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

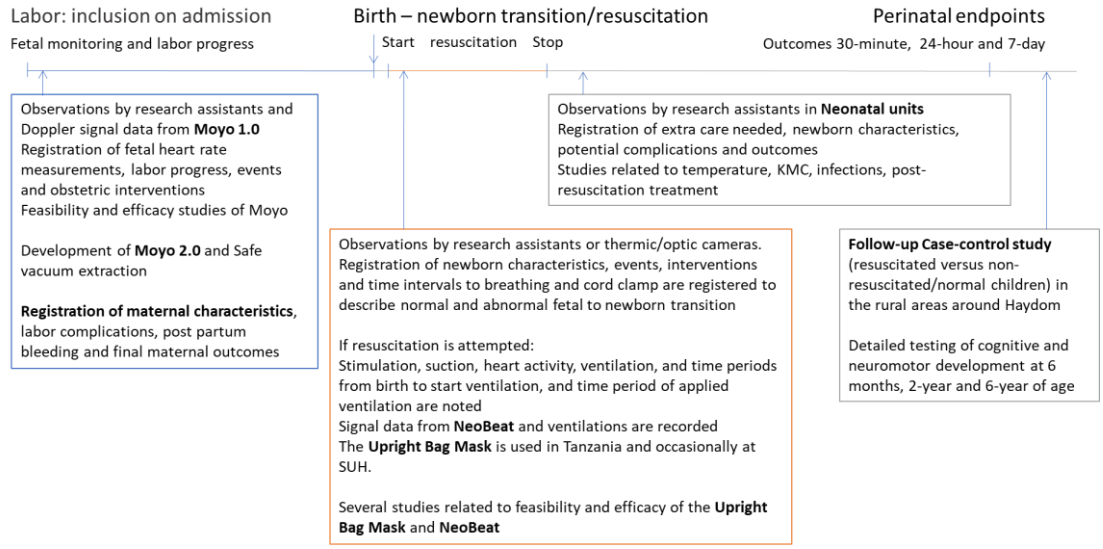

Figure 1. Research logic of the Safer Births program.

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.

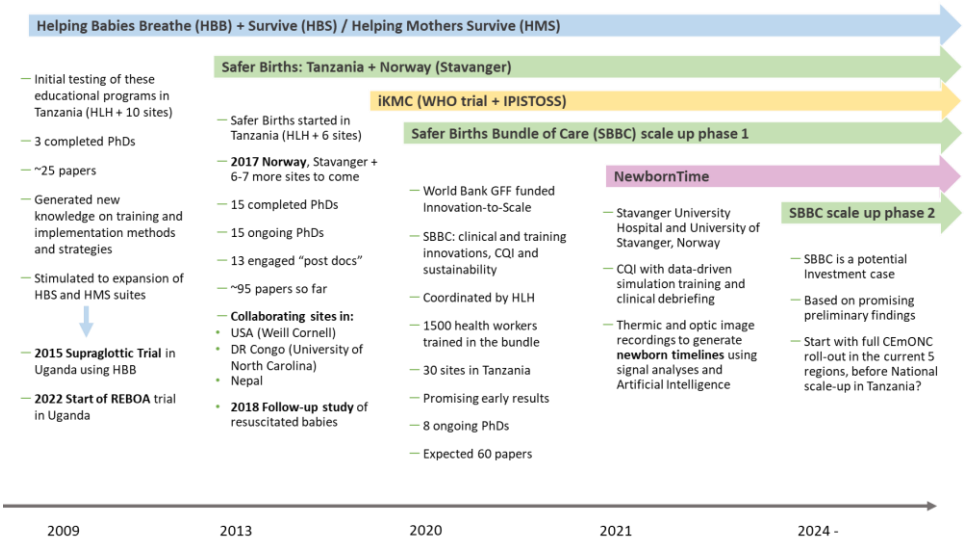

Figure 2. Evolution of Safer Births program components.

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.
- Olsson H, Kartasalo K, Mulliqi N, Capuccini M, Ruusuvuori P, Samaratunga H, Delahunt B, Lindskog C, Janssen EAM, Blilie A; ISUP Prostate Imagebase Expert Panel, Egevad L, Spjuth O, Eklund M. Estimating diagnostic uncertainty in artificial intelligence assisted pathology using conformal prediction. Nat Commun. 2022 Dec 15;13(1):7761.

- 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.