomized controlled trial. *BMC Psychiatry. 17:180*: 1-11. Download paper
2. Mathisen TF, Bratland-Sanda S, Rosenvinge JH, Friborg O, **Pettersen G**, Vrabel K-A & Sundgot-Borgen J, (2018). Treatment effects on compulsive exercise and physical activity in eating disorders. *Journal of Eating Disorders. 6*: 1-9. Download paper
3. Mathisen TF, Rosenvinge JH, Friborg O, Vrabel K, Bratland-Sanda S, **Pettersen G** & Sundgot-Borgen J, (2020). Is physical exercise and dietary therapy a feasible alternative to cognitive behavior therapy in treatment of eating disorders? A randomized controlled trial of two group therapies. *International Journal of Eating Disorders. 53*(4): 574-585. Download paper
4. **Pettersen G**, Sørdal S, Rosenvinge JH, Skomakerstuen T, Mathisen TF & Sundgot-Borgen J, (2017). How do women with eating disorders experience a new treatment combining guided physical exercise and dietary therapy? An interview study of women participating in a randomised controlled trial at the Norwegian School of Sport Sciences. *BMJ Open. 7*: 9. Download paper
5. Mathisen TF, **Pettersen G**, Rosenvinge JH, Schmidt UH & Sundgot-Borgen J, (2023). Effectiveness and acceptability of the physical exercise and dietary therapy in a healthy life center. *International Journal of Eating Disorders.* 1-10. Download paper

6. Bakland M, Rosenvinge JH, Wynn R, Sundgot-Borgen J, Mathisen TF, Liabø K, Hanssen TA & **Pettersen G,** (2019). Patients' views on a new treatment for Bulimia nervosa and binge eating disorder combining physical exercise and dietary therapy (the PED-t). A qualitative study. *Eating Disorders.* 19. Download paper

4. Details of the impact (indicative maximum 750 words)

The output of the PED-t (research in terms of effectivity and effectiveness has Physical Exercise and Dietary therapy) study has been proved effective in a controlled contact against a gold-standard evidence-based treatment (cognitive behavioral therapy- CBT), and a wait-list control group. The early primary studies have so far been promisingly cited (range 20-49 as per January 2024 - Google scholar), which is indicative of a reasonable scientific recognition. Including more recent publications, and a resubmitted international paper, the sum of finding is very promising in the pursuit of offering a treatment option for people suffering from eating disorder, and who may not benefit from treatment as usual in the specialist health care, or who for many reasons are not captured by the standard level of care. The treatment (16 weeks, 20 group sessions) was carried out in one local Healthy life center (frisklivssentral) in Fredrikstad, fall 2021. The recruitment and interviews were conducted in June -2021- August 2021. Therapists in 10 HLC appointed by the authorities as research centers, were in fall 2021 invited to be trained on ED literacy and to run PED-t and 9 completed August 2021.
As for dissemination and recognition within the general public, we refer to several attentions in the popular media (please see below). Impact of this research in popular media can be displayed referring to the following:

- Fredriksstad Blad: Menn, mat og håpløshet – en ukjent psykisk lidelse. 2022
- Fredriksstad Blad: Slik lærte Linda (31) å takle overspising – nå skal også menn få behandling for sykdommen, 2022
- Fredriksstad Blad: Starter nytt behandlingstilbud for pasienter med spiseforstyrrelser. 2022
- Fredriksstad Blad: Fredrikstad først i landet med nytt tilbud som behandling for overspising og bulimi 2021
- Fredriksstad Blad: Noen spiser for å dempe smerte, andre for å føle lykke. 2021.

5. Sources to corroborate the impact (indicative maximum of ten references)

To corroborate the impact new research is published:

Mathisen, T. F., Pettersen, G., Rosenvinge, J. H., Schmidt, U., & Sundgot-Borgen, J. (2023). Effectiveness and acceptability of the physical exercise and dietary therapy in a healthy life center. *International Journal of Eating Disorders*, 1– 10. https://doi.org/10.1002/eat.24020

Mathisen, T. F. Pettersen, G., Rosenvinge, J. H., Schmidt, U., & Sundgot-Borgen, J. (2024). Expectations of a new eating disorder treatment and its delivery. *International Journal of Eating Disorders*, resubmitted for publication.

Publications from PED-t

Mathisen TF, Sundgot-Borgen J, Rosenvinge JH, Bratland-Sanda S, Svendsen M, **Pettersen G**, Vrabel K & Friborg O, (2023). Metabolic profile in women with bulimia nervosa or binge-eating disorder before and after treatment: secondary analysis from the randomized PED-t trial. *Eating and Weight Disorders. 28*: 14. Download paper

Mathisen TF, **Pettersen G**, Rosenvinge JH, Schmidt UH & Sundgot-Borgen J, (2023). Effectiveness and acceptability of the physical exercise and dietary therapy in a healthy life center. *International Journal of Eating Disorders.* 1-10. Download paper

Mathisen TF, Rosenvinge JH, Friborg O, Vrabel K, Bratland-Sanda S, **Pettersen G** & Sundgot-Borgen J, (2020). Is physical exercise and dietary therapy a feasible alternative to cognitive behavior therapy in treatment of eating disorders? A randomized controlled trial of two group therapies. *International Journal of Eating Disorders. 53*(4): 574-585. Download paper

Bakland M, Rosenvinge JH, Wynn R, Sørlie V, Sundgot-Borgen J, Mathisen TF, Hanssen TA, Jensen F, Innjord K & **Pettersen G,** (2020). A new treatment for eating disorders combining physical exercise and dietary therapy (the PED-t): experiences from patients who dropped out. *International Journal of Qualitative Studies on Health and Well-being. 15*(1): 7. Download paper

Pettersen G, Rosenvinge JH, Skomakerstuen T, Sørdal S, Mathisen TF & Sundgot-Borgen J, (2019). Patient expectations of a new treatment for eating disorders combining guided physical exercise and dietary therapy: An interview study of women participating in a randomised controlled trial at the Norwegian School of Sport Sciences. *BMJ Open. 9*(4): 6. Download paper

Bakland M, Rosenvinge JH, Wynn R, Sundgot-Borgen J, Mathisen TF, Liabø K, Hanssen TA & **Pettersen G,** (2019). Patients' views on a new treatment for Bulimia nervosa and binge eating disorder combining physical exercise and dietary therapy (the PED-t). A qualitative study. *Eating Disorders.* 19. Download paper

Pettersen G, Rosenvinge JH, Bakland M, Wynn R, Mathisen TF & Sundgot-Borgen J, (2018). Patients' and therapists' experiences with a new treatment programme for eating disorders that combines physical exercise and dietary therapy: The PED-t trial. A qualitative study protocol. *BMJ Open. 8*(1): 5. Download paper

Mathisen TF, Rosenvinge JH, Friborg O, **Pettersen G,** Stensrud T, Hansen BH, Underhaug K, Teinung E, Vrabel K-A, Svendsen M, Bratland-Sanda S & Sundgot-Borgen J, (2018). Body composition and physical fitness in women with bulimia nervosa or binge-eating disorder. *International Journal of Eating Disorders. 51*(4): 331-342. Download paper

Mathisen TF, Bratland-Sanda S, Rosenvinge JH, Friborg O, **Pettersen G**, Vrabel K-A & Sundgot-Borgen J, (2018). Treatment effects on compulsive exercise and physical activity in eating disorders. *Journal of Eating Disorders. 6*: 1-9. Download paper

Bakland M, Sundgot-Borgen J, Wynn R, Rosenvinge JH, Stornæs AV & **Pettersen G,** (2018). Therapists' experiences with a new treatment combining physical exercise and dietary therapy (the PED-t) for eating disorders: An interview study in a randomised controlled trial at the Norwegian School of Sport Sciences. *BMJ Open. 8*(1): 7. Download paper

Pettersen G, Sørdal S, Rosenvinge JH, Skomakerstuen T, Mathisen TF & Sundgot-Borgen J, (2017). How do women with eating disorders experience a new treatment combining guided physical exercise and dietary therapy? An interview study of women participating in a randomised controlled trial at the Norwegian School of Sport Sciences. *BMJ Open. 7*: 9. Download paper

Mathisen TF, Rosenvinge JH, **Pettersen G**, Friborg O, Vrabel K-A, Bratland-Sanda S, Svendsen M, Stensrud T, Bakland M, Wynn R & Sundgot-Borgen J, (2017). The PED-t trial protocol: The effect of physical exercise –and dietary therapy compared with cognitive behavior therapy in treatment of bulimia nervosa and binge eating disorder. Study protocol of a randomized controlled trial. *BMC Psychiatry. 17:180*: 1-11. Download paper

UiT-IHO-Impact case 4

Institution: UiT the Arctic University of Norway
Administrative unit: Department of Health and Care sciences
Title of case study: Improving patient reported outcomes in patients with heart diseases
Period when the underpinning research was undertaken: 2016-2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2016-2022
Period when the impact occurred: 2016-2022

Summary of the impact

This case illustrates impacts of collaborative clinical project between the research group (RG) and University hospital North Norway.

This case has involved collaboration regarding planning, developing, pilot-testing, implementing, and reporting of patient reported outcomes (PRO) in clinical trials in several projects.

The impact is manyfold: it has shown worldwide that that bare mineral stents are as good as drug eluting stents, led to innovative treatment initiatives to improve uptake of cardiac rehabilitation in particular in Norway, and used PRO to document effects of diagnostic and treatment interventions internationally. Furthermore, built multidisciplinary research collaboration, competence and capacity in Northern Norway.

2. Underpinning research

The Norwegian Stent Trial (NORSTENT) included 9013 patient from 2009 to 2011 and followed patients five year (until 2015). PI was Kaare H Bønaa. In this national megatrial evaluating the effects of bare mineral and drug eluting stents on different endpoints, TAH from the RG was responsible for planning, collecting and analysing PRO. Furthermore Hanssen was PI on a substudy assessing and evaluating effects of cardiac rehabilitation (CR) and the main supervisor for PhD student Siv JS Olsen in this substudy. Four publications from this study are highlighted in the next section. The main publication from this study by Bønaa et al is Cited by 630 and underpin guidelines and changes in clinical practice worldwide. The publication from the substudy on national participation in CR was one of the first and most comprehensive to assess CR in patients having had stents after coronary revascularisation, in Norway. As the results from this substudy indicated that only 28% participated in CR in Norway, this study has led to new intervention studies e.g. in the Southern and Western Norway health region, with reference to our study.

In the CTangio trial PI was Amjid Iqbal. The study followed implementation of CT Angio as an alternative to invasive coronary angiography in Northern Norway. Hanssen oversaw measuring PRO. Based on this study eligibility of patients and the sensitivity and specificity of the diagnostic properties of this new intervention was tested. Alongside PRO was assessed. The latter study provided new knowledge to researchers, clinicians and the public of vulnerable patients with normal vessels that were in need of follow -up, due to reported problems.

In the ReShape study ongoing clinically from 2013- 2016 PI was Terje Steigen. This clinical study at the University hospital assessed the effects of renal sympathetic denervation in treatment-resistant hypertensive patients. TA Hanssen was project member and main author on the paper

related to assessing and analyzing PRO. Besides assessing broadly the effects of this new innovative treatment on traditional outcomes, this study was one of few documenting the effects of having the diagnosis of treatment resistant hypertension on quality-of-life aspects.

All the studies in this case were multidisciplinary with nurses with different specializations, physicians with different specializations, statisticians etc. and has included Ph.D. and/or postdoc candidates from Northern Norway. Having multidisciplinary teams involved made it possible to assess all relevant outcomes also those important from the patient perspectives.

Key researchers from the RG at IHO in these studies was Tove Aminda Hanssen (nurse, associate professor 2014- 2018, professor 2019-) and associate member Siv J Storli Olsen (nurse, Ph.D. student 2016-2020, researcher 2021-)

This case illustrated that research competence in a research weak area i.e. nursing research, compared to medicine, is improved.

3. References to the research (indicative maximum of six references)

Bønaa, K. Mannsverk, JT. Wiseth, R. Aaberge, L. Myreng, Y. Nygård, O. Nilsen, DWT. Kløw, NE. Uchto, M. Trovik, T. Bendz, B. Stavnes, S. Bjørnerheim, R. Larsen, AI. Slette, MK. Steigen, T. Jakobsen, OJ. Bleie, Ø. Fossum, E. **Hanssen, TA.** Dahl-Eriksen, Ø. Njølstad, I. Rasmussen, KE. Wilsgaard, T. Nordrehaug, JE. **Drug-Eluting or Bare-Metal Stents for Coronary Artery Disease.** New England Journal of Medicine 2016 ;Volume 375.(13) p. 1242-1252
DOI: 10.1056/NEJMoa1607991 cited by 630

Olsen SJ, Schirmer H, Bønaa K, **Hanssen TA. Cardiac rehabilitation after percutaneous coronary intervention: results from a nationwide survey**. Eur J Cardiovasc Nurs. 2018:17(3):273-79
DOI: 10.1177/1474515117737766 cited by 45

Olsen SJ, Schirmer H, Bønaa K, Wilsgård T, **Hanssen TA. Cardiac rehabilitation and symptoms of anxiety and depression after percutaneous coronary intervention.** European Journal of Preventive Cardiology 2018:25 (10):1017-25 https://doi.org/10.1177/2047487318778088 Cited by 78

Olsen Olsen SJS, Schirmer H, Wilsgaard T, Bønaa KH, **Hanssen TA. Employment status three years after percutaneous coronary intervention and predictors for being employed. A nationwide prospective cohort study**. Eur J Cardiovasc Nurs 2020:19 (5):433-39
https://doi.org/10.1177/1474515120903614 Cited by 5

Hanssen TA, Iqbal A, Forsdahl S, Trovik T, Schirmer H. **Changes in symptoms of anxiety and depression following diagnostic angiography - a prospective cohort study.** Eur Heart J Qual Care Clin Outcomes. 2018:4 (2)106-112. DOI: 10.1093/ehjqcco/qcx039 Cited by 8

Hanssen TA, Subbotina A, Miroslawska A, Solbu MD, Steigen TK. **Quality of life following renal sympathetic denervation in treatment-resistant hypertensive patients: a two-year follow-up study.** Scandinavian Cardiovascular Journal, 2022, 56 (1)174-179
DOI: 10.1080/14017431.2022.2084562 cited by 3

4. Details of the impact (indicative maximum 750 words)

The studies included in this case has made an impact as they have been published and presented to researchers and clinicians. All the studies were collaborations between Department of Heart Disease at University Hospital North Norway and Department of Health and Care Sciences and Department of Clinical Medicine at UiT. The studies have fostered multidisciplinary collaboration and have contributed to building research capacity for both nurses and physicians. The good collaboration has led to new research projects not described in this case e.g. the PhD project for nurse Anette Krane and physiotherapist Margrethe Muller, as well as forskerlinjestudents and the PhD for MD Anna Subbotina. The studies have also improved clinical practice.

The researcher initiated and independent from industry **NORSTENT** study was presented in a main hotline session 30 august 2016 in Rome at the European Society of Cardiology annual conference attracting more than 30 000 clinicians and researchers. At the same day the first and main publication from this study was published in New England Journal of Medicine. **According to editorials published simultaneously, this study was unique and set standard for future studies. Furthermore, for society worldwide and in particular poor in countries the results that bare mineral stents were as good as drug eluting stents was good news, as drug eluting stents was more costly and less available**. After the presentation of these results the researchers were invited to a panel discussion in the main session. TA Hanssen joined together with three of the other authors and discussed aspects and questions related to the reported outcomes on quality of life. The PhD student presented her first results from the substudy and got on the shortlist (of in total 3) for the ESC CCNAP Young investigator award and presented her results orally at this conference in August 2016.

Based on publication from the NORSTENT **substudy clinicians and researchers obtained valuable information regarding to what extent Norwegian patients participate in CR after myocardial infarction. Although our study showed that only in average 28% participated in CR, with evident regional differences, those in most need of CR were the ones that had participated. These results have led to new studies testing CR initiatives in this patient group and with reference to our results.**

In the **CTAngio** study we developed **new knowledge for clinicians' and researchers related to the accuracy of this new diagnostic test alongside improved clinical knowledge for those involved.** Furthermore, we assessed PRO **providing insight to patients' experiences undergoing this diagnostic procedure**. **This new knowledge relevant for clinicians and researchers indicated that one group was vulnerable and in need of follow-up services**: research findings not previous known.

In the **ReShape** study were we provided new knowledge for clinicians and researchers on different outcomes of this new innovative treatment, traditional outcomes as well as PRO. **We assessed as one of the first studies, quality of life from an overall-, generic- and disease- specific level. Based on these results we both documented side effects of traditional treatment and the possible effect of the reduction of antihypertensive medication. During the implementation of this study clinical practice evolved and improved as we develop and evaluate a research-based nurse administered sedation procedure for this new treatment that improved clinical practice and sedation procedures at the lab performing different cardiovascular procedures'.**

5. Sources to corroborate the impact (indicative maximum of ten references)

Sources to corroborated impact:

Dagens medicine reported about the impact of the NORSTENT study: La frem norsk gigant-studie (dagensmedisin.no) 30.08.2016

Editorial following the NEJM 2016 article about impact of the results Balancing the Evidence Base on Coronary Stents | NEJM

The study influenced international guidelines Nye STEMI-retningslinjer går på tvers av norsk studie (dagensmedisin.no)

Scientific paper summing up impact of the first study Potential Implications of NORSTENT (Norwegian Coronary Stent Trial) in Contemporary Practice | Circulation (ahajournals.org)

Impact of NORSTENT CR substudy in making the case for need for new rehabilitation initiatives:
Hjerterehabilteringsseminar, LHL - CERG - NTNU
The follow-up after myocardial infarction – is it good enough? | Tidsskrift for Den norske legeforening (tidsskriftet.no) 05.03.2018

Impact of The CT Angio study documenting a patient group in need of increased follow-up
Større angstreduksjon hos hjertesyke enn friske (dagensmedisin.no) (22.11.2017)
Friskmelding gav ikkje angstreduksjon | UiT

Documentation of the impact in a nursing initiated project alongside the ReShape trial
15fo4_art._hanssen_3561.pdf (sykepleien.no) published 2015

UiT Department of Health and Care sciences case number 5

Institution: UiT the Arctic University of Norway
Administrative unit: Department of Health and Care sciences (IHO)
Title of case study: the Care Library / Omsorgsbiblioteket.no
Period when the underpinning research was undertaken: 2016-2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2016-2022
Period when the impact occurred: 2016-2022

1. Summary of the impact (indicative maximum 100 words)
This section should briefly state what specific impact is being described in the case study.

The Care Library, which was established in 2016, provides openly accessible knowledge summaries on various topics within health care research and innovation in Norway (so far: 28 topics). The online library is co-managed by all five Centers of Care Research in Norway, including SOF north, which has UiT and the IHO as host institution. Target groups for the Care Library are leaders and employees in Norwegian municipal healthcare services, politicians, patients, students, researchers and others. User statistics show that the knowledge summaries in the Care Library are downloaded across Norway. Some of the summaries are referred to in national and regional policy documents.

2. Underpinning research (indicative maximum 500 words)
This section should outline the key research insights or findings that underpinned the impact, and provide details of what research was undertaken, when, and by whom. This research may be a body of work produced over a number of years or may be the output(s) of a particular project. References to specific research outputs that embody the research described in this section, and evidence of its quality, should be provided in the next section.

SOF North has taken the lead in developing knowledge summaries within 6 topics; user involvement, health services for the Sami population, LGBT elderly, and immigrants, and public reform work (i.e., knowledge summaries relevant for the white paper "Live your whole life – a quality reform for the elderly 2017-2018", and the "Live safely at home reform 2022-2023")

The background for the establishment of The Care Library was the fact that a vital part of healthcare services is provided in the municipalities. Nevertheless, while a considerable amount og research on secondary healthcare services existed, very little research and knowledge about municipal healthcare services was available. Furthermore, there was a need to better convey the existing knowledge to municipalities and other relevant parties.

The research presented in the Care library is conducted by researchers at SOF and other researchers, and the research, resources, and projects presented should always be relevant to the Norwegian context. Since its inception in 2016, the Care Library has been instrumental in disseminating knowledge summaries that encapsulate pertinent research findings from the Centre for Care Research (SOF) and other sources, presenting them in Norwegian for broader accessibility. Moreover, the platform has served as a repository for insights from development

projects, as well as a trove of valuable resources tailored for leaders and healthcare personnel operating within municipal settings and beyond.

Key researchers and what positions they held at the administrative unit at the time of the research:

Bodil Hansen Blix (Post Doctoral Candidate 2016), Marianne Eliassen (Associate Professor, 2020-), Astrid Gramstad (Editor-in-chief the Care Library, 1.1.-2018--1.8.2021), Trude Hartviksen (Researcher, 2020-), Monika Dybdahl Jakobsen (Post Doctoral Candidate, Regional Coordinator and member of the Editorial Team in the Care Library, 2019-), Martin Sollund Krane (Researcher, 2021-), Jill-Marit Moholt (Post Doctoral Candidate, 2021), Rita Sørly (Researcher, 2016-2018).

3. References to the research (indicative maximum of six references)

Examples of knowledge summaries produced by researchers at our administrative unit:

1. Krane, Martin Sollund. Health services for the sami population in Norway – an updated summary. [Helse- og omsorgstjenester til den samiske befolkningen i Norge - Oppdatert kunnskapsoppsummering (2016-2021).] 2021. https://hdl.handle.net/11250/2976847
2. Jakobsen, Monika Dybdahl; Spilker, Ragnhild Storstein. Immigrants and patient participation in the health and care services; how can we foster immigrants' participation in decisions concerning own health, in service design and in health service research. [Innvandrere og brukermedvirkning i helse- og omsorgstjenestene; Hvordan ivareta innvandreres brukermedvirkning i avgjørelser om egen helse, utforming av tjenester og tjenesteforskning - En oppsummering av kunnskap.] 2020. https://hdl.handle.net/11250/2686533
3. Jakobsen, Monika Dybdahl; Krane, Martin Sollund Research on how to design health services that are inclusive for older LGBT persons. [Sammenfatning av forskning om kompetansen som kreves for å få mer inkluderende tjenester til eldre LGBT-personer.] 2021. https://hdl.handle.net/11250/3013193
4. Eliassen, Marianne; Hartviksen, Trude. Existing knowledge on the white paper "Live your whole life – a quality reform for the elderly" : activities and communities. [Kunnskapsnotat: Leve hele livet – En kvalitetsreform for eldre. Beskrivelser av eksisterende kunnskap om reformens utfordringsområder. Aktivitet og fellesskap.] 2020. https://hdl.handle.net/11250/2654393
5. Cappelen, Kathrine; Solstad, Liv Jorunn; Andfossen, Nina Beate; Hartviksen, Trude; Devik, Siri Andreassen. Government and management, quality improvement work and innovation. [Styring og ledelse, forbedringsarbeid og innovasjon.] 2020. https://hdl.handle.net/11250/2654411
6. Rita Sørly. User involvement in dementia care. [Brukermedvirkning i demensomsorgen.] 2017. http://hdl.handle.net/11250/2453749

4. Details of the impact (indicative maximum 750 words)

The Care Library, established in 2016 by the Centre for Care Research, has made a significant and material contribution to the impact on healthcare services within Norwegian municipalities. The research conducted by the Centre for Care Research and other scholars has been pivotal in

underpinning the library's resources, which have been instrumental in shaping policy, informing clinical practice, and enhancing the quality of care.

The Care Library serves as a national electronic repository that synthesizes and disseminates research findings relevant to municipal health and care services. It has been **a key vehicle for translating research into practice**, ensuring that the latest evidence-based knowledge is accessible to healthcare professionals, policymakers, and other stakeholders. The library's knowledge summaries, which cover a range of topics pertinent to Norwegian healthcare, are downloaded and referenced in national and regional policy documents, demonstrating their influence on users and beneficiaries.

SOF North, as part of the collaborative network of Centers for Care Research in Norway, has led the **development of knowledge summaries within six critical areas**, including user involvement and health services for the Sami population. These summaries have been directly cited in government white papers, such as Meld. St. 24 (2022–2023), indicating the specific contribution of SOF North's research to the broader impact. Upon publication of a new knowledge summary there is always a dissemination plan including activities such as e.g., writing commentaries in newspapers, press releases, and webinars.

The primary beneficiaries of The Care Library's impact are leaders and staff in Norwegian municipal healthcare services, who utilize the knowledge summaries to inform their practice and decision-making. Additionally, policymakers, patients, students, researchers, and the general public benefit from the accessible and relevant information that supports healthcare delivery and policy formulation.

The impact is multifaceted, improving the quality of healthcare services, informing policy, and enhancing the education of healthcare professionals. For instance, during the COVID-19 pandemic, strategies proposed in the knowledge summary about immigrants were employed to effectively reach immigrant groups for vaccination efforts.

The extent of **the impact is evidenced by user statistics and citations in policy documents**. The knowledge summary on "Immigrants and User Participation" has garnered 2,955 views, while the summary on "Live Your Whole Life – A Quality Reform for the Elderly" has 2,806 views. These figures indicate the reach and utilization of the research.

The impacts have been ongoing since the establishment of The Care Library in 2016, with specific references to the research in government documents and the application of knowledge summaries in policy and practice during the COVID-19 pandemic and beyond.

5. Sources to corroborate the impact (indicative maximum of ten references)

Kvaal, Bjørn: “Hva vet du egentlig om eldre samer» [What do you know about the Sami elderly?] (2016), commentary in *The journal of Care research* Vol2. Iss.1 https://doi.org/10.18261/ISSN2387-5984-2016-01-03

Meld. St. 24 (2022–2023) Fellesskap og meistring — Bu trygt heime. (the *"Live Safely at Home"* reform). https://www.regjeringen.no/no/dokumenter/meld.-st.-24-20222023/id2984417/

Monika Dybdahl Jakobsen og Ragnhild Storstein Spilker: Innvandrere og brukermedvirkning i helse- og omsorgstjenestene - en oppsummering av kunnskap [Immigrants and user involvement in the health and care services] (2020). Conference Presentation. Link to abstract:

https://www.uib.no/sites/w3.uib.no/files/attachments/abstract_bok_-_migrasjonskonferanse_2020.pdf

Terje Emil Fredwall terje.e.fredwall@uia.no , Editor in chief, The Care library

Ragnhild Storstein Spilker ragnhild.storstein.spilker@nsfverv.no , Co-author and Group Leader for Migration Health and Multicultural Nursing, Norwegian Nurses Organization

Jacqueline Sæby Jacqueline.Saeby@helsedir.no , SOF contact point in the Norwegian Directory of Health

Siv Øverås sio@forskningsradet.no , SOF contact point in the Norwegian Research Council

UiT – FacHealthSci_DepMedBiol, IMB – Case_1

Institution: UiT – The Arctic University of Norway
Administrative unit: Department of Medical Biology (IMB)
Title of case study: Improving diagnostics of bacterial infections
Period when the underpinning research was undertaken:
Period when staff involved in the underpinning research were employed by the submitting institution:
Period when the impact occurred: - now

Summary of the impact (indicative maximum 100 words)
Improvement of diagnostic routines for bacterial infections: i) Discovery of new linezolid resistance gene implemented in international resistance databases, ii) research on silent resistance mechanisms leading to new recommendations for vancomycin resistance detection and reporting to clinicians by Nordic diagnostic microbiology laboratories and the American Clinical & Laboratory Standards Institute and iii) clinical implementation of rapid diagnostics for periprosthetic joint infections. These activities directly impact patient wellbeing and treatment both locally at the University Hospital of Northern Norway and worldwide.

2. Underpinning research (indicative maximum 500 words)

i) <u>On novel linezolid resistance gene and mechanism:</u>

- Kristin Hegstad (Professor, HMI/K-res, 2018-2022, discovered a novel gene involved in linezolid resistance in multi resistant isolates of *Enterococcus faecium,* initiated collaboration with international experts to reveal the mechanism (ribosomal protection) involved in this resistance and to which other antimicrobials it confers cross-resistance, provided material and AST data)
- Arnfinn Sundsfjord (Professor, HMI/K-res, 2019-2022, managed collaboration with international experts and gave clinical advice)

ii) <u>Silent resistance mechanisms:</u>

- Kristin Hegstad (Professor, HMI/K-res, 2013-2022, project leader)
- Arnfinn Sundsfjord (Professor, HMI/K-res, 2016-2022, co-project leader)
- Audun Sivertsen (PhD candidate, HMI, 2014-2017, bioinformatics and experimental work)
- Jessin Janice (researcher, HMI/K-res, 2015-2022, bioinformatics)
- Theresa Wagner (Postdoctoral researcher HMI 2019-2022, experimental work)

iii) <u>ID of bacteria from blood culture bottles for PJI diagnosis:</u>

- Anne-Merethe Hanssen (Associate Prof., HMI, project leader)
- Adriana Sanabria (PhD candidate, HMI, 2016-2021, experimental work, analyses)
- Mona Johannessen (Professor, research group leader, co-project leader)
- Gunnar Simonsen (Prof. University Hospital of Northern Norway, co-project leader)
- Johanna Ericsson (Prof, HMI, co-project leader)

Merethe EO Røkeberg (PhD candidate, HMI, collaborator)

3. References to the research (indicative maximum of six references)

i) On novel linezolid resistance gene and mechanism:
Crowe-McAuliffe C, Murina V, Turnbull KJ, Huch S, Kasari M, Takada H, Nersisyan L, Sundsfjord A, Hegstad K, Atkinson GC, Pelechano V, Wilson DN, Hauryliuk V. 2022.

Structural basis for PoxtA-mediated resistance to phenicol and oxazolidinone antibiotics. Nature Comm 13:1860. doi: 10.1038/s41467-022-29274-9.

ii) On Silent resistance:
Sivertsen A, Pedersen T, Larssen KW, Bergh K, Rønning TG, Radtke A, Hegstad K. 2016. A silenced *vanA* gene cluster on a transferable plasmid caused an outbreak of vancomycin-variable enterococci. Antimicrobial Agents Chemother 60:4119-27. DOI: 10.1128/AAC.00286-16
Wagner TM, Janice J, Sivertsen A, Sjögren I, Sundsfjord A, Hegstad K. 2021. Alternative *vanHAX* promoters and increased *vanA*-plasmid copy number resurrect silenced glycopeptide resistance in *Enterococcus faecium*. J Antimicrob Chemother 76:876-82. doi: 10.1093/jac/dkaa541.

iii) On ID of bacteria from blood culture bottles for PJI diagnosis:
Sanabria A, Røkeberg MEO, Johannessen M, Sollid JE, Simonsen GS, Hanssen AM. 2019. Culturing periprosthetic tissue in BacT/Alert® Virtuo blood culture system leads to improved and faster detection of prosthetic joint infections. BMC Infect. Dis. DOI:10.1186/s12879-019-4206-x/ https://doi.org/10.1186/s12879-019-4206-x. The study was part of a PhD thesis https://munin.uit.no/handle/10037/19740

4. Details of the impact (indicative maximum 750 words)

i) Our discovery and characterization of a novel linezolid resistance gene has led to its implementation in global antimicrobial resistance databases that are used by clinical laboratories worldwide to predict resistance from bacterial whole genome sequences. It is important to contribute to expansion of the public databases when new antimicrobial resistance mechanisms/genes are detected since when using such tools, one only can detect what is already known. After we published the study describing the new resistance gene (2022), Hegstad contacted the administrative personnel of the international databases and made sure they were aware of the new resistance gene and included it in their databases (2023). The novel resistance gene was discovered in enterococci and sent to the Norwegian national advisory unit on detection of antimicrobial resistance (K-res) where Hegstad and Sundsfjord also are affiliated. We then contacted international experts to resolve the mechanism involved in this resistance.

ii) Our research on silent resistance mechanisms (also termed vancomycin variable enterococci) is an important contribution to avoiding treatment failure for enterococcal infections. Phenotypic detection of resistance is the standard in clinical microbiological laboratories worldwide. Our finding of resistance genes that are not expressed (silent) but can lead to a resistant phenotype during a few days' exposure to vancomycin (like during infection treatment) has led to:
1) new recommendations on detection of vancomycin resistance in enterococci by genotypic methods in Nordic diagnostic microbiology laboratories and
2) new recommendations on reporting silent vancomycin resistance genes as resistant to the clinicians prescribing the antibiotics although the phenotypic methods reveal the bacteria as susceptible by the American Clinical & Laboratory Standards Institute (CLSI). Enterococci with silent resistance genes were sent for further investigation to K-res which have a high standing nationally and internationally among people working within the field of antimicrobial resistance detection. The primary laboratories that detected the bacterial strains were involved in describing the cases and personnel at K-res and HMI were involved in the bioinformatic and experimental work to reveal the mechanisms involved. Our first publication of silent vancomycin resistance got attention

by the CLSI subcommittee on antimicrobial susceptibility testing and Hegstad was consulted by CLSI in 2016 before their recommendation was communicated to the clinical laboratories through a newsletter. Our dissemination (publications and oral presentations at meetings) has also led to consultation by national (2017) and Scandinavian (2019) working groups recommending methods to the clinical laboratories on detection of antimicrobial resistance.

iii) In our research we assessed the use of a BacT(Alert VirtuO blood culture system for culturing periprosthetic tissue (PJT) specimens. Our finding is an important contribution to faster detection and diagnosis of prosthetic joint infection (PJI). We presented a laboratory procedure that may be an important tool in the diagnosis of PJI. We recommended using the BacT/Alert® Virtuo blood culture system for culturing periprosthetic tissue, and we showed that the blood culture bottle (BCB) method detected a wider range of bacteria more efficiently and more rapidly than the conventional microbiological method. The use of BCB is a convenient approach to be used in the routine in the clinics facilitating early clinical decision making and in diagnosis of PJI cases.
The diagnostic method was implemented in the routine laboratory at Department for microbiology and infection control (AMS) at UNN for diagnosis of PJI in 27.08.2018 (internal document no. PR21396). This impact case resulted in one publication, and formed the basis for a PhD thesis on metagenomics which led to three publications on the subject.

5. Sources to corroborate the impact (indicative maximum of ten references)

i) The novel linezolid resistance gene termed poxtA-Ef has been included in the international antimicrobial resistance databases ResFinder and NCBIs AMRFinderPlus used for detecting resistance genes in bacterial genome sequences.
See ResFinder oxazolidinone.fsa 2023-09-19 updated sequence on poxtA-Ef at: https://bitbucket.org/genomicepidemiology/resfinder_db/src/master/ and NCBIs reference gene catalogue search for poxtA-Ef: https://www.ncbi.nlm.nih.gov/pathogens/refgene/#poxtA-Ef

ii) Recommendations on how to report silent resistance by the American Clinical & Laboratory Standards Institute Subcommittee on Antimicrobial Susceptibility Testing see conclusion and acknowledgement in CLSI AST News Update 2016, volume 1, issue 2, page 10 - Resistance Hot Topic: https://clsi.org/media/1700/clsi-news-winter-2016.pdf
Our findings/publications on silent resistance in Scandinavia has led to new national and Scandinavian recommendations on how to detect vancomycin resistant enterococci to avoid therapy failure by performing genotypic testing on invasive enterococci in addition to standard phenotypical testing. See the Norwegian recommendations: https://www.unn.no/4a240e/siteassets/documents/kompetansetjenester--sentre-og-fagrad/afa---arbeidsgruppen-for-antibiotikasporsmal/metoder/20170427-afa-anbefalning-vre.pdf and methods section in the Nordic recommendations: https://www.nordicast.org/d/5448?store_referer=true

iii) The diagnostic method on ID of bacteria from prosthetic tissue on blood culture bottles for diagnosis of PJI, was implemented in the routine laboratory at Department for microbiology and infection control (AMS) at the University Hospital of North Norway (UNN) in 2018. The AMS internal method document number is PR21396 «Vevsprøver

med proteserelaterte infeksjoner» and it was published at AMS 27.08.18. Revision of method is named «Prøver homogeniseres på flasker». This is an internal method only available through the internal AMS/UNN system, but the method and recommendations are presented in the following publication: https://doi.org/10.1186/s12879-019-4206-x.

The study formed the basis for a PhD thesis called "A metagenomics approach for laboratory diagnostics in clinical microbiology" (2016-2020) (https://munin.uit.no/handle/10037/19740) and paved the way for a proof of principle publication called "Shotgun-metagenomcis on positive blood culture bottles inoculated with prosthetic joint tissue: A proof of concept study" /Frontiers Microbiol/2020/https://doi.org/10.3389/fmicb.2020.01687

UiT – FacHealthSci_DepMedBiol, IMB – Case_2

Institution: UiT The Arctic University of Norway
Administrative unit: Department of Medical Biology (IMB)
Title of case study: Development of an antibody-based prophylaxis to prevent FNAIT
Period when the underpinning research was undertaken: 2003 - 2023
Period when staff involved in the underpinning research were employed by the submitting institution: 2000 - 2023
Period when the impact occurred: 2025

1. Summary of the impact (indicative maximum 100 words)

Scientists at Immunology research group at IMB, UiT, have developed an antibody-based prophylaxis (vaccine) to prevent a seldom, but severe pregnancy complication; Fetal and Neonatal Alloimmune Thrombocytopenia (FNAIT). The prevalence of FNAIT in the white population is 1:1000 complicated with intracranial hemorrhage in 10% of the cases, which can result in fetal death or life-long disability. The commercial rights for the treatment, including a monoclonal antibody, was recently acquired by a US-based drug development company, and the treatment is now in phase 1 clinical trials. If the prophylaxis is successful, it will be the first effective prevention of FNAIT.

2. Underpinning research (indicative maximum 500 words)

Early after the formation of Immunology research group, Prof. Bjørn Skogen, Prof Anne Husebekk, and PhD student Mette Kjær Killie, in collaboration with researchers at Oslo University Hospital Ullevål, Prof. Jens Kjeldsen-Kragh, acquired a governmental grant to conduct a national screening of FNAIT incidence in all pregnancies in Norway for 2 consecutive years, involving more than 100 000 pregnancies. The study took place in the period 2000 - 2004 and was led from UiT by Husebekk and Skogen. A conclusion from the data from this trial (Kjeldsen-Kragh et al., Blood 2007) was that it may be possible to prevent the maternal alloimmune response that results in FNAIT in the fetus and newborn by an antibody prophylaxis targeting human platelet antigen (HPA)-1a. Therefore, a process was initiated by Skogen, Husebekk, Kjeldsen-Kragh and Kjær in 2005 to investigate the feasibility of such a treatment. A new MD/PhD student at Immunology research group, Heidi Tiller, performed a proof-of-concept study in a murine model of FNAIT, demonstrating that an anti-HPA-1a antibody prophylaxis could indeed block alloimmunization in mice (Tiller et al., Transfusion 2012). This was performed in collaboration with Dr. Heyu Ni in his lab in Toronto, Canada, where Tiller worked as a visiting scientist in 2010/2011. In the same period, a human monoclonal antibody against HPA-1a (mab 26.4) was developed by Prof. Tor Stuge, PhD student Mariana Eksteen, Heidi Tiller and Bjørn Skogen in Immunology research group as the main protagonists (Eksteen et al., Journal of Immunology 2009). It was reasoned that anti-HPA-1a antibodies could be isolated from immune plasma from HPA-1a-negative alloimmunized women, or that human monoclonal antibody could substitute the plasma-derived antibodies. The polyclonal plasma-derived antibodies were tested in proof-of-principle studies in human subjects to determine the potential of the drug to eliminate transfused HPA-1a+ platelets to prevent alloimmunization (Geisen et al., Journal of Thrombosis and Haemostasis 2023). This study was performed in Frankfurt am Main, Germany, in the period 2020 – 2022. Mette Kjær and Bjørn Skogen in Immunology research group collected the plasma and produced the drug for the study, in addition to reviewing the study protocol. The conclusion was that the anti-HPA-1a antibody preparation was indeed efficient in clearing platelets from circulation, and therefore suitable for FNAIT prophylaxis. Simultaneously, a recent study led by Dr. Maria Therese Ahlen at Immunology research group with PhD student Trude Victoria Mørtberg as the main protagonist demonstrated that anti-HPA-1a monoclonal antibody 26.4 as was efficient as a prophylactic drug to prevent alloimmunization and FNAIT in a preclinical murine model (Mortberg et al., Immunohorizons 2022). Furthermore, a separate study comparing polyclonal and monoclonal anti-HPA-1a antibodies for FNAIT prophylaxis in mice (Zhi et al., Blood 2022) was performed by our

collaborators in Wisconsin together with the drug development company Rallybio; in 2019 Rallybio acquired the commercial rights to the development of the vaccine as well as the use of mab 26.4. The study demonstrated that both the polyclonal and monoclonal anti-HPA-1a antibody preparations performed equally well as prophylactic drugs to prevent FNAIT.

3. References to the research (indicative maximum of six references)

1.
Kjeldsen-Kragh J, **Killie MK**, Tomter G, Golebiowska E, Randen I, Hauge R, Aune B, Oian P, Dahl LB,Pirhonen J, Lindeman R, Husby H, Haugen G, Gronn M, **Skogen B**, **Husebekk A**. 2007. A screening and intervention program aimed to reduce mortality and serious morbidity associated with severe neonatal alloimmune thrombocytopenia. *Blood* 110: 833-9
https://doi.org/10.1182/blood-2006-08-040121

2.
Tiller H, **Killie MK**, Chen P, Eksteen M, **Husebekk A**, **Skogen B**, Kjeldsen-Kragh J, Ni H. 2012. Toward a prophylaxis against fetal and neonatal alloimmune thrombocytopenia: induction of antibody-mediated immune suppression and prevention of severe clinical complications in a murine model. *Transfusion* 52: 1446-57
https://doi.org/10.1111/j.1537-2995.2011.03480.x

3.
Eksteen M, **Tiller H**, Averina M, **Heide G**, **Kjaer M**, Ghevaert C, Michaelsen TE, Ihle O, **Husebekk A**, **Skogen B**, **Stuge TB**. 2015. Characterization of a Human Platelet Antigen-1a-Specific Monoclonal Antibody Derived from a B Cell from a Woman Alloimmunized in Pregnancy. *J Immunol* 194: 5751-60
https://doi.org/10.4049/jimmunol.1401599

4.
Geisen C, **Kjaer M**, Fleck E, **Skogen B**, Armstrong R, Behrens F, Bhagwagar Z, Braeuninger S, Mortberg A, Olsen KJ, Gaston Schafer SM, Walter C, Seifried E, Wikman A, Kjeldsen-Kragh J, Koehm M. 2023. An HPA-1a-positive platelet-depleting agent for prevention of fetal and neonatal alloimmune thrombocytopenia: a randomized, single-blind, placebo-controlled, single-center, phase 1/2 proof-of-concept study. *J Thromb Haemost* 21: 838-49
https://doi.org/10.1016/j.jtha.2022.11.041

5.
Mortberg TV, Zhi H, Vidarsson G, Foss S, Lissenberg-Thunnissen S, Wuhrer M, Michaelsen TE, **Skogen B**, **Stuge TB**, Andersen JT, Newman PJ, **Ahlen MT**. 2022. Prevention of Fetal/Neonatal Alloimmune Thrombocytopenia in Mice: Biochemical and Cell Biological Characterization of Isoforms of a Human Monoclonal Antibody. *Immunohorizons* 6: 90-103
https://doi.org/10.4049/immunohorizons.2100097

6.
Zhi H, Sheridan D, Newman DK, Newman PJ. 2022. Prophylactic administration of HPA-1a-specific antibodies prevents fetal/neonatal alloimmune thrombocytopenia in mice. *Blood* 140: 2146-53
https://doi.org/10.1182/blood.2022015666

4. Details of the impact (indicative maximum 750 words)

FNAIT (fetal and neonatal alloimmune thrombocytopenia) is a condition that can affect both the fetus and the newborn. It is caused by a maternal immune response to an alloantigen present on the fetal platelets. The most common alloantigen involved is determined by a single amino acid difference at position 33 of the integrin β3 protein, known as human platelet antigen (HPA)-1. Integrin β3 is found in high density on the surface of platelets as part of the αIIbβ3 heterodimer complex. A fetus is at risk for FNAIT if it inherits the HPA-1 allotype with a leucine in position 33 (HPA-1a) from the father, while the mother is homozygous for proline at the same position (HPA-1b). In such cases, the mother may develop an immune response against the HPA-1a allotype. The allele frequencies for HPA-1a and HPA-1b are approximately 0.85 and 0.15, respectively, in White individuals, with about 2% being homozygous for HPA-1b.

Pregnant women who develop an immune response against HPA-1a may produce antibodies that react with the fetal platelets. These anti-HPA-1a antibodies can cause a significant reduction in the fetus's platelet count, leading to a risk of bleeding. FNAIT is detected in about 1 in 1,200 births, with severe cases occurring in 1 in 1,500 births. The most serious complications include intracranial hemorrhage, neurological damage, and death. In Norway, FNAIT is responsible for an average of 3 to 5 deaths annually. Approximately twice that number survive with lifelong disabilities. Currently, there are no methods to prevent immunization against HPA-1a, nor are there any safe and effective treatments for FNAIT before delivery.

A national screening of FNAIT incidence and HPA-1a alloimmunization in Norway was conducted by our research group in collaboration with researchers at Oslo University Hospital Ullevål in the period of 2000 – 2004. A conclusion from analysis of the data from this study was that it may be possible to prevent the maternal anti-HPA-1a alloimmunization that causes FNAIT by an antibody prophylaxis. In 2005, the company Prophylix Pharma AS was established to handle the logistics for commercial development of the treatment, with Prof. Bjørn Skogen as the first CEO (and later CMO) with UiT and its TTO, Norinnova AS, as owners. To produce the prophylactic drug, anti-HPA-1a antibodies were isolated from plasma from HPA-1a-negative women who had become alloimmunized against HPA-1a in connection with HPA-1 incompatible pregnancies. Clinical grade polyclonal anti-HPA-1a antibody preparation was named “NAITgam” and received so-called orphan drug designation from the US Federal Drug Administration and the Medicines Agency in EU, providing market exclusivity for a designated period of time and other incentives to support the development of new treatments. In 2012, Prophylix Pharma was awarded an € 5 986 000 EU grant to form a consortium to develop the NAITgam drug and perform a multicenter clinical trial for FNAIT prophylaxis. By then, Immunology research group and collaborating researchers had performed proof-of-principle studies demonstrating that anti-HPA-1a antibodies prevented alloimmunization and FNAIT in preclinical murine models. Also at that period, the anti-HPA-1a human monoclonal antibody (mab) 26.4 was developed by Immunology research group. While a process had been initiated to patent it, the commercial rights for mab 26.4 was acquired by Prophylix, who eventually secured a European patent. Both NAITgam and mab 26.4 were demonstrated to be efficient as prophylactic drugs to prevent FNAIT in murine models. Previously, the FNAIT prophylactic treatment itself had been patented by Prophylix. By the end of the EU project funding period, the consortium had still not been able to perform clinical trials for FNAIT prophylaxis. However, in 2019 the commercial rights to both the treatment and mab 26.4 were acquired by the US-based drug development company Rallybio, and the treatment with the mab as the lead drug is now in phase 1 clinical trials for FNAIT prophylaxis. Members of Immunology research group are working closely with Rallybio in development and testing of the prophylactic drugs.

If the clinical trials demonstrate that the prophylactic treatment works, FNAIT prophylaxis will predictably be introduced worldwide. It will be the first treatment to prevent FNAIT and will spare lives and prevent disability for thousands of newborns each year. If performed as expected, the prophylactic vaccine is ready for clinical use in 2025.

5. Sources to corroborate the impact (indicative maximum of ten references)

1. The Tromsø-based company Prophylix Pharma AS (www.prophylix.com)
2. The US-based drug development company Rallybio (www.rallybio.com)
3. The EU-funded ProfNAIT project managed by Prophylix. (https://cordis.europa.eu/project/id/305986)
4. The Norwegian National Unit for Platelet Immunology at the University Hospital North Norway (https://www.unn.no/nnupi)
5. Description of the ProfNAIT project at NAIT Babies (https://www.naitbabies.org/resources/profnait-project/)

UiT – FacHealthSci_DepMedBiol, IMB – Case_3

Institution: UiT – The Arctic University of Tromsø
Administrative unit: Department of Medical Biology (IMB)
Title of case study: Oncolytic molecules as novel immunotherapeutic agents
Period when the underpinning research was undertaken: 2012-2015
Period when staff involved in the underpinning research were employed by the submitting institution: 2012-2015
Period when the impact occurred: 2012-2015

1. Summary of the impact

Development of oncoloytic molecules for immunotherapy of cancer.

Synthesis and screening of oncolytic peptides by structure activity relationship (SAR) studies revealed drug candidates that were further tested in preclinical models. Research on mechanism of action revealed a unique immunogenic cell death mechanism that induces both local and systemic immune response after local treatment of solid tumors. The lead candidate LTX-315, a 9-mer peptide, has entered clinical trials for skin cancer.

2. Underpinning research

Host defense peptides, also called cationic antimicrobial peptides (CAPs) are a part of the innate immune system and are present in virtually all species of life, from fungi, plants to ammals. Their most studied function is the defense against bacteria, but they also have shown to exert activities against cancer cells. Bovine lactoferricin (LfcinB) is a well studied 25 amino acid CAP with selective antimicrobial and anticancer proterties. Through extensive SAR-studies of LfcinB, shorter chemically modified peptides were genrated, and a lead series of nine amino acid peptides was developed. One of the candidate developed, named “LTX-315” has the ability to kill human cancer cells of diverse origin and is equally effective against both drug-resistant and drug-sensitive cancer cells. Selectivity for cancer cells results from the cationic amino acid side chains of LTX-315 that interacts with negatively charged membrane components present at higher level on cancer cells than normal cells. The oncolytic effect of LTX-315 involves perturbation of both the cancer cell membrane and intracellular organelles with subsequent release of danger-associated molecular pattern molecules (DAMPs) and tumor antigens. Intra tumoral treatment with LTX-315 results in growth inhibition, complete regression and a long-lasting immune specific immune response in a wide variety of experimental models. An abscopal effects in non-treated lesions has been observed in both experimental metastasis model and in clinical trials. The treatment efficacy is associated with increased infiltration of immune cells (T-cells) into the tumor post-treatement and reprogramming of the tumor microenvironment, including decreases in the local immunosuppressive T-cell and myeloid-derived suppressor cell populations. Based on the preclinical research, the oncolytic peptides stand out as a promising therapeutic tools based on their ability to drive immunogenic cell death associated with a strong anticancer immune responses.

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- Baldur Sveinbjørnsson (Professor at Dept. of Immunology/Dept of Molecular Inflammation Research Group MIRG, IMB, Full-time position).
- Øystein Rekdal Professor 2012, Prof. II 2013-2015 MIRG
- Ketil Camilio (PhD candidate and Post Doc, MIRG, 2010-2015).
- Liv-Marie Eike (PhD candidate MIRG 2012-2015).
- Gerd Berge Post doc (Dept of Immunology 2012-2013)

3. References to the research

Reference list for the research in the period 2012-2015; Open Access via Pubmed.gov

1. Rekdal Ø, Haug BE, Kalaaji M, Hunter HN, Lindin I, Israelsson I, Solstad T, Yang N, Brandl M, Mantzilas D, Vogel HJ. Relative spatial positions of tryptophan and cationic residues in helical membrane-active peptides determine their cytotoxicity. J Biol Chem. 2012 Jan 2;287(1):233-244, DOI: 10.1074/jbc.M111.279281
2. Camilio KA, Berge G, Ravuri CS, Rekdal O, Sveinbjørnsson B.(2014) Complete regression and systemic protective immune responses obtained in B16 melanomas after treatment with LTX-315. Cancer Immunol Immunother. Jun;63(6):601-13: DOI: 10.1007/s00262-014-1540-0
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6. Forveille S, Zhou H, Sauvat A, Bezu L, Müller K, Liu P, Zitvogel L, Pierron G, Rekdal Ø, Kepp O, Kroemer G.(2015) The oncolytic peptide LTX-315 triggers necrotic cell death. Cell Cycle. Nov 2;14(21):3506-12; https://doi.org/10.1080/15384101.2015.1093710
7. Heng Zhou, Sabrina Forveille, Allan Sauvat, Takahiro Yamazaki, Laura Senovilla, Yuting Ma, Peng Liu, Heng Yang, Lucillia Bezu, Kevin Müller, Laurence Zitvogel, Øystein Rekdal, Oliver Kepp and Guido Kroemer (2016). The oncolytic peptide LTX-315 triggers immunogenic cell death. Cell Death & Disease ; Mar 10;7:e2134. https://doi.org/10.1038/cddis.2016.47
8. Bengt Erik Haug, Ketil André Camilio, Liv Tone Eliassen, Wenche Stensen, Johns-Sigurd Svendsen, Kristel Berg, Bjarte Mortensen, Guillaume Serin, Jean-Francois Mirjolet, Francis Bichat, Øystein Rekdal. (2016) Discovery of a 9-mer cationic peptide (LTX-315) as a potential first in class oncolytic peptide. J. Medicinal Chemistry, 2016, 59:2918-27 , https://doi.org/10.1021/acs.jmedchem.5b02025
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3. **Details of the impact**

Preclinical research assessing efficacy, safety and mode of action is a fundamental platform that needs to be established before moving forward to clinical trials. In that context, it was fundamental to learn that the oncolytic peptides, due to their membranolytic effect, were equally active towards drug-sensitive and drug-resistant cancer cells. Also, the peptides demonstrated efficacy towards basically all types of cancer cells (genotypic/phenotypic character). As drug-resistance and heterogeneity of tumor cells represent the major hurdle in cancer therapy in general, the oncolytic peptides address this problem quite well.

Another significant knowledge achieved by the preclinical research was the mechanism of action (MoA) which refers to the specific interaction between the peptides and the cancer cells, most importantly how they induce a strong immunogenic cell death (ICD). ICD involves the release of intracellular components of the cancer cells that provoke strong immune response and made the fundament for strong protective immune response in animal models. The studies were performed at IMB, UiT and in collaboration with Guido Kroemer´s Lab at Institut Gustavo Roussy in France and Mikael Pittet´s Lab at Harvard medical School U.S.A.

Cancer immunotherapies either stimulate specific components of the immune system or counteract signals produced by cancer cells that suppress immune responses. Antibodies targeting inhibitory receptors (checkpoints) have shown promising efficacy in several types of cancer. However, considerable number of patients does not experience a durable response after treatment, mostly because the effect is dependent on the presence of immune cells (T-cells) within the tumor since they are capable of recognizing and killing cancer cells. To enable and increase the effect of the antibodies (checkpoint inhibitors), patients with tumors that lack T-cells ("cold" tumors") may require therapeutic interventions that increases T-cell infiltration into the tumor.

The ability of LTX-315 to increase T cell infiltration makes LTX-315 an ideal as a combination partner for other immunotherapies, including immune checkpoint inhibitors. Indeed, both preclinical and clinical data have demonstrated evidence of synergy. The potential of LTX-315 to expand the number of patients responding to immunotherapy could extend the clinical and commercial potential of LTX-315 as a preferred combination partner for several types of immunotherapy – such as checkpoint inhibitor therapy, adoptive T cell transfer cell therapy and cancer vaccines.

As early as 2003, a spin-off company from UiT, Lytix Biopharma, was established with the aim to commercialize the technology platform. Today, Lytix Biopharma is a clinical-stage biotech , with a broadly patent protected oncolytic molecule platform. The lead candidate, LTX-315, is administered through intra-tumoral injection, and works through a unique mode of action. The research at UiT has been an important part of the development of LTX-315 that has already resulted in a commercial licensing deal for Lytix Biopharma.

During summer 2020, Lytix formed a strategic partnership with Verrica Pharmaceuticals Inc. Verrica is a dermatology therapeutics company developing medications for skin diseases requiring medical interventions. At present, LTX-315 is in a two clinical phase II trials, one led by Lytix Biopharma and one led by Verrica Pharmaceuticals (U.S).

5. Sources to corroborate the impact

News and publications;

https://www.lytixbiopharma.com

Clinical trials

https://pharma.dagensmedisin.no/industri-legemidler/lytix-studie-utvides-til-norge-far-med-ahus-og-radium/163210

https://medwatch.no/nyheter/legemidler_biotek/article16676345.ece

https://medwatch.no/nyheter/legemidler_biotek/article16386262.ece

https://www.highnorthnews.com/nb/norske-lytix-biopharma-inngar-milliardavtale-med-amerikansk-biotekgigant

https://www.clinicaltrials.gov/search?term=LTX-315

Preclinical collaboration

https://oslocancercluster.no/wp-content/uploads/2021/03/Lytix-Biopharma_UiT-Aurelius_March-2021.pdf

Spin-offs from Lytix Biopharma

https://www.pharmaholdings.no/about-us/

https://amicoat.com/

UiT – FacHealthSci_DepMedBiol, IMB – Case_4

Institution: UiT
Administrative unit: Department of Medical Biology (IMB)
Title of case study: Oral insulin
Period when the underpinning research was undertaken: 2016-present
Period when staff involved in the underpinning research were employed by the submitting institution: 1999-present
Period when the impact occurred: 2021 onwards

1. Summary of the impact

Development of an oral insulin formulation

2. Underpinning research

The research insights in this case study stem from work done at UiT from the 1990s to present on the scavenger function of various liver cells, and how to circumvent this to target other liver cells. Further research at the ANZAC Research Institute/University of Sydney (ANZAC) – in collaboration with UiT – found a clinical application for the above research from UiT. ANZAC researchers developed 5nm silver nanoparticle formulations (NPs) that target different liver cells after oral administration, and coupled various drugs to these, including insulin. All coupled drugs survived passage through the digestive systems of research animals. The insulin worked as expected in the experimental animals.

The development of the oral insulin formulation roughly followed this timeline:
2016 – discovery that silver nanoparticles (NPs) (5 nm) in blood are taken up by the liver, especially by liver sinusoidal endothelial cells (LSEC)
2018 – coupling of drugs to silver NPs targets oral drug delivery to liver cells, and different protein coats on the NPs can improve or inhibit uptake by LSEC – in the latter case, hepatocytes became the main target.
2019 – coupling of insulin to silver NPs and its encapsulation in a glucose/chitosan coat resulted in insulin survival in the digestive system and its effective delivery to hepatocytes in mice via the oral route. Demonstration of its efficacy in diabetic mice, rats and baboons.
January 2023 – preprint published in Research Square, accepted for publication in Nature Nanotechnology **November 2023** https://doi.org/10.1038/s41565-023-01565-2

Key researchers: ANZAC: Nicholas Hunt/Victoria Cogger/David le Couteur; UiT Peter McCourt

3. References to the research

Nicholas J. Hunt, Glen P. Lockwood, Scott J. Heffernan, Jarryd Daymond, Meng Ngu, Ramesh K. Narayanan, Lara J. Westwood, Biswaranjan Mohanty, Lars Esser, Charlotte C. Williams, Zdenka Kuncic, Peter A. G. McCourt, David G. Le Couteur, Victoria C. Cogger

"Oral nanotherapeutic formulation of insulin with reduced episodes of hypoglycaemia."

2023 Nature Nanotechnology https://doi.org/10.1038/s41565-023-01565-2

4. Details of the impact

The underpinning research from IMB/UiT for this impact is the demonstration that liver scavenger cells have a voracious appetite for nanoparticles and colloids, with LSEC removing those smaller than 200nm and Kupffer cells removing those that are larger (Sørensen et al. 2012 https://doi.org/10.1152/ajpregu.00686.2011). In addition, IMB/UiT research led to developing ways to avoid this unwanted uptake, for example to direct drugs to hepatocytes instead. ANZAC (in collaboration with UiT) used this knowledge to develop a clinically useful means to deliver insulin, via the oral route, directly to hepatocytes.

The insulin-conjugated silver NPs coated with a chitosan/glucose produce a responsive oral insulin nanoformulation. This formulation is pH responsive, is insoluble in acidic environments and shows increased absorption in human duodenum explants and *Caenorhabditis elegans* at neutral pH. The formulation is sensitive to glucosidase enzymes to trigger insulin release. The formulation distributes to the liver in mice and rats after oral administration and promotes a dose-dependent reduction in blood glucose without promoting hypoglycaemia or weight gain in diabetic rodents. Non-diabetic baboons also show a dose-dependent reduction in blood glucose. No biochemical or haematological toxicity or adverse events were observed in mice, rats and non-human primates. The formulation demonstrates the potential to orally control blood glucose without hypoglycaemic episodes.

The beneficiaries are all type I diabetes patients, if the formulation passes all clinical trials. Impacts for beneficiaries are therefore expected in 3-4 years' time.

5. Sources to corroborate the impact (indicative maximum of ten references)

- Professor Trond Jenssen, IKM/UiO trond.jenssen@medisin.uio.no

- New medicine can create a new life for diabetes patients – without needles! Newsletter UiT
- UiT-forskere utvikler ny medisin-pasienter kan slippe sprøyter, iTromsø
- Vil erstatte insulinsprøyter med sukkerfri sjokolade, Diabetes Wellness Norge
- Lovende diabetesforsøk: Insulin via sukkerfri sjokolade ga god effekt, NRK
- NRK radio

Impact case guidelines

Each case study should include sufficiently clear and detailed information to enable the evaluation committee to make judgements based on the information it contains, without making inferences, gathering additional material, following up references or relying on members' prior knowledge. References to other sources of information will be used for verification purposes only, not as a means for the evaluation committee to gather further information to inform judgements.

In this evaluation, impact is defined as an effect on, change or benefit to the economy, society, culture, public policy or services, health, the environment or quality of life, beyond academia.

Timeframes

- The impact must have occurred between 2012 and 2022
- Some of the underpinning research should have been published in 2012 or later
- The administrative units are encouraged to prioritise recent cases

Page limit

Each completed case study template will be limited to **five pages** in length. Within the annotated template below, indicative guidance is provided about the expected maximum length limit of each section, but institutions will have flexibility to exceed these so long as the case study as a whole remains no longer than **five pages** (font Calibri, font size 11). Please write the text into the framed template under the sections 1–5 below. The guiding text that stands there now, can be deleted.

Maximum number of cases permitted per administrative unit

For up to 10 researchers: one case; for 10 to 30 researchers: two cases; for 30-50 researchers: three cases; for 50-100 researchers: four cases, and up to five cases for units exceeding 100 researchers.

Naming and numbering of cases

Please use the standardised short name for the administrative unit, and the case number for the unit (1,2,3, etc) in the headline of the case. Each case should be stored as a separate PDF-document with the file name: [Name of the institution and name of the administrative unit] [case number]

Publication of cases

RCN plans to publish all impact cases in a separate evaluation report. By submitting the case the head of the administrative units consents to the publication of the case. Please indicate below if a case may not be made public for reasons of confidentiality.

If relevant, describe any reason to keep this case confidential:

Please write the text here

[Name of the institution and name of the administrative unit] [case number]

Institution: UiT The Arctic University of Norway
Administrative unit: Department of Psychology
Title of case study: Auto ATES – Automatic classification of avalanche terrain
Period when the underpinning research was undertaken: 2020-2023
Period when staff involved in the underpinning research were employed by the submitting institution: 2019
Period when the impact occurred: 2020 onwards

1. Summary of the impact (indicative maximum 100 words)

Snow avalanches lead to a yearly average of 140 fatal accidents in Europe and Northern America More than 80% of fatal avalanche accidents are related to recreational activity and triggered by the victim or someone in their party. This means that avalanche accidents are not random, but rather a result of less-than-optimal decisions. Strengthening people's ability to make better decisions by raising awareness, providing information and education is important and may ultimately save lives. The most important decision is choice of terrain. The Norwegian Avalanche Warning Service and CARE has been developed an automatic avalanche terrain classification to guide people's terrain choices. This model is implemented in avalanche maps and used by most avalanche warning services across the world.

2. Underpinning research (indicative maximum 500 words)

Background

Parks Canada developed the avalanche terrain exposure scale (ATES v1.0). The terrain was initially clustered in three classes and graded from: Simple (1), Challenging (2), and Complex (3). The system was recently updated to include two additional terrain classes: Non-avalanche terrain (0), and Extreme (4). The updated system is referred to as ATES v2.0. This initial ATES mapping was done using a combination of manual mapping and Geographic Information System (GIS)-assisted mapping workflows. This work was labor intensive, relied heavily on expert judgement and as a result ATES maps were typically only available in high-use areas. Campbell and Gould (2013) called for a more quantifiable model and suggested a new spatial ATES model for GIS-assisted classification.

Developed by CARE and collaborators

The first attempt at a fully automated ATES classification was made by Larsen et al. (2020) using a combination of the zonal and technical model of ATES (AutoATES v1.0). This algorithm produced spatial ATES maps for all of Norway, using only a digital elevation model (DEM) as input. The main limitations of this work were that the algorithm did not account for forest data or overhead exposure, and the performance of the simple avalanche runout simulation was insufficient in flatter terrain. The algorithm was also heavily dependent on proprietary software, thereby increasing the monetary and computing costs to operate the model and limiting open-source access.

In 2022, the model was revised by Larsen and his international collaborators Sykes, Schauer and colleagues at CARE Hendrikx, and Hetland**.** Several significant improvements were included. Forest density is important for improving avalanche runout estimations in low-angle runout zones. To improve this section of the model, new forest density data for all of Norway was acquired using Lidar radar to measure stem density and canopy cover in %. In

addition, the model was improved to account for overhead exposure and finally, according to the open-access principles, the algorithm was recoded and made available as open-source software. The new algorithm also supports the new ATES v2.0 standard with the exception of class 0 – non avalanche terrain.

Håvard Toft, né Larsen – is a PhD student at UiT The Arctic University of Norway and CARE since 01.07.2021. He has been working for the Norwegian Avalanche Warning (NAWS) since 2019. NAWS is a partner in CARE.

Audun Hetland is head of CARE and works at Department for Psychology at UiT The Arctic University of Norway.

Rune Engeset is head of the NAWS and professor II (adjunct professor) at UiT The Arctic University of Norway from January 2017- December 2021.

Jordy Hendrikx was head of Snow and Avalanche Lab at Montana State University until July 2022. He is a professor II (adjunct professor) at CARE since 2020.

3. References to the research (indicative maximum of six references)

Toft, H. B., Sykes, J., Schauer, A., **Hendrikx, J.,** & **Hetland, A.** (2023). AutoATES v2. 0: Automated avalanche terrain exposure scale mapping. *Natural Hazards and Earth System Sciences Discussions*, *2023*, 1-19.
(CARE personel in bold)

The AutoATES model is implemented in Norwegian avalanche warning service maps and toolbox
https://temakart.nve.no/link/?link=kast

For more information on map and related tools see: https://www.varsom.no/om-varsom/varsom-app-regobs/kart/
https://www.varsom.no/nyheter/nyheter-snoskred/nytt-kart-med-skredterreng-pa-varsom-appen/

4. Details of the impact (indicative maximum 750 words)

A changing climate will lead to 40% more precipitation combined with more wind and varying temperatures. For Arctic countries, this means that the avalanche hazard will increase substantially in the coming years. A changing climate will also lead to a shorter ski season in the European Alps and a further increase in backcountry tourism in the Arctic. The ability to recognize avalanche terrain is fundamental in avalanche mitigation and a presentation of the challenges for different types of terrain enables people to take the necessary precautions or choose different terrain if the avalanche danger is high. ATES classification is fundamental in hazard ratings or descriptions to inform the users of the challenges they will encounter while navigating different types of terrain. ATES classification is also a fundamental base layer in safety management for workers that need to navigate avalanche terrain – like powerline workers, armed forces, reindeer herders, tourists or local skiers. ATES has been implemented in of different products, maps or safety systems. An example is the backcountry app CARE which is currently being developed. In this app several thousand trips will be presented and each of them will be given an ATES rating to enable participants to choose the correct trip for the current avalanche conditions.
See www.topptur.guide for an example of how ATES ratings Is implemented in safety features for end users. A full version will be launched spring 2024.

5. Sources to corroborate the impact (indicative maximum of ten references)

Sykes, J., **Toft, H**., Haegeli, P., & Statham, G. (2023). Automated Avalanche Terrain Exposure Scale (ATES) mapping–Local validation and optimization in Western Canada. *Natural Hazards and Earth System Sciences Discussions*, *2023*, 1-37.

Toft, H. B., Sykes, J., Schauer, A**., Hendrikx, J., & Hetland, A**. (2023). AutoATES v2. 0: Automated avalanche terrain exposure scale mapping. *Natural Hazards and Earth System Sciences Discussions*, *2023*, 1-19.

Sykes, J., **Larsen, H. T**., & Haegeli, P. (2022, December). Validation and Localization of an Automated Method for Large Scale Avalanche Terrain Exposure Scale (ATES) Mapping. In *AGU Fall Meeting Abstracts* (Vol. 2022, pp. C33B-07).

Toft, H. B., Müller, K., **Hendrikx, J.,** Jaedicke, C., & Bühler, Y. (2023). Can big data and random forests improve avalanche runout estimation compared to simple linear regression?. *Cold Regions Science and Technology*, *211*, 103844.

Larsen, H. T., Hendrikx, J., Slåtten, M. S., & **Engeset, R. V**. (2020). Developing nationwide avalanche terrain maps for Norway. *Natural Hazards*, *103*(3), 2829-2847.

Schumacher, J., **Toft, H.,** McLean, J. P., Hauglin, M., Astrup, R., & Breidenbach, J. (2022). The utility of forest attribute maps for automated Avalanche Terrain Exposure Scale (ATES) modelling. *Scandinavian Journal of Forest Research*, *37*(4), 264-275.

N.B. Members of the CARE research group in bold.

UiT The Arctic University of Norway and Regional Centre for Child and Youth Mental Health and Child Welfare [case number 1]

Institution: UiT The Arctic University of Norway (UiT)
Administrative unit: Regional Centre for Child and Youth Mental Health and Child Welfare (RKBU North)
Title of case study: Ungsinn [Youngmind]
Period when the underpinning research was undertaken: 2016 -
Period when staff involved in the underpinning research were employed by the submitting institution: 2016 -
Period when the impact occurred: 2016 -

1. Summary of the impact (indicative maximum 100 words)

Ungsinn is a digital scientific journal that publishes systematic reviews assessing the effectiveness of psychosocial interventions aimed at children and young people's mental health. It aims to advance evidence-based practices and quality in services by 1. making information about the evidence of interventions available, 2. uncovering knowledge gaps, and 3. stimulating to more research. Ungsinn has been used by an increasing number of people over the years, and the journal is used by practitioners in the field. Ungsinn has been an inspiration for the development of a similar journal in Finland and is referred to in governmental reports, research reports, online resources, and student papers.

2. Underpinning research (indicative maximum 500 words)

Ungsinn was established in 2009 as a database that presented information of interventions for children and young people including assessments of their evidence. In 2016, Ungsinn was approved as a scientific journal by The National Board of Scholarly Publishing. At this time the criteria for classification of interventions were revised. Since the second issue of 2015, all published articles are scientific in the form of systematic reviews and developed in accordance with the new criteria. All articles have the same research question: "Is the intervention effective when used in ordinary practice in Norway?" To make it easy for the target group to use the articles, each article results in a summary conclusion in the form of a classification of the intervention's evidence (https://ungsinn.no/post_artikkel/new-criteria-for-classification).

As of December 2023, a total of 82 reviews have been conducted on 55 interventions (https://ungsinn.no/arkiv/). Summaries within Ungsinn can be revised in classification if new evidence emerges, indicated in the article's edition ('utg' in Norwegian). A total of 30 interventions have undergone a single assessment, 22 of the interventions have been evaluated twice, and 3 have been assessed three times.

Based on the latest classification of interventions assessed from the second issue of 2015, the distribution of classifications are: one of the interventions has evidence *level 0: No effect*; one intervention has evidence *level 1: Well described*; nine interventions have evidence *level 2: Theoretically based;* nine interventions have evidence *level 3: Some documentation*; eleven interventions have evidence *level 4: satisfactory documentation;* and 6 interventions have evidence *level 5: strong documentation* of effect. Overview of all interventions assessed in Ungsinn: https://ungsinn.no/tiltak-liste.

The number of visits to Ungsinn was tracked with Google Analytics from 2009 to 2022. It was then discontinued by UiT due to GDBR regulations. The number of page views per year increased from 15,855 in 2009 to 110,000 in 2022. While these statistics have primarily served internal analysis,

they have also been referenced in various news articles, including the one available at https://ungsinn.no/post_aktuelt/fikk-du-med-deg-dette-i-2022/

In 2017, Helse-Nord (the Northern Norway Regional Health Authority which is responsible for the public hospitals in Northern Norway) commissioned the editorial team of Ungsinn to conduct a specialized review. The objective was to compile a comprehensive overview of interventions available for infants and toddlers in Norway, along with their corresponding evidence. The Ungsinn editorial members developed a specific methodology for this assignment and published the results in a report. A total of 31 interventions were located and assessed.

In 2019, Ungsinn was contacted by a project initiated by the Nordic Council of Ministers. The topic for the project was the first 1000 days of infants and toddlers in the Nordic countries. The project consisted of three sub-projects, one of which was to assess the evidence of interventions and tests used in the Nordic countries. A total of 14 authors from Ungsinn and Kasvuntuki (described below) developed the report in which a total of 66 interventions and 33 tests were reviewed.

The editorial board consists of the chief editor, two assistant editors, editorial member, managing editor and editorial staff member. As of December 2023, there are 51 active authors https://ungsinn.no/organisasjonen-2/ and 8 colleagues from the field of practice associated with Ungsinn. https://ungsinn.no/post_artikkel/the-publisher-and-organization.

The role of chief editor at Ungsinn was held by researchers from the RKBU North, with Professor Monica Martinussen serving from 2016 to 2021 followed by Professor Charlotte Reedtz from 2021 to 2023. In autumn 2023, the leadership role is held by an external researcher outside the RKBU North. Other editorial roles have been held by people at the RKBU North, except from one of the assistant editors from 2018-2023.

3. References to the research (indicative maximum of six references)
Ungsinn articles are published in Norwegian, but they include a summary in English.

Example of an Ungsinn-article where the intervention is assessed on evidence level 0:

Bjørknes, R., Koposov, R. & Eng, H. (2021). Kunnskapsoppsummering og klassifisering av tiltaket Kjærlighet og Grenser [Systematic review and classification of the intervention Kjærlighet og Grenser] (3.utg.). Ungsinn 2:3. https://ungsinn.no/post_tiltak_arkiv/kjaerlighet-og-grenser-3-utg/

Example of an Ungsinn-article where the intervention is assessed on evidence level 5:

Kaasbøll, J., & Brøndbo, P. H. (2023). Kunnskapsoppsummering og klassifisering av tiltaket: Cool Kids [Systematic review and classification of the intervention Cool Kids] (1. utg.). Ungsinn. Tidsskrift for virksomme tiltak for barn og unge. 2:3 https://doi.org/10.7557/25.7289

Example of an Ungsinn-article where the intervention has increased evidence level in an updated edition:

Haugland, B. S. & Bjåstad, J. F. (2022). Kunnskapsoppsummering og klassifisering av tiltaket Mestingskatten [Systematic review and classification of the intervention Coping Cat] (3.utg) Ungsinn 1:1. https://ungsinn.no/post_tiltak_arkiv/mestringskatten-3-utg/

Report to Helse Nord:

Eng, H., Reedtz, C. & Martinussen, M. (2018). Effekter av psykososiale intervensjoner for sped- og småbarn [Effects of psychosocial interventions for infants and toddlers] (ISBN 978-82-93031-

57-4). UiT The Arctic University of Norway. https://ungsinn.no/post_aktuelt/rapport-om-effekter-av-tiltak-for-sped-og-smabarn/

Report from the 1000 first year project by the Nordic Council of Ministers:
Martinussen, M., Kurki M. (Ed.). (2021). *The first 1000 days in the Nordic Countries. Psychosocial interventions and psychological tests: A review of the evidence*. Nordic Counsil of ministers. https://norden.diva-portal.org/smash/get/diva2:1571297/FULLTEXT01.pdf

4. Details of the impact (indicative maximum 750 words)

Ungsinn is a scientific journal with target groups and main objectives beyond the academic field, primarily targeting decision-makers in the field of practice. The main goal is to ensure that more children and young people benefit from effective prevention and treatment interventions. To achieve the aim, two critically conditions must be met: firstly, the articles must present correct and reliable conclusions; secondly, the target groups must not only be aware of Ungsinn`s existence, but also fully comprehend the articles applying the insights gleaned, to inform their selection of which interventions should be implemented.

To ensure accurate conclusions and consistent assessment and classification across interventions and authors, we have developed an explicit method for how the reviews should be conducted (https://ungsinn.no/wp-content/uploads/2013/02/Ungsinn_kriterier_engelsk_2020_oppslag.pdf). We recruit authors with relevant research competence. All authors are required to undergo specialized training in these criteria to ensure consistency in their evaluations. The quality assurance of articles is rigorously upheld through a comprehensive editorial process, involving critical appraisal by an editor, two reviewers, a practitioner peer, and the owner of the intervention under review. This multi-layered review system ensures that each article meets Ungsinn`s high standards for accuracy and reliability.

To promote the visibility and awareness of Ungsinn among the target groups and to encourage the use of the knowledge, we actively promote the journal through various channels. These include distributing newsletters, engaging our audience on social media platforms, and write op-eds. We also provide educational opportunities to further disseminate findings. Ungsinn`s commitment to accessibility, ensure that the language used in summaries is clear and straightforward. Additionally, we create short summaries in plain language that highlight the key findings of our reviews.

The editorial team participates in a Nordic network called Nordic DataPrev, a collaborative assembly of organizations from Denmark, Sweden, Finland, and Norway, each operating website akin to Ungsinn. The goal is to learn from each other and exchange ideas and knowledge. Through this collaboration, the Finnish organization Itla (https://itla.fi/in-english) has been inspired by Ungsinn in the development of their website; Kasvuntuki. They have adapted Ungsinn's criteria and procedures into Finnish twice, formulating their bespoke versions (https://kasvuntuki.fi/en/about-kasvun-tuki). On Kasvuntuki's website, one can find their assessment of programs made after the first criteria they developed inspired by Ungsinn's old criteria (https://kasvuntuki.fi/en). From 2023, Kasvuntuki began publishing a scientific journal that includes knowledge summaries on individual interventions, employing methodologies that closely mirror the current criterias used by Ungsinn.

In collaboration with other similar websites in Norway, the Ungsinn editorial team has conducted two surveys. The first was a user survey (https://ungsinn.no/post_aktuelt/gode-nettressurser-om-barn-og-unge). The results from this survey showed that Ungsinn was the best-known website among those surveyed (*N* = 407). A total of 56% of those who responded to the survey had visited Ungsinn. Of those who had visited the site, 88% found the site useful, and 70% had used information from Ungsinn in their work. As part of an ongoing survey on the use of interventions and tests in the field of practice (results have not been published yet), we also asked about Ungsinn. In this survey, 62% said they were familiar with Ungsinn. Of those who knew the site, 61% had used the website to learn about interventions. Some had used information from Ungsinn as part of the decision-making basis in choosing interventions, and most of those found the information in Ungsinn to be of great help in the decision.

The company HealthLine has developed the system La Linea (https://tcmn.no/lalinea). This is a strategic decision-support system designed to assist municipalities in selecting interventions to implement. It also helps to keep an overview of what interventions they have and communicate to the public what interventions are available within the municipality. La Linea incorporates Ungsinn as a source in its overviews, and thus Ungsinn articles are also part of the municipalities' presentation to the public, such as in Kristiansand municipality (https://lalinea.healthline.no/kristiansand).

Ungsinn's contributions are recognized and cited across a spectrum of influential documents, including policy documents, master's theses, and research reports. The Norwegian Official Reports (NOU), which are studies on various social issues commissioned by the government, frequently reference to Ungsinn. For example, in NOU 2012:5, titled "Bedre beskyttelse av barns utvikling — Ekspertutvalgets utredning om det biologiske prinsipp i barnevernet" (Better protection of children's development — The expert committee's study on the biological principle in child welfare, https://www.regjeringen.no/no/dokumenter/nou-2012-5/id671400), which advocates for the description of all child welfare interventions aimed at enhancing parental care abilities within Ungsinn. It further suggests that information from Ungsinn should underpin decision-making regarding the implementation of child welfare interventions. This recommendation was influential in shaping the proposal for a new child welfare law in 2013 (Prop. 106 L (2012–2013)). Ungsinn is also mentioned in several other NOUs and reports from central authorities and subordinate organizations, it is linked to from services and other organizations' websites, and the articles are used as sources in bachelor's and master's theses.

5. Sources to corroborate the impact (indicative maximum of ten references)

Example of a popular science presentations of an Ungsinn article:

Eng, H. (2023). *Behandlingsmodell for ungdommer med alvorlige atferdsvansker.* [Treatment Model for Adolescents with Severe Behavioral Difficulties]. Ungsinn. https://ungsinn.no/post_aktuelt/behandlingsmodell-for-ungdommer-med-alvorlige-atferdsvansker/

Example of a systematic review of an intervention in the Kasvuntuki scientific journal (in Finnish):

Karjalainen, P., Backman, H., & Heikkilä, L. (2023) ProKoulu-toimintamalli (Schoolwide Positive Behavioral Interventions and Supports). Kasvuntuki aikakauslehti, 1. p. 47. https://journal.fi/kasvuntuki/article/view/130617/79077

Example of Ungsinn referred to in policy documents:
Ministry of Children and Families. (2013). *Prop. 106 L (2012–2013). Endringer i barnevernloven* [Changes in the Child Welfare Act], section 11.6, https://www.regjeringen.no/no/dokumenter/prop-106-l-20122013/id720934/

Ministry of Children and Families (2023). *NOU 2023:7 Trygg barndom, sikker fremtid— Gjennomgang av rettssikkerheten for barn og foreldre i barnevernet.* [Safe Childhood, Secure Future— Review of the Legal Protections for Children and Parents in Child Welfare Services], section 29.2.3. https://www.regjeringen.no/no/dokumenter/nou-2023-7/id2966836/?q=ungsinn&ch=1

Ministry of Children and Families (2023). *En barndom for livet. Økt tilhørighet, mestring og læring for barn i fattige familier.* [A Childhood for Life. Increased Belonging, Mastery, and Learning for Children in Poor Families.], section 6.2.1. https://www.regjeringen.no/no/dokumenter/en-ny-barndom-for-livet/id3000835/

Examples of municipalities presenting their services with reference to Ungsinn:
Moss Municipality (2023). TIBIR foreldreveiledning 3 - 12 år (PMTO) [TIBIR Parental Guidance 3 - 12 years (PMTO)] https://www.moss.kommune.no/alle-tjenester/barne-og-familietjenester/foreldrekurs-og-foreldreveiledning/tibir-foreldreveiledning-3-12-ar-pmto/

Kinn Municipality. (2023). Foreldrerettleing [Parent guidance].https://kinn.kommune.no/vare-tenester/oppvekst-og-utdanning/familiehjelpa/foreldrerettleiing/

Example of an Op-ed about interventions in school:
Reedtz, C., Eng, H., Rye, M., Breivik, K. & Martinussen, M. (2023). Mål: Mobbekutt innen 2025 Vi har fire anbefalinger. [Goal: Reduction of Bullying by 2025. We have four recommendations]. *Dagbladet*. https://www.dagbladet.no/nyheter/vi-har-fire-anbefalinger/80158629

Examble of Educational Offerings based on Ungsinn:
RKBU North (n.d.). Hvordan ta gode beslutninger for å skape de beste tjenestene? [How to Make Good Decisions to Create the Best Services?] https://uit.no/enhet/rkbu-nord/kurs?p_document_id=791157

Example of a master's degree thesis referring to Ungsinn:
Andreassen, B. (2017). *Hva er Collaborative and Proactive Solutions, og hvor effektiv er modellen i behandling av atferdsvansker hos barn og unge?* [What are Collaborative and Proactive Solutions, and how effective is the model in treating behavioral problems in children and adolescents?] [Master's degree thesis]. University of Oslo. Hva er Collaborative and Proactive Solutions, og hvor effektiv er modellen i behandling av atferdsvansker hos barn og unge? (uio.no)

UiT The Arctic University of Norway and Regional Centre for Child and Youth Mental Health and Child Welfare [case number 2]

Institution: UiT The Arctic University of Norway (UiT)
Administrative unit: Regional Centre for Child and Youth Mental Health and Child Welfare (RKBU North)
Title of case study: De Utrolige Årene (DUÅ) [The Incredible Years (IY) Norway]
Period when the underpinning research was undertaken: 2012 – **[Some background research from earlier]**
Period when staff involved in the underpinning research were employed by the submitting institution: 2012 -
Period when the impact occurred: 2012 -

Summary of the impact (indicative maximum 100 words)

The Incredible Years (IY) have been in use in Norway since 1999. RKBU North has a coordinating function for the implementation of IY in Norway. IY along with other evidence-based interventions has improved practices in Norway to assist children and youth with behavior-related difficulties and to prevent the onset or development of such difficulties. IY in Norway has spurred innovation by participating in the development of service offerings not directly tied to IY by contribution to the implementation of other types of interventions in Norway and across Europe (e.g., Triple P in the Czech Republic and Invest in Play).

2. Underpinning research (indicative maximum 500 words)

The first trial and evaluation of IY in Norway began in 1999. This involved the IY BASIC Parenting Program for 3-8-year-olds, which was part of a research project associated with a 12-week treatment program in groups. The target group were parents of children referred to Child and Adolescent Psychiatric Outpatient Clinics (BUP) in Tromsø and Trondheim for the treatment of behavioural problems. This was a research project with an RCT design, including an intervention group and a waiting-list control group. The project was conducted RKBU North and RKBU Central Norway. The research results showed significant positive changes in favour of the IY program. Key findings after the intervention included improved relationships between parents and children and a significant reduction in children's behavioural problems.

Example of an article from research on a Norwegian clinical IY study: Larsson, B., Fossum, S., Clifford, G., Drugli, M. B., Handegård, B. H., & Mørch, W. T. (2009). Treatment of oppositional defiant and conduct problems in young Norwegian children: Results of a randomized controlled trial. Eu*ropean Child and Adolescent Psychiatry, 18(1),* 42-52. https://doi.org/10.1007/s00787-008-0702-z

Follow up article from research on a Norwegian clinical IY study: Drugli, M. B., Larsson, B., Fossum, S., & Mørch, W. T. (2010). Five- to six-year outcome and its prediction for children with ODD/CD treated with parent training. *Journal of child psychology and psychiatry, 51(5),* 559-566. https://doi.org/10.1111/j.1469-7610.2009.02178.x

3. References to the research (indicative maximum of six references)

The IY parenting programs for 3-6 years/6-12 years scored at evidence level 5 (strong documentation for effect) and the IY's universal program for 2-6 years and IY`s Teacher Classrom

Management program scored at evidence level 4 (satisfactory documentation for effect) in Ungsinn.

1. Aasheim, M., Drugli, M.-B., Reedtz, C., Handegård, B.-H. & Martinussen, M. (2018b). Change in teacher–student relationships and parent involvement after implementation of the Incredible Years Teacher Classroom Management programme in a regular Norwegian school setting. *British Educational Research Journal, 44,* 1064-1083. https://doi.org/10.1002/berj.3479
2. Aasheim, M., Reedtz, C., Handegård, B.H., Martinussen, M. & Mørch, W-T. (2018a). Evaluation of the Incredible Years Teacher Classroom Management program in a regular Norwegian school setting. *Scandinavian Journual of Education Research*, https://www.tandfonline.com/doi/full/10.1080/00313831.2018.1466357
3. Fossum, S., Handegård, B. H. & Drugli, M. B. (2017). The Incredible Years Teacher Classroom Management Programme in kindergartens: effects of a universal preventive effort. *Journal of Child and Family Studies, 26*, 2215-2223. https://doi.org/10.1007/s10826-017-0727-3
4. Reedtz, C., Handegard, B. H., & Mørch, W.-T. (2011). Promoting positive parenting practices in primary pare: Outcomes and mechanisms of change in a randomized controlled risk reduction trial. *Scandinavian Journal of Psychology, 52(2),* 131–137. https://doi.org/10.1111/j.1467-9450.2010.00854.x
5. Reedtz, C., & Klest, S. K. (2016). Improved parenting maintained four years following a brief parent training intervention in a non-clinical sample. *BMC Psychology, 4(1)*, 43. https://doi.org/10.1186/s40359-016-0150-3

4. Details of the impact (indicative maximum 750 words)
In the period 2012 – 2022, RKBU North has offered the following IY programs in Norway:

- IY Parent Training: 0-1 year; 1-3 years; universal prevention 2-6 years; 3-6 years; 6-12 years; 2-6 years, autism spectrum and language difficulties
- IY Teacher Classroom Management program (TCM)
- IY Dinosaur school in small groups (3-8 years), child group, indicated offer, and treatment.
- IY Dinosaur school in classrooms, SFO (after-school programs), and preschools (3-8 years), child group, universal prevention measure.

Additionally, RKBU North has contributed to adapting some IY programs for specific target groups, followed by subsequent research. This includes IY Parent Training adapted for immigrant and refugee families 6-12 years (PIRM study), and IY School and Preschool Program adapted for delivery as a two-step training model through the concept of Relational and Developmental Supportive School, SFO, and Preschool.

Anchoring Competence in Strong Academic Communities, Regions, and Municipalities

The IY program in Norway is founded on research-based implementation theory and is supported by political and administrative leadership within municipalities and organizations. The program's training and guidance infrastructure is provided by three RKBU centers and the RBUP East and South, which are connected to academic institutions (UiT and NTNU), research centers (NORCE), and foundations (Pilar). The IY leadership and professionals, including mentors and trainers, are employed by RKBU/RBUP. A network of regional and local IY facilitators, who are specially trained experienced group leaders from municipalities and BUPs, offer crucial support to local group leaders. RKBU North promotes the IY program through various activities, including training, research, conferences, support services, media engagement, and online platforms. IY is also integrated into university and college curricula across Norway.

Adaptation of Training and Educational Materials

RKBU North has facilitated the translation of IY program materials, including manuals, video vignettes, workbooks, posters, and textbooks, to ensure adherence to the program's effective components in Norway. These materials support both academic training for IY group leaders and participants in parent and classroom management programs. Seven of C. Webster-Stratton's textbooks have been translated, published by Gyldendal Norsk Forlag, and are available in bookstores and as audiobooks for parent groups. The IY School and Kindergarten program's reach is extensive; for example, if a school with 40 staff and 350 students implements the program, and each person is part of a four-member family, the program could potentially reach 1,560 individuals. Training 40 staff would require two courses with six days of training each. As staff apply their training over time, the program's influence will extend to new students and families.

Training and Guidance in the IY Programs in Norway

Since 2015, the IY Parenting Programs for ages 3-6 and 6-12 have been part of further and continuing education at UiT, with standardized workshops and follow-up guidance organized by the RKBU/RBUP. IY in Norway caters to various groups, offering universal, indicated, and treatment interventions, helping thousands of families. Additionally, the Dinosaur School program allows children in BUPs and Educational Psychological Services to develop social and emotional skills, with themes including bullying, violence, and abuse since 2018. This program is also implemented universally in schools, after-school programs, and kindergartens to foster these skills in group settings.

Dissemination of the IY Programs in Norway

Since 1999, more than 3200 IY group leaders in Norway have been trained. Approximately two-thirds of these have been trained between 2012 and 2022. IY's group offerings target children with behavioral difficulties, ADHD, autism spectrum disorders, and aim to prevent the onset or development of these difficulties. Behavioral problems and ADHD are frequently comorbid issues for children in the indicated IY groups and in treatment groups. Over the years of IY implementation in Norway, professionals from approximately every third municipality and about 45 Child and Adolescent Psychiatric Outpatient Departments (BUP) have received training in one or more IY programs. Some municipalities have multiple IY programs in their portfolio, while others have few or only one. There are BUPs and municipalities in Norway that have regularly offered IY parent guidance for more than 20 years. With offerings to at least 6 families every half year for 20 years, they have reached the following number: 12 children x 20 years = at least 240 families in parent guidance in their area alone. Many municipalities have provided training in IYs school and kindergarten programs to almost all their staff. For example, a municipality with 20 kindergartens has trained all its kindergarten staff in IY kindergarten program. If one calculates that each kindergarten, on average, has four departments with 15 staff members and that each department, on average, has 15 children, this amounts to 300 staff and 60 children x 20 kindergartens = 1200 children during the training period. As the staff continues to apply the knowledge and tools from the program, the benefits will be transferred to new hires and to new children in the kindergarten in the coming years.

Professional Development in Connection with IY in Norway

IY in Norway has actively contributed to professional development in collaboration with IY internationally, through the development of IY's universal preventive program, in the tailored parent program for immigrants and refugees (PIRM), and in components of IY child groups

addressing the theme of abuse, violence, and maltreatment, as well as in the further development of the school and kindergarten program. Currently, research is conducted on several IY programs related to ADHD, autism, immigrant families, and kindergartens. The PIRM project is a comparative study where IY parent guidance and International Child Development Programme (ICDP) parent guidance is offered simultaneously and compared in terms of effectiveness. IY in Norway regularly collaborates with user associations such as ADHD Norway, the Autism Association, parent representatives, to disseminate knowledge and develop or adopt relevant educational and treatment offerings. In connection with the implementation of various IY programs, many thousand pages of training materials have been translated from English to Norwegian, including group leader manuals, workbooks, textbooks, subtitling and dubbing of video vignettes, and more. Some of the books are also offered as audio files. In the period 2012 – 2022, RKBU North has been primarily responsible for translating six complete IY programs, a translation of video and handout materials, four textbooks, and a significant amount of additional training and guidance material.

International Collaboration

RKBU North and IY has had close collaboration with international professional communities and has contributed to various professional networks. IY in Norway has participated in EU projects through Norway Grants and EEA Grants in Portugal, Slovenia, Lithuania, as well as in the CYAR project (Children and Youth at Risk in the Barents region 2008 - 2015) in Russia and Estonia. Through the network of IY's original environment in Seattle, USA, IY in Norway has had annual meetings with professionals from the USA, Canada, New Zealand, Australia, England, Wales, Scotland, Ireland, Northern Ireland, the Netherlands, Portugal, and Russia. In 2006, IY in Norway played a central role in establishing a Nordic collaboration network for countries that had implemented or wished to implement programs from the IY program series. The purpose of the network was the exchange of implementation knowledge, research design, and research results from the work with IY in different countries. Later, the network expanded into a European IY (EIY) Network. In the period 2012 – 2022, professionals from the following countries have participated in meetings in the EIY: Sweden, Denmark, England, Estonia, Lithuania, Slovenia, Wales, Scotland, Ireland, Portugal, Poland, Malta. Through various European projects, IY in Norway has contributed as professional support and guidance at the initiation of IY in Sweden, Denmark, Russia, Portugal, Estonia, Lithuania, Slovenia, and has provided implementation knowledge for the initiation and research on Triple P parenting guidance in the Czech Republic. Based on international collaboration around IY, entirely new initiatives have also been developed, including the non-profit program Invest in Play (IiP). The development work originated in the EIY network, and several of the initiators of IiP came from professional environments around The Incredible Years internationally and in Norway. RKBU North has contributed to the adaptation of materials and testing of the IiP program in Norway. As a result of research-based programs and thorough implementation, training, and guidance, interventions from the IY program series have shown positive effects in Norway for over 20 years. This has been demonstrated through various research projects, targeting clinical populations, indicated populations, and as universal preventive measures. IY in Norway has also influenced public discourse through active participation in the media. Research has shown that evidence-based parenting guidance is among the most effective interventions for achieving lasting changes in behavioral problems in children and adolescents. IY parenting guidance is recommended by the Norwegian Directorate of Health as a measure for preventing and treating behavioral problems. The IY program in Norway that has the most far-reaching effects in society is the School and Kindergarten Program. With proper implementation, this program has ripple effects on school, after-school care (SFO), and kindergarten staff, the

children attending school/SFO and kindergarten, as well as on parents and networks. Simultaneously, the portfolio of various IY interventions is essential to prevent broadly and assist many. The availability of programs from the IY program series in Norway for approximately 25 years has contributed to making these models widely known in Norway. However, many municipalities and services in Norway do not utilize evidence-based interventions, indicating that the work is not complete. Professionals with expertise in IY programs in Norway are frequently sought after as lecturers in health and care education. In the period 2012-2022, the staff has contributed conference presentations at numerous national and international conferences. These include conferences and other professional presentations on behavioral problems, autism spectrum disorders, ADHD, implementation, class/group management, mental health in schools and kindergartens, among others. Parental guidance has ripple effects reaching beyond the parents participating in IY courses. The courses have the most significant impact on the child for whom participation was referred, but they also influence other children in the family. In addition, parents are encouraged to collaborate closely with schools, SFO, or kindergartens to align the topics they are working on in the parental guidance courses. The courses also lead to participating parents sharing new knowledge and tools with grandparents, other family members, friends, etc. The implementation of IY and other evidence-based programs in Norway has contributed to introducing a more specialized and nuanced language regarding various conditions, interventions, and understanding of different types of challenges and disorders, especially in the field of behavioral problems, interaction difficulties, ADHD, class, and group management, etc.

5. Sources to corroborate the impact (indicative maximum of ten references)

1. Report from the Norwegian Public Health Institute about Children, Youth, and Crime (2020) recommends the use of IY for prevention and treatment (p. 40). In Norwegian: Barn, unge og kriminalitet - 2020 (fhi.no)
2. The Norwegian Directorate of Health recommends the use of IY for ADHD/Hyperkinetic Disorder and conduct disorders. In Norwegian: Ved ADHD/Hyperkinetisk forstyrrelse og atferdsforstyrrelser hos førskolebarn og barn i tidlig skolealder anbefales det å prøve om foreldretreningsprogrammer har effekt - Helsedirektoratet
3. Presentation of IY Norway (DUÅ) at the Norwegian Directorate for Children, Youth, and Families (Bufdirs) In Norwegian: De Utrolige Årene (DUÅ) førskole | Bufdir
4. Article in the magazine Utdanningsnytt from professionals working in different sectors according children and families. In Norwegian: Programmet De utrolige årene er ikke uetisk (utdanningsnytt.no)
5. Information on Helse Bergen's web site about prevention and treatment for conduct disorders. In Norwegian: De Utrolige Årene - Helse Bergen HF (helse-bergen.no)
6. Information at Asker municipality's web site about their IY parent groups. In Norwegian: Kurs i barneoppdragelse: "De utrolige årene" | Asker kommune
7. Information on The Norwegian Center for Child Behavioral Development (NUBU) website about comparative studies related to PMTO and DUÅ. In Norwegian: PMTO og De utrolige årene: en sammenlikning - NUBU
8. Information on the Norwegian Public Health Institute about use of evidence-based programs for preventing Crime (2020). In Norwegian: De beste tiltakene mot barne- og ungdomskriminalitet brukes for lite - FHI
9. Brochure from the advocacy group ADHD Norway with information about measures and how DUÅ parenting guidance can help children with ADHD. In Norwegian: 601821651e733888eccf4d08_dua-adhd-guide-compressed.pdf (website-files.com)
10. IY Norway's website where information about the program series is presented. In Norwegian: https://dua.uit.no

UiT The Arctic University of Norway, School of Sport Sciences - Case 1 of 1

Institution: UiT The Arctic University of Norway
Administrative unit: School of Sport Sciences
Title of case study: Informing the physical activity guidelines for public health: Physical activity prevalences, trends, and cardiovascular health in the Arctic population (ACTIHEALTH)
Period when the underpinning research was undertaken: 2015-2023
Period when staff involved in the underpinning research were employed by the submitting institution: 2013-2023
Period when the impact occurred: 2016-2023

1. Summary of the impact

The research output emanating the ACTIHEALTH programme has informed the revision of national guidelines for physical activity. This influence is primarily attributed to the utilisation of large, longitudinal cohort studies to measure the efficacy of policies via the surveillance of physical activity. In particular, our unique data on trends in physical activity over the last five decades has created awareness among health authorities. Our research has evidenced sports cardiology guidelines for atrial fibrillation, thereby facilitating the progression of clinical policy and practice in a field lacking specific guidelines and practices. Moreover, we have challenged previous studies on how physical activity can mitigate potential detrimental effects of prolonged sitting, in order to advance policies on sedentary behaviour.

2. Underpinning research

Initiated in 2014, the ACTIHEALTH programme is an ongoing research endeavour aiming to contribute to the evidence on trends and prevalence of physical activity in the Arctic population, and implications on health. Physical inactivity is a main cause of morbidity and premature mortality, therefore ACTIHEALTH's overall objective is to inform physical activity policy and interventions by leveraging data from comprehensive, longitudinal population-based studies.

Evaluating the efficacy of physical activity policies: Secular trends and prevalence of physical activity

The team examined secular trends in physical activity over the last five decades in the large, population-based Tromsø Study in Northern Norway and showed that the proportion of adults engaging in exercise in leisure time increased significantly over the last two decades, from 16% in 2001 to 28% in 2015-16 **(R1)**. However, there was a notable increase in participants who reported spending most of their time sitting at work, rising from 36% to 57% over the same period. This surge in sedentary work behaviours could potentially offset the health gains achieved through increased physical activity during leisure time.

To further inform the government regrading surveillance of physical activity, we again measured physical activity with accelerometer devices in the 7th Tromsø Study in 2015-16 to gather more objective data on physical activity levels (**R2).** The study showed that when basing the analyses on the WHO guidelines <2020, which recommended that MVPA [moderate to vigorous physical activity] should be performed in bouts of at least 10 minutes duration for at least 150 minutes/week, 22% of adults met the MVPA recommendation in the 7th Tromsø Study. Intriguingly, analysing the same data in accordance with the new WHO guidelines launched in 2020, which has removed this 10-minute bout requirement, allowing all MVPA activity to count, as much as 70% accumulated ≥150 minutes of non-bouted MVPA per week. The study **(R2)** also showed that older people, people with higher BMI, and people reporting low education level had

lower MVPA levels. However, sedentary time did not differ between age, education, or BMI groups.

Evidencing cardiovascular health benefits of physical activity by use of large cohort studies
ACTIHEALTH is focused on utilising large cohort studies to study physical activity in the prevention of cardiovascular disease, predominantly atrial fibrillation, and mortality, aiming to advocate guidelines for physical activity, exercise, and cardiovascular disease.

Our prospective cohort study on 20 484 adults from the 3rd Tromsø Study indicated a J-shaped association between atrial fibrillation and physical activity, as moderate physical activity reduced the risk of AF, whereas vigorous activity attenuated these benefits **(R3)**. Our results led to the hypothesis that the mechanisms underlying an increased risk of atrial fibrillation with intensive exercise are different from those underlying a reduced risk with moderate physical activity.

In a prospective cohort study from the 2nd Tromsø Study **(R4)**, we followed 16 104 adults for 34 years. The study showed that risk of myocardial infarction increased with increasing BMI but was lower for active compared to inactive individuals within the same BMI category. The study suggests that physical activity could attenuate but not eliminate the risk of myocardial infarction associated with excess bodyweight.

As reported in **R1**, the proportion of the population sitting most of their workday has increased considerably over the last decades, while over the same time period people exercised more during leisure time. These trends necessitate an exploration of the implications of elevated sedentary time on non-communicable diseases and mortality rates. We therefore assessed the association of sedentary time and physical activity with mortality using accelerometer data in pooled participant data from the Tromsø Study, the Healthy Ageing Initiative in Sweden, the Norwegian National Physical Activity Survey ("KAN"), and NHANES **(R5)**. We showed that being sedentary >12 hours/day was associated with higher mortality risk but only in those not meeting the guidelines of 150 minutes MVPA per week. The study suggests that increasing MVPA is more effective than reducing sedentary time in reducing the risk of dying prematurely.

Names:	**Roles (e.g. job title):**	**Period employed by unit:**
Bente Morseth	Professor (Associate Professor <15.09.2020)	2013-date
Edvard Hamnvik Sagelv	PhD student (Lecturer <01.02.2019)	2016-2023
Anna H. Nordström	Professor II	2017-date

3. References to the research

R1. Morseth B, Hopstock LA: **Time trends in physical activity in the Tromsø study: An update**. *PLoS One* 2020, 15(4):e0231581. https://doi.org/10.1371/journal.pone.0231581

R2. Sagelv EH, Ekelund U, Pedersen S, Brage S, Hansen BH, Johansson J, Grimsgaard S, Nordström A, Horsch A, Hopstock LA, Morseth B: **Physical activity levels in adults and elderly from triaxial and uniaxial accelerometry. The Tromsø Study**. *PLoS One* 2019, 14(12):e0225670. https://doi.org/10.1371/journal.pone.0225670

R3. Morseth B, Graff-Iversen S, Jacobsen BK, Jørgensen L, Nyrnes A, Thelle DS, Vestergaard, P, Løchen ML. **Physical activity, resting heart rate, and atrial fibrillation: the Tromsø Study.** *Eur Heart J.* 2016;37(29):2307-13. https://doi.org/10.1093/eurheartj/ehw059

R4. Renninger M, Løchen ML, Ekelund U, Hopstock LA, Jørgensen L, Mathiesen EB, Njølstad I, Schirmer H, Wilsgaard T, Morseth B: **The independent and joint associations of physical activity and body mass index with myocardial infarction: The Tromsø Study**. *Prev Med* 2018, 116:94-98. https://doi.org/10.1016/j.ypmed.2018.09.005

R5. Sagelv EH, Hopstock LA, Morseth B, Hansen BH, Steene-Johannessen J, Johansson J, Nordström A, Saint-Maurice PF, Løvsletten O, Wilsgaard T, Ekelund U, Tarp J: **Device-measured physical activity, sedentary time, and risk of all-cause mortality: an individual participant data analysis of four prospective cohort studies**. *Br J Sports Med* 2023, 57(22):1457-1463. https://doi.org/10.1136/bjsports-2022-106568

4. Details of the impact

Informing national physical activity guidelines and policies on health and built environment
Research and researchers from the unit **(R1, R2)** have contributed to the development of national physical activity guidelines, recommendations, and plans. In particular, the unique data on trends in physical activity over a period of 40 years have been of importance for national health authorities.

In 2018, Morseth was part of the working group delivering a knowledge base for the new action plan for physical activity ("Kunnskapsgrunnlag for ny handlingsplan for fysisk aktivitet") led by the Norwegian Institute of Public Health and initiated by the Norwegian parliament **(S2)**. Moreover, data on trends in physical activity from the Tromsø Study **(R1)** contributed to the knowledge base, as attachment 2 in the plan **(S2)** included a summary of findings from **R1**.

Similarly, data from **R1** has contributed to the Public Health Report ("Folkehelserapporten") in 2023 **(S1)**: *"Although the data are not directly comparable due to different methods (activity monitors and questionnaires), data from the Tromsø Study conclude that the proportion who report regular exercise in leisure time has increased over the last three decades. The proportion is about 28 percent in 2015-2016 (Morseth and Hopstock, 2020)."* Furthermore, the work **(S1)** was peer reviewed by Morseth *("03.12.2021:. ....Peer reviewed by Bente Morseth, professor UiT Norges arktiske universitet.»).*

In 2020, the Norwegian Directorate of Health (Helsedirektoratet) appointed Morseth to the working group that revised the national guidelines for physical activity based on the WHO global recommendations for physical activity and sedentary behavior **(S3)**. The working group had an advisory role to the Directorate of Health in an early phase in 2020. The task was to assess WHO's advice with regard to the need for adaptations to the Norwegian context and use in Norway. In relation to **R2**, there was a public debate on the effects of removing the 10 minutes bout requirement in the guidelines for physical activity, with active participation from the team **(S4)**.

Moreover, data from **R1** has contributed to various policies, such as *"Better health and longer life for people with serious mental illness or substance use and addiction disorders"* **(S5)** and *"The sports facilities of the future - challenges and opportunities"* **(S6)**.

Advocating cardiology guidelines
Epidemiological research may aid health guidelines or aim to reach the general public in order to inform about the importance and level of physical activity needed to make a change.

Our research on physical activity and atrial fibrillation **(R3)** has contributed to a position statement on participation physical activity and sports in patients with arrhythmias from the European Society of Cardiology **(S7)** and ESC Guidelines on sports cardiology and exercise in patients with cardiovascular disease **(S8)**, corroborating the evidence suggesting a U-shaped association between physical activity and atrial fibrillation. Based on this, the recommendations **(S7, S8)** conclude that *"moderate physical activity is a cornerstone of AF prevention…"* and that *"…the slightly increased risk of AF in endurance athletes does not reduce the significant overall CV benefit of sports participation."* **(S7)** and *"Counselling about the effect of long-lasting intense sports participation on (recurrence of) AF is recommended in individuals with AF who exercise vigorously for prolonged periods, especially in middle-aged men."* **(S8).**

Enhancing public health impact

The findings from **R4** attracted media interest, through Morseth being interviewed by BBC World Radio in the program Newsday about the public health impact of the study **(S9)**, which ensured widespread relevance of physical activity versus overweight on cardiovascular health. Similarly, the findings from **R5** got extensive worldwide attention as the findings of the study have been reported by more than 290 news outlets and posted by >1200 X (Twitter) users, spreading the impact to all corners of the world with the message that a rather modest amounts of MVPA (22 min/day, not necessarily done at once) may ameliorate the mortality risk from high sedentary time.

5. Sources to corroborate the impact

S1. Folkehelserapporten - Fysisk aktivitet i Norge 03.12.2021
S2. «Kunnskapsgrunnlag for ny handlingsplan for fysisk aktivitet» - FHI 19.09.2018 / Link to the plan: 31.august2018_sendt-003.pdf (fhi.no)
S3. Norwegian guidelines for physical activity - Fysisk aktivitet i forebygging og behandling 09.05.2022
S4. Norske anbefalinger for fysisk aktivitet bør endres, mener forskere (forskning.no) 23.09.2017
S5. Bedre helse og lengre liv (legeforeningen.no)
S6. Fremtidens idrettsanlegg - utfordringer og muligheter | Gode idrettsanlegg
S7. Heidbüchel et al. Recommendations for participation in leisure-time physical activity and competitive sports in patients with arrhythmias and potentially arrhythmogenic conditions: Part 1: Supraventricular arrhythmias. A position statement of the Section of Sports Cardiology and Exercise from the European Association of Preventive Cardiology (EAPC) and the European Heart Rhythm Association (EHRA), both associations of the European Society of Cardiology. Eur J Prev Cardiol. 2021;28(14):1539-51
S8. Pelliccia et al. 2020 ESC Guidelines on sports cardiology and exercise in patients with cardiovascular disease. Eur Heart J. 2021;42(1):17-96
S9. BBC World - Newsday Radio interview - new study on physical activity, overweight, and heart attack 31.10.2018 (42.20 into the broadcast) / Link to UiT article
S10. Altmetric – Device-measured physical activity, sedentary time, and risk of all-cause mortality: an individual participant data analysis of four prospective cohort studies

Impact case guidelines

Each case study should include sufficiently clear and detailed information to enable the evaluation committee to make judgements based on the information it contains, without making inferences, gathering additional material, following up references or relying on members' prior knowledge. References to other sources of information will be used for verification purposes only, not as a means for the evaluation committee to gather further information to inform judgements.

In this evaluation, impact is defined as an effect on, change or benefit to the economy, society, culture, public policy or services, health, the environment or quality of life, beyond academia.

Timeframes

- The impact must have occurred between 2012 and 2022
- Some of the underpinning research should have been published in 2012 or later
- The administrative units are encouraged to prioritise recent cases

Page limit

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Maximum number of cases permitted per administrative unit

For up to 10 researchers: one case; for 10 to 30 researchers: two cases; for 30-50 researchers: three cases; for 50-100 researchers: four cases, and up to five cases for units exceeding 100 researchers.

Naming and numbering of cases

Please use the standardised short name for the administrative unit, and the case number for the unit (1,2,3, etc) in the headline of the case. Each case should be stored as a separate PDF-document with the file name: [Name of the institution and name of the administrative unit] [case number]

Publication of cases

RCN plans to publish all impact cases in a separate evaluation report. By submitting the case the head of the administrative units consents to the publication of the case. Please indicate below if a case may not be made public for reasons of confidentiality.

If relevant, describe any reason to keep this case confidential:

Not relevant.

Name of the institution and name of the administrative unit

Institution: UiT The Arctic University of Norway
Administrative unit: Department of Pharmacy
Title of case study: Audit and feedback to increase adherence to antibiotic prescribing guidelines
Period when the underpinning research was undertaken: 2014-2015
Period when staff involved in the underpinning research were employed by the submitting institution: 2009-2015
Period when the impact occurred: 2015 - onwards

1. Summary of the impact (indicative maximum 100 words)

This project demonstrated that antibiotic treatment of community-acquired pneumonia (CAP) and acute exacerbations of chronic obstructive pulmonary disease (AECOPD) according to guidelines increased prescription of appropriate antibiotics in lower doses and reduced treatment duration. However, to maintain the beneficial results we found continuous follow-up to be necessary. Based on these data, the University Hospital of North Norway (UNN) chose to hire a pharmacist in a permanent position designated to work with antibiotic stewardship. We later demonstrated that treatment with narrow spectrum penicillin in immunocompetent patients was associated with lower risk of 30-day readmission.

2. Underpinning research (indicative maximum 500 words)

Empirical antibiotic prescribing in hospitals for CAP and AECOPD should cover common airway pathogens accounting for their pattern of antimicrobial resistance (AMR). The prevalence of AMR in Norway is low and recommended empirical treatment in non-severe cases is narrow spectrum therapy. This clinical intervention study at UNN was undertaken in the period January 2014 – March 2015 and included a pre-intervention audit phase (Phase1), a feed-back intervention phase (Phase2), and a post intervention audit (Phase3). In Phase1, we collected data on 30-day mortality and 30-day unplanned readmission, and retrospectively evaluated whether choice of empirical antibiotic treatment, dose, and treatment duration were according to clinical practice guidelines (CPG). In Phase2, we informed physicians on the result of the audit, presented a pocket version of the CPG and encouraged physicians to discuss discrepancies between CPG recommendations and documented performance. In Phase3, we collected the same data as in Phase1 and analysed the change in empirical antibiotic prescribing using interrupted time series. This method enabled assessment of both a trend and a level effect. Following the clinical intervention, the prescribing of appropriate empirical antibiotics increased from 62-84% mainly caused by a reduction in use of broad spectrum cephalosporins and tetracyclines. There was no change in 30-day mortality or 30-day readmission. After the intervention we found an immediate reduction in treatment duration, but the post-intervention trend was increasing and at six months post-intervention treatment duration reached pre-intervention levels. In a follow-up study in 2020, we demonstrated that treatment with other antibiotics than narrow spectrum penicillin increased the risk of 30-day readmission, without decreasing the length of stay in the hospital.

Appropriate antibiotic prescribing through interdisciplinary collaboration is beneficial for treatment outcomes, reduced treatment costs and to halt development of AMR. Consequently, antibiotic stewardship programs that address all three aspects are important in both patient and societal perspectives. We have approached this by conducting transdisciplinary projects addressing both pharmaco-epidemiological and clinical pharmacy topics by collaborating with medical doctors and nurses at the university hospital. Our finding of a transient effect on treatment duration suggested the need for a continuous focus on antibiotic treatment in the hospital, and consequently the university hospital chose to create a permanent position for a clinical pharmacist with a main responsibility for follow-up.

In combination with national efforts and continuous follow-up, this intervention has contributed to a favourable development in antibiotic use at UNN. This is documented in yearly reports from the hospital pharmacy and the regional centre for infection control.

There is solid documentation for an association between use of broad-spectrum antibiotics and subsequent development of AMR. Substituting broad spectrum antibiotics with narrow spectrum when indicated in treatment of airway infections apparently have no detrimental effects for the patient but may contribute to halt the development of AMR.

3. References to the research (indicative maximum of six references)

Høgli JU, Garcia BH, Skjold F, Skogen V, Småbrekke L. An audit and feedback intervention study increased adherence to antibiotic prescribing guidelines at a Norwegian hospital. BMC Infect Dis 2016;16:96. doi: 10.1186/s12879-016-1426-1. PMID: 26920549

Høgli JU, Garcia BH, Svendsen K, Skogen V, Småbrekke L. Empirical prescribing of penicillin G/V reduces risk of readmission of hospitalized patients with community-acquired pneumonia in Norway: a retrospective observational study. BMC Pulm Med 2020;20(1):169. doi: 10.1186/s12890-020-01188-6. PMID: 32539706

https://www.pingvinavisa.no/antibiotikabruken-pa-vei-ned/

https://www.pingvinavisa.no/et-eventyrlig-engasjement-gir-gode-resultater/

4. Details of the impact (indicative maximum 750 words)

Norwegian authorities adopted “Handlingsplan mot antibiotikaresistens” (Action plan against antibiotic resistance) in 2012 and later funded four permanent regional positions designated to work with antibiotic stewardship. In 2015, as the only regional health authority in Norway, the North-Norway Regional Health Trust, based on the results from this project, chose to hire a pharmacist in this position. This pharmacist was the PhD graduate from the project, and she was later assigned responsibility for the regional health authority program for antibiotic stewardship. This has provided important support for other hospitals in the region. The pharmacist has also been appointed to the National Center for Antibiotic Use in Hospitals where she holds a position in the reference group.

Dissemination: Articles. Meetings at ward level and hospital level.

The beneficiary of this measure is foremost the patients, but in the short perspective UNN and other hospitals in North-Norway Regional Health thrust have a financial gain by optimizing antibiotic treatment through reduced treatment duration and increased use of narrow spectrum antibiotics. In addition, reducing the use of broad-spectrum antibiotics is a cornerstone in halting the development antimicrobial resistance. Initially, the pharmacist focused on antibiotic treatment in hospitals but has later also contributed to infectious disease prevention and antibiotic treatment in community primary health care.

-Evidence: Reports from UNN and link to web-pages.
https://www.unn.no/4a865f/siteassets/documents/kompetansetjenester--sentre-og-fagrad/kompetansesenter-i-smittevern-helse-nord-korsn/antibiotikabruk-i-helse-nord/antibiotikabruk-i-sykehusene/antibiotikastyringsprogram/antbiotikastyringsprogram-unn-2019-2022.pdf

-Dates when the impact occurred: Continuous from project period until now.
-Collaboration with other institutions: Department of infectious diseases, UNN. Dr. med. Vegard Skogen, physician, specialist infectious diseases

5. Sources to corroborate the impact (indicative maximum of ten references)

https://www.researchgate.net/profile/June-Utnes-Hogli
https://www.antibiotika.no/2023/09/28/referansegruppemote-nsas/
https://www.smittevernforum.no/om-oss/styret/

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Not relevant

Name of the institution and name of the administrative unit

Institution: UiT The Arctic University of Norway
Administrative unit: Department of Pharmacy
Title of case study: Change in the national guidelines for storage time of injection after opening and transfer to non-original containers
Period when the underpinning research was undertaken: 2012-2022
Period when staff involved in the underpinning research were employed by the submitting institution: 2012-2022
Period when the impact occurred: 2020-2022

1. **Summary of the impact** (indicative maximum 100 words)

This Impact case is given to illustrate that our department is highly involved in regulatory processes, that includes updating the pharmacopeia guidelines and current practise in drug handling. ***Thus, the departments competence, which in this case was related to drug formulations and stability, impact on new guidelines that assures that safe handling of medications in our society.***

Specifically, we have

- ***Adjusted national guidelines in line with international guidelines.***
- ***Changed the clinical practice with regards to storage of injectables.***

2. **Underpinning research** (indicative maximum 500 words)

Professor Flaten was selected for the Norwegian Pharmacopeia committee based on her competence build over many years as a researcher and teacher at our department. Her basic research, described in her homepage, might not have a direct impact beyond academia, but through her involvement in the Pharmacopoeia commission, indirectly made a big difference to society.

Our knowledge of microbiological, chemical and physical stability issues of both sterile and non-sterile preparations is a result of years of research and education in this area. Over the years we have in particular been doing research on parenteral formulation of liposomal preparations as well as are running several courses for pharmacy students at both bachelor, master and PhD level where the stability of drug preparations and the interaction with the containers they are stored in are important topics where we thus continuously also must be in the knowledge front.

The work with the new guidelines was organized under the Norwegian Pharmacopeia commission and took place from 2020 to its publishing in 2021 as well as the rebattle and following specifications of the guidelines based on feedback from the hospitals up to 2022/23.

- *The key researcher for this Impact case is Professor Gøril Eide Flaten.*
- *Work that concerned the Impact case was maintained in between regular research- and teaching duties at our department.*
- *Context of the Impact case in regulatory work that affects current practice in manufacturing of pharmaceuticals.*

3. References to the research (indicative maximum of six references)

Reference to the guidelines that was the result of the work:

- *Norsk legemiddelstandard (NLS), Legemidler etter anbrudd, Veiledende brukstider etter anbrudd for legemidler med krav om sterilitet (https://www.dmp.no/godkjenning/nls/nasjonale-veiledninger/legemidler-etter-anbrudd)*

Relevant research from the DTD research group:

- *A.M. Holsæter et al. (2022). How docetaxel entrapment, vesicle size, zeta potential and stability change with liposome composition–A formulation screening study. European Journal of Pharmaceutical Sciences, 177, 106267. https://doi.org/10.1016/j.ejps.2022.106267*
- *E.A.L. Rustad et al. (2022). The pH-responsive liposomes – The effect of PEGylation on release kinetics and cellular uptake in glioblastoma cells. Pharmaceutics, 14, 1125. https://doi.org/10.3390/pharmaceutics14061125*
- *J. Cauzzo et al. (2020). Following the fate of dye-containing liposomes in vitro. International Journal of Molecular Sciences, 21, 4847. https://doi.org/10.3390/ijms21144847*
    - *Øverbye et al ,(2017) Ceramide-containing liposomes with doxorubicin: Time and cell-dependent effect of C6 and C12 ceramide, Oncotarget, 8(44), 76921-76924, https://doi.org/10.18632/oncotarget.20217*
- *V. Staven et al. (2016), Physical compatibility of total parenteral nutrition and drugs in Y-site administration to children from neonates to adolescents. Journal of Pharmacy and Pharmacology, https://doi.org/10.1111/jphp.12647*
- *R.D. Whitaker et al (2013), Investigation of parameters influencing incorporation, retention and cellular cytotoxicity in liposomal formulations of poorly soluble camptothecin, J Lip Res, 23(4), 298-310, https://doi.org/10.3109/08982104.2013.805338*
- *G.E. Flaten, et al. (2013), Liposomal Formulations of Poorly Soluble Camptothecin -Drug Retention and Biodistribution. Journal of Liposome Research, 23, 70-80, https://doi.org/10.3109/08982104.2012.742537*

4. Details of the impact (indicative maximum 750 words)

From 2021-2023, NLS underwent a thorough updated. This update particularly improved the guidelines related to storage of sterile and non-sterile drugs after first opening and transfer to other containers. The updated guidelines were made to improve safety of medication as well as to harmonize guidelines with the other national formularies in the Nordic countries, especially Sweden. The most prominent change in the updated version of this guideline, was the change in allowed storage time of sterile medications after transfer of injectables from the original container to syringes. The rationale behind the reduced allowed storage time (from 48 to 24 hrs) was that a syringe as such is not a suitable container for storing of injectables over time unless this is validated by the institutions where this is being practiced. This update highly impacted production practises and thus also medication safety, since transfer into non-original containers is regularly performed in hospitals and nursing facilities in Norway.
This Impact case is given to illustrate that our department is highly involved in regulatory processes, that includes updating the pharmacopeia guidelines and current practise in drug handling. Thus, the departments competence, which in this case was related to drug formulations and stability, impact on new guidelines that assures that safe handling of medications in our society.

5. Sources to corroborate the impact (indicative maximum of ten references)

The tightening of the guidelines leaves more responsibility to the hospitals and the regional health authority to ensure and document that the current practice with storing the intravenous formulations

in syringes before administration is not interfering with the quality of the drug. This will avoid potential harmful incidences and increase the safety for the patient receiving the drug in the end. However, it is still too early to expect to have direct references showing and describing the effect of this implementations and the described impact case.

The Research Council of Norway

Norges forskningsråd
Besøksadresse: Drammensveien 288
Postboks 564
1327 Lysaker

Telefon: 22 03 70 00
Telefaks: 22 03 70 01

post@forskningsradet.no
www.forskningsradet.no

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