Oslo University Hospital

UiO : University of Oslo

Norwegian PSC Research Center

ANNUAL REPORT 2024

NOPSC

Visit the NoPSC web pages: *www.ous-research.no/nopsc and www.med.uio.no/klinmed/english/research/centres/nopsc/index.html*

Norwegian Primary Sclerosing Cholangitis Research Center (NoPSC)

ANNUAL REPORT 2024

What is PSC?

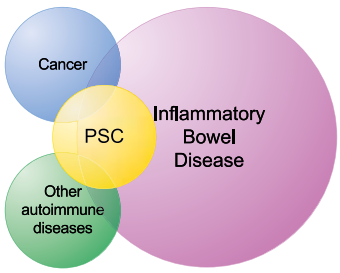
Primary Sclerosing Cholangitis (PSC) belongs to the group of autoimmune liver diseases.

PSC is a chronic inflammatory disorder of the bile ducts, that leads to progressive strictures of the bile ducts and ultimately to liver cirrhosis.

PSC is more common in Northern Europe, where approximately 1:10.000 individuals are affected. There is an increased risk of cancer of both the bile ducts (160-1500x) and the large bowel (5x). There is currently no effective medical treatment available, and PSC is one of the most common indications for liver transplantation in Scandinavia.

Affected individuals are typically young (30-40 years old) and have concurrent inflammatory bowel disease (IBD) in 60-80% of the cases. Disease course is highly variable from patient to patient, but the median time from diagnosis to liver transplantation is 10-15 years. Individuals with PSC often suffer from fatigue, itching and repeated bacterial infections in the bile ducts.

Primary Sclerosing Cholangitis (PSC) is a patchwork of different phenotypes in addition to the bile duct affection. Most important are inflammatory bowel disease (IBD), malignancy and other autoimmune diseases.



Content:

NOPSC ANNUAL REPORT 2024

More information at the web pages:
www.ous-research.no/nopsc
www.med.uio.no/klinmed/english/research/groups/primary-sclerosing-cholangitis/index.html
FRONT PAGE:
Background photo: Working in the germ free animal facility.
Purple circle: Haemotoxylin-eosin staining of murine colonic tissue (known as swiss-roll).
Red circle: Drawing of the liver on agar by plating of E. coli.
EDITORS: Merete Tysdahl
PUBLISHER: Oslo University Hospital
PRINT: Møklegaard Print Shop AS, 2025.
SAMPLES: 250

Leader's comments 2024

Professor Tom Hemming Karlsen

On behalf of the Leadership,
Professor
Tom Hemming Karlsen
Head of NoPSC

The year of 2024 achieved a next plateau of the upscaling of NoPSC activities which became feasible due to the expanded support from Stein Erik Hagen and Canica A/S for the period of 2022-2031. This third phase of NoPSC (internally we refer to it as NoPSC 3.0), has a strong emphasis on clinical implementation of tools and treatments, to translate insights gained of the preceding research periods into clinical benefit for people with PSC.

One important development over 2024 hence was the further distinction of three separate clinical research groups, each with its own topic emphasis: at Rikshospitalet the NoPSC main biobank and cholangiocarcinoma research, in Bergen biomarker development and ScandPSC coordination, and at Akershus University Hospital a hub for clinical trials of new drugs in PSC. The groups will continue to work closely together, but our experience has been that allowing space for slightly distinct agendas in separate groups is important for growth, this was also how NoPSC originally expanded from one into the first three groups.

The backbone that philanthropy has provided for PSC research, with time not only in Oslo, but also at the Mayo clinic with strong support from the Halloran family foundation (who also supports the ScandPSC and associated clinical trials infrastructure at NoPSC) and now in Boston with the Resnek Family Center for PSC research, has become an exemplary model of how to build momentum in rare diseases outside the scope of programmatic priorities of public funding; what we witness in our small field thanks to the support is a "mission". A project was initiated by Petter Skavlan in 2024, aiming to profile involved individuals and how they generate the dynamics of the NoPSC "mission-like" research orientation.

And there is traction to this mission; at the biennial meeting of the International PSC Study group, founded in Oslo in 2010, more than 120 PSC researchers from all over the world gathered in Stockholm in September for two full days to align and discuss priorities, showcasing how many of the key problems we have been chasing for the last decade are now closer to solutions. An important demonstration on this point is also now coming from the promising results of key clinical trials for norucholic acid and PPAR-agonists. Whilst each individual step of this progress is the result of individuals and entities, results are to me unimaginable without this ongoing international joint venture.
In Oslo, one novelty of the NoPSC v3.0 program, has been to expand collaborations beyond the academic setting. We have from last year onwards thus created a new position of an "industry collaborations liason" intended to specifically foster an underdeveloped landscape of mutual benefit – i.e. NoPSC involvement in PSC-related research by industry and NoPSC supporting such initiatives (e.g. with biomaterial from the NoPSC biobank), and reversely, as we see for the Novartis-supported drug-screening project in the experimental research group. These industry-academic partnerships open for the utilization of know-how and technical resources which are unavailable in a purely academic setting.

I am proud and humble to serve as a coordinator for the experienced team of group leaders now driving the research at NoPSC. So many things can be mentioned from last year; Johannes Hov receiving his second ERC grant (only one being almost impossible to acquire); Espen Melum launching the Ductmimic company to facilitate provision of bile-duct-on-a-chip services; Mette Vesterhus and Kristin Kaasen Jørgensen with ScandPSC inclusion going "through the roof" and their contributions to the norucholic acid success; Trine Folseraas using exome sequencing to, for the first time, comprehensively describe how PSC cholangiocarcinoma is biologically distinct and potentially can be treated.

Finally, I wish to highlight two persons not taking up much space and attention. First, our coordinator Merete Tysdahl, who has created this annual report for your reading. The way she manages all our bureaucratic and administrative hurdles allows our researchers to focus on what they are best at – doing research. Second, Kirsten Muri Boberg, after more than three decades serving PSC research, is now retiring. Her meticulousness and excellence sit deep with everything we do at NoPSC and we are indebted in so many of our achievements to the groundwork she provided. Also, her retirement marks a significant generational change at NoPSC. With the young talents now in charge I am not worried.

NoPSC 2024 at a glance

27,9
mill NOK awarded in new competitive research grants

26
research articles published

1
company incorporated

1
investigator initiated clinical trial started

42
presentations at scientific events

4
research awards received

6
new employees engaged

38
people working in research at NoPSC

177000
sample tubes in our PSC biobank

1488
patients included in ScandPSC

12
shipments of PSC biobank samples to
9 sites in
5 countries

Overview of the Norwegian PSC Research Center

NoPSC was established in 2007 at the Medical Department, Rikshospitalet, upon signing the contract between the University of Oslo and Rikshospitalet on the handling of funds from Canica A/S. The basis of NoPSC is the philanthropic donations from Stein Erik Hagen, having been made regularly since 2007 to substantially strengthen long-term research related to basic and clinical aspects of the chronic liver disease Primary Sclerosing Cholangitis.

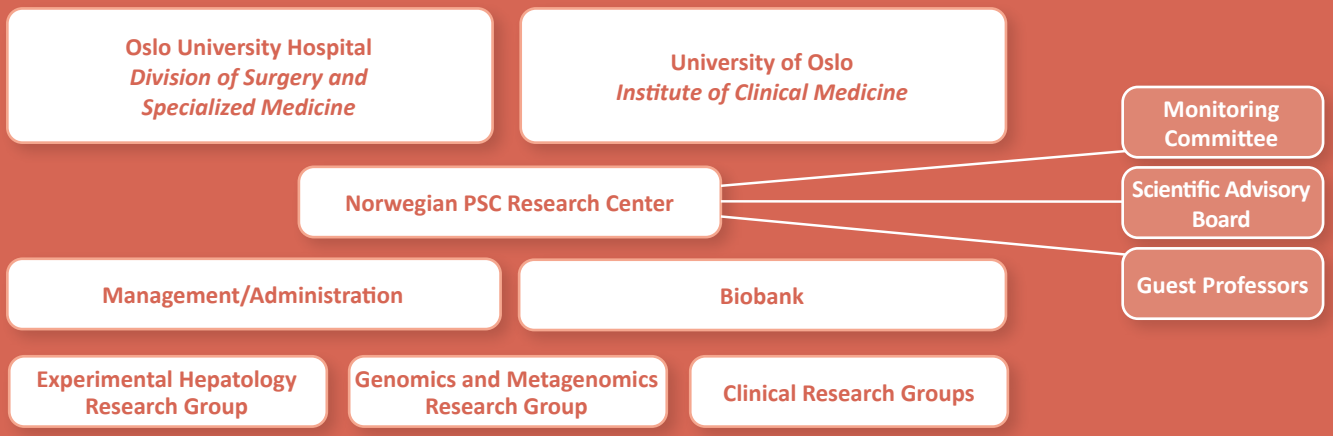
The philantropic funding is made with a grand vision of making a difference for people with PSC, and has given the research environment stability to prosperously grow its activity with 10 year horizons for each funding period.

Aims of the PSC Research Center

- Facilitate high standard PSC research via prudent and targeted use of research funds
- Support the development and implementation of clinical tools and relevant drugs
- Run PSC biobanks and registries to strengthen high quality PSC research globally
- Promote research on critical disease mechanisms in PSC
- Enhance awareness on PSC and PSC research and seek patient partnership when relevant

ORGANIZATION

NoPSC has status as a center at the Medical Faculty, Institute of Clinical Medicine, University of Oslo, and is organized within Oslo University Hospital as a section (level 4 unit) within the Department of Transplantation Medicine at the Division of Surgery and Specialized Medicine. The Experimental Hepatology Group and the Genomics and Metagenomics Group are organized at the Research Institute of Internal Medicine, Oslo University Hospital, while the Clinical Groups are organized within the Section of Gastroenterology at the Department of Transplantation Medicine at Oslo University Hospital, Haraldsplass Deaconess Hospital in Bergen and Akershus University Hospital, respectively.



MANAGEMENT GROUP

The Management Group has the overall responsibility for the research activities performed at the Center and the day-to-day management.

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MONITORING BOARD

The Monitoring Board oversees that the Center is managed according to the aims. Scientific plans and next years budget are dicussed in the autumn, while the Annual report and the accouting are rewieved at the spring/summer meeting.

LEADER
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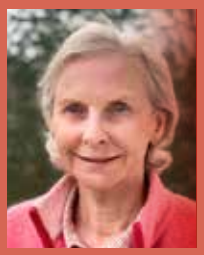
Head of the Institute of Clinical Medicine, University of Oslo

Astrid Aksnessæther
Assistant director, Institute of Clinical Medicine, University of Oslo



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Canica A/S

MD Daniel Sørli
Canica A/S

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Head of department of transplantation medicine, Oslo University Hospital

Prof. Bente Halvorsen,
Head of the Research Institute of Internal Medicine, Oslo University Hospital

Jan Ole Stangeland
CEO, Canica A/S

Prof. Tom Hemming Karlsen, and Merete Tysdahl *are also part of the monitoring board.*

GUEST PROFESSORS 2023 - 2025

Dr. Jan Tchorz
Institutes for BioMedical Research, Basel, Switzerland

Dr. Fotios Sampaziotis
Wellcome - MRC Cambridge Stem Cell Institute, UK

Prof. Tom Lüdde
University of Düsseldorf, Germany

SCIENTIFIC ADVISORY BOARD 2023 - 2026

The Scientific Advisory Board (SAB) reviews the center biannually.

Prof. Ole Andreassen
University of Oslo, Norway

Prof. Pål Rasmus Njølstad
University of Bergen, Norway

Prof. Frank Tacke
Charité - Universitäts-medizin Berlin, Germany

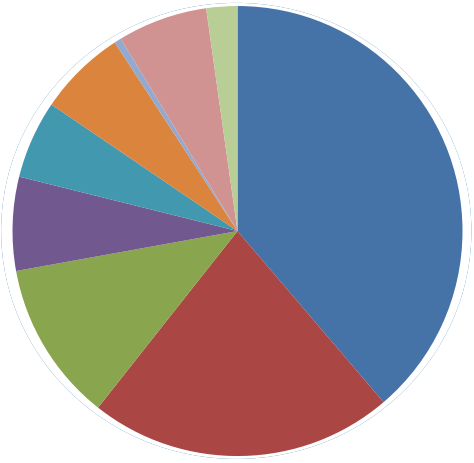
ACCOUNTING

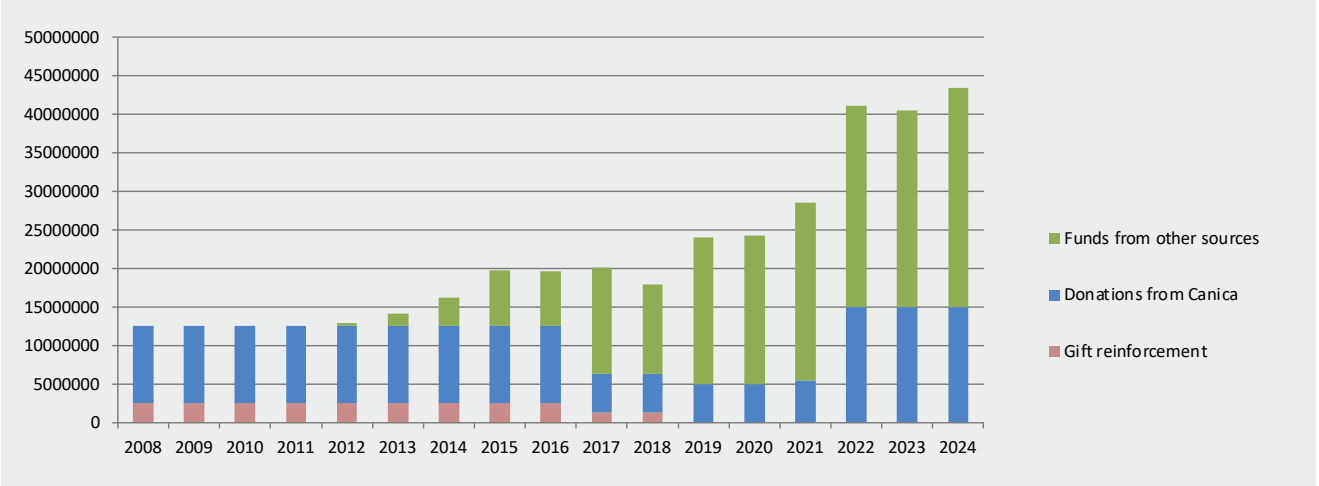
Expenditures from Canica AS funding in 2024 was NOK 15.409.487,- . The overall expenditure of all projects within the center amounted to NOK 39.759.000,- of these NOK 5.187.000,- was provided by University of Oslo and Oslo University Hospital, and NOK 15.512.000,- was from independent, competitive grants from Regional Health Authorities, the Norwegian Research Council and EU. The remaining NOK 3.651.000,- was from various public and private institutions, with the main contributions being generously provided by the Halloran Family Foundation in the US.

2024	OSLO UNIVERSITY HOSPITAL		UNIVERSITY OF OSLO	
	INCOME	EXPENSES	INCOME	EXPENSES
TRANSFER FROM 2023	-3 636 609		17 845 060	
INTEREST			983 834	
FROM CANICA			15 000 000	
OTHER INCOME	300 000			
TRANSFER FROM UIO	**8 632 145**			8 632 145
WAGES		4 232 705		3 332 226
OVERHEAD		249 514		**257 375**
OPERATING EXPENCES		7 148 779		188 888
TRANFER TO 2025		-6 335 463		**21 418 260**

Expenditures	2024
Canica	15 409
Regional Health Authorities in Norway	8 700
Norwegian Research Council	4 580
University of Oslo	2 675
EU funding (ERC/Scientia Fellow)	2 232
Oslo University Hospital	2 512
PSC Partners	198
The Halloran Family Foundation	2 567
Other	886
Thousand NOK	39 759

The pie chart shows the expenditure distribution between different sources





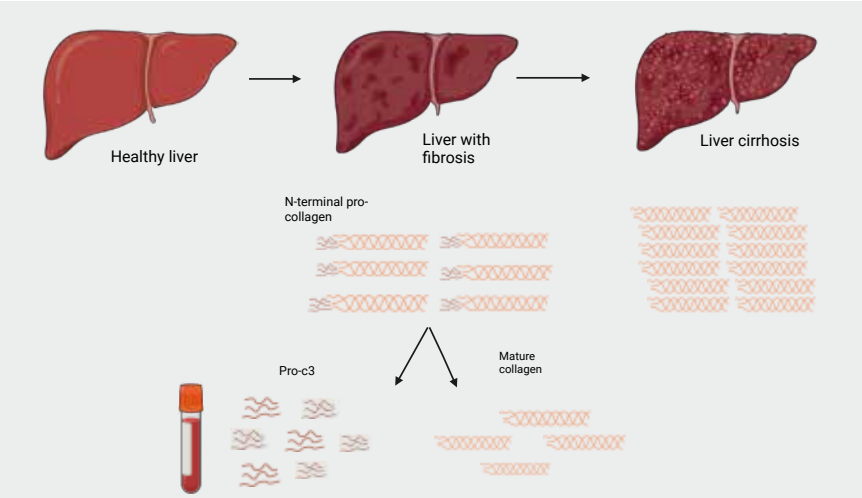
Focus areas

PRO-C3 – A NEW WAY TO TRACK LIVER FIBROSIS IN PRIMARY SCLEROSING CHOLANGITIS

Usha Tharmathas, Kristin Kaasen Jørgensen and Mette Vesterhus

The level and progression of liver fibrosis (scar tissue) are firmly associated with prognosis in chronic liver diseases. In PSC, biomarkers of fibrosis such as liver stiffness measurements (e.g., by Fibroscan) and the Enhanced Liver Fibrosis (ELF) test, a patented serum fibrosis panel, are among the strongest and best documented predictors of clinical outcome. Underscoring the importance of liver fibrosis assessment, liver stiffness measurements and ELF test are currently the only biomarkers that are recommended by recent international guidelines for prognostication and risk assessment in clinical follow-up of people with PSC (1). However, surrogate markers to assess the effect of treatments in clinical trials in PSC are still lacking and are sorely needed to improve our chances of developing effective therapy in PSC. For this purpose, there is a need to develop more dynamic markers that show change within weeks rather than months or years.

PRO-C3 is a promising prognostic biomarker in PSC as well as a potential surrogate marker for clinical trials. During scar tissue formation, several types of procollagens are activated into mature collagen. PRO-C3 is released as a fragment when type III procollagen is converted into mature collagen and



Figure; Illustration of liver fibrosis progression and the role of PRO-C3 as a biomarker

reflects the formation of type III collagen, a key component of liver fibrosis; i.e., PRO-C3 is a biomarker specifically targeting extracellular matrix (ECM) remodeling. Biomarkers of ECM remodeling reflect the balance between fibrogenesis and tissue breakdown; they can differentiate between early and established fibrosis and allow accurate assessment of both fibrosis formation and regression, respectively, via measurements of specific end-products of extracellular remodeling (for each of the various collagens that make up liver fibrosis). Hence, they capture change more dynamically than other existing biomarkers. Over the last decade, a range of ECM markers have been developed and PRO-C3 has demonstrated associations with disease stage and prognosis in various chronic liver diseases, including chronic viral hepatitis, alcohol-related liver disease, metabolic dysfunction-associated steatotic liver disease (MASLD), and autoimmune liver diseases. PRO-C3 has resently been accepted by the US Food and Drugs Administration (FDA) for a biomarker qualification program evaluating its use in MASLD, and ECM markers have also been studied as surrogate efficacy markers.

Several studies have shown that PRO-C3 levels correlate with fibrosis stage and predict clinical outcomes in PSC. As part of a strategic collaboration with corporate partner Nordic Biosciences, who developed PRO-C3 and the “fingerprint” technology to design the specific ECM markers, in a single-center study published 2018. In that study we were the first to report PRO-C3 as a potent prognostic marker and an independent predictor for transplant-free survival (2). In a follow-up study including UK and Norwegian patient

panels, we showed that PRO-C3 correlated well with liver stiffness measurements and ELF test and was strongly and independently associated with advanced PSC (3). The inclusion of PRO-C3 as an exploratory surrogate endpoint in several clinical trials has generated further evidence promoting its candidacy as a promising surrogate marker. An intervention study investigating an anti-fibrotic drug (aldafermin, an FGF19 analogue) in PSC patients did not demonstrate any significant difference in the mean change from baseline in ALP between the two groups, but PRO-C3 and other fibrosis markers were significantly improved in the intervention group (5). Furthermore, the 96-week long phase 2b placebo-controlled trial of simtuzumab, which failed to show any effect of the trial drug, showed that PRO-C3 correlated with fibrosis stage, provided discrimination of advanced fibrosis and cirrhosis, and predicted PSC-related events (4).
The intraindividual coefficient of variation of PRO-C3 was 17% over 24 weeks in this study.

Based on these findings PRO-C3 represents a promising biomarker for future clinical use. It reflects active fibrosis formation, potentially enabling early detection of PSC progression and improved risk stratification and also holds potential as a surrogate endpoint in clinical trials; however, more data on the short- and long-term natural variation of PRO-C3 and validation in larger and prospective studies are needed. A novel high-precision, high-throughput platform (Roche) for the analysis of PRO-C3 was recently launched, and we are currently evaluating this in several ongoing studies. Early studies of PRO-C3 are encouraging, warranting further studies to allow implementation for routine clinical use and to hopefully achieve regulatory approval for use in clinical trials.

1. *EASL Clinical Practice Guidelines on sclerosing cholangitis. J Hepatol. 2022;77(3):761-806.*

2. *Nielsen MJ, Thorburn D, Leeming DJ, Hov JR, Nygård S, Moum B, et al. Serological markers of extracellular matrix remodeling predict transplant-free survival in primary sclerosing cholangitis. Aliment Pharmacol Ther. 2018;48(2):179-89.*

3. *Vesterhus M, Nielsen MJ, Hov JR, Saffioti F, Manon-Jensen T, Leeming DJ, et al. Comprehensive assessment of ECM turnover using serum biomarkers establishes PBC as a high-turnover autoimmune liver disease. JHEP Rep. 2021;3(1):100178*

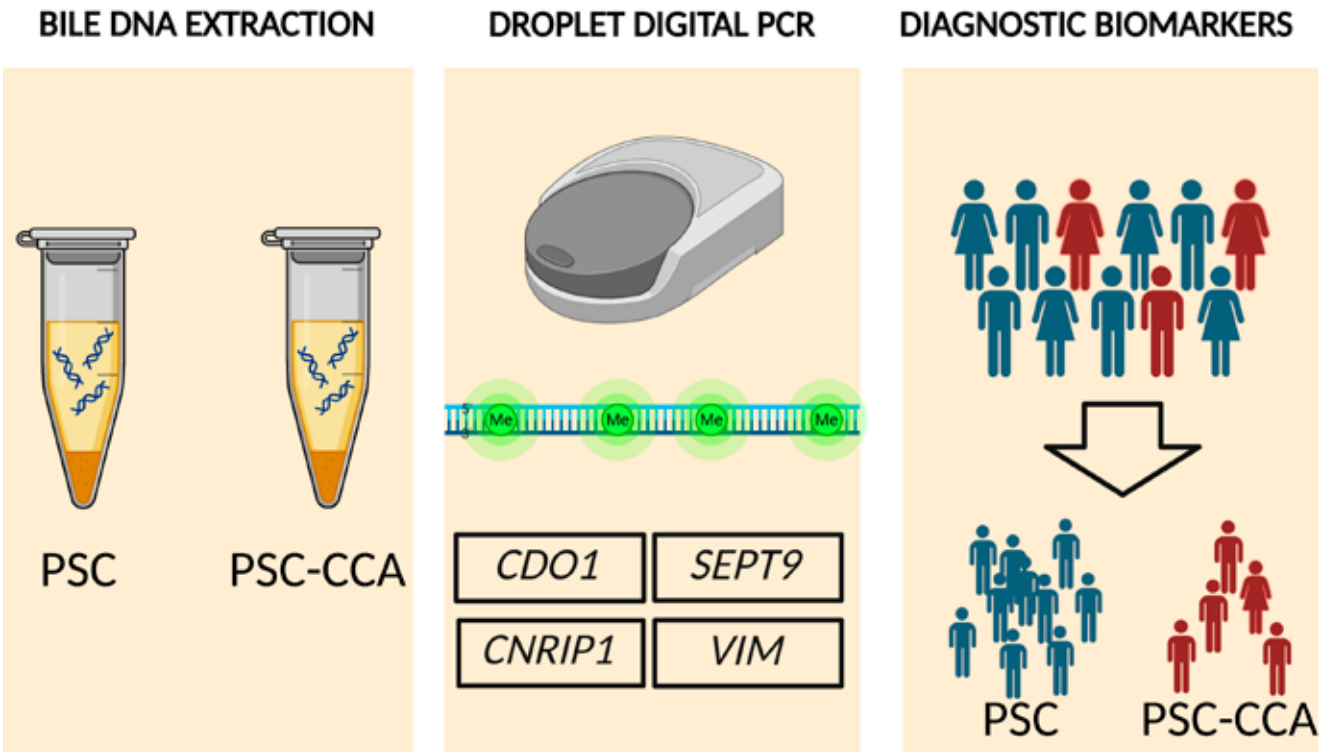
4. *Hirschfield GM, Chazouillères O, Drenth JP, Thorburn D, Harrison SA, Landis CS, et al. Effect of NGM282, an FGF19 analogue, in primary sclerosing cholangitis: A multicenter, randomized, double-blind, placebo-controlled phase II trial. J Hepatol. 2019;70(3):483-93.*

5. *Thorburn D, Leeming DJ, Barchuk WT, Wang Y, Lu X, Malkov VA, et al. Serologic extracellular matrix remodeling markers are related to fibrosis stage and prognosis in a phase 2b trial of simtuzumab in patients with primary sclerosing cholangitis. Hepatol Commun. 2024;8(7).*

METHYLATION BIOMARKERS FOR EARLY DETECTION AND DIAGNOSIS OF CHOLANGIOCARCINOMA IN PSC

Trine Folseraas

Cholangiocarcinoma (CCA) is a serious and often late-diagnosed cancer of the bile ducts. Unfortunately, CCA occurs more frequently in PSC than in the general population and may sometimes also affect young individuals (1). Current methods for diagnosing CCA, like blood tests, imaging and analysis of cell and tissue material from the bile ducts, often detect CCA too late for curative treatment. Establishment of novel tools that can accurately diagnose CCA at an early stage is therefore sought-for to provide effective treatment and better outcomes to individuals with CCA. Methylation markers have emerged as promising tools for early diagnosis of cancer. Methylation specific changes in the DNA where methyl groups are added to the DNA molecule. These changes can affect how genes are turned on or off. Methylation patterns specific for a cancer type can occur early during cancer development, making them useful for early diagnosis (2).
In a close and long-term collaboration with the Epigenetics group at the Institute for Cancer Research at the Norwegian Cancer Hospital we have aimed at identifying specific methylation patterns that occur in the early phase of CCA development in PSC. We first detected a panel of methylation markers that held



Research workflow for early detection of PSC-CCA. Using bile DNA methylation biomarkers via Droplet Digital PCR.

promise as early diagnostic markers for CCA using archived tissue samples from individuals with PSC alone and PSC with CCA (3). We further identified that a subset of four methylation markers (*CDO1*, *CNRIP1*, *SEPT9*, *VIM*) could diagnose CCA in PSC at early stage using DNA derived from biliary brush material and bile, see figure 1 (4, 5).
Subsequently, whole-genome methylome sequencing of fresh frozen liver tissue from individuals with PSC and PSC-CCA was conducted to identify additional markers that further enhance the distinction between benign and malignant PSC. Promising markers from this effort have been validated using bile samples from PSC biobanks in Norway, Sweden, and Finland. The manuscript from this study is expected to be finalized in 2025. Overall, the findings suggest that methylation biomarkers in bile as a liquid biopsy material have the potential to complement standard diagnostic methods for early CCA detection and may be incorporated into future diagnostic algorithms for CCA in individuals with PSC. These advancements were made possible by the technological developments led by the Epigenetics group at The Norwegian Cancer Hospital, combined with the clinical expertise and biobank resources built by the Norwegian PSC Research Center over decades.

1. *Boonstra K, Weersma RK, van Erpecum KJ, Rauws EA, Spanier BW, Poen AC, et al. Population-based epidemiology, malignancy risk, and outcome of primary sclerosing cholangitis. Hepatology. 2013;58(6):2045-55.*

2. *Vedeld HM, Folseraas T, Lind GE. Detecting cholangiocarcinoma in patients with primary sclerosing cholangitis - The promise of DNA methylation and molecular biomarkers. JHEP Rep. 2020;2(5):100143.*

3. *Andresen K, Boberg KM, Vedeld HM, Honne H, Hektoen M, Wadsworth CA, et al. Novel target genes and a valid biomarker panel identified for cholangiocarcinoma. Epigenetics. 2012;7(11):1249-57.*

4. *Andresen K, Boberg KM, Vedeld HM, Honne H, Jebsen P, Hektoen M, et al. Four DNA methylation biomarkers in biliary brush samples accurately identify the presence of cholangiocarcinoma. Hepatology. 2015;61(5):1651-9.*

5. *Vedeld HM, Grimsrud MM, Andresen K, Pharo HD, von Seth E, Karlsen TH, et al. Early and accurate detection of cholangiocarcinoma in patients with primary sclerosing cholangitis by methylation markers in bile. Hepatology. 2022;75(1):59-73.*

Project portfolio / Research groups

CLINICAL LIVER RESEARCH GROUP, OSLO

Photo: Øystein Horgmo, University of Oslo

From left: Ina Marie Andersen, Merete Tysdahl, Kristine Wiencke, Sigurd Breder, Sissel Åkra and Trine Folseraas.

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RESEARCH PROFILE

The aims of Clinical Liver Research group at Oslo University Hospital Rikshospitalet:

1. Establish and implement accurate markers of risk, early diagnosis, and therapeutics in cholangiocarcinoma (CCA) in PSC.
2. Evaluate and improve the selection and clinical outcomes in liver transplantation for individuals with PSC.

The overall aim of our research is to enhance outcomes for individuals with PSC before and after liver transplantation. The Norwegian PSC biobank and patient registry, coordinated and operated daily by the clinical research group, provides an essential resource to achieve these research objectives.

The Norwegian PSC biobank and patient database

We prioritize supporting and strengthening PSC research both nationally and internationally by contributing patient material and clinical data to various PSC-related registries and projects. By providing

data and samples to initiatives like the National Network for Autoimmune Liver Diseases, the International PSC Study Group (IPSCSG), the International PSC Registry (IPSCR), and the European Network for the Study of Cholangiocarcinoma (ENSCCA), we actively facilitate research on PSC, other liver diseases, and hepatobiliary cancers. In 2024, we contributed clinical data and biobank samples to multiple research projects and observed the results and publications from previous contributions (see publication list for details).

Biomarkers of risk and early diagnosis of PSC-associated cholangiocarcinoma

We continue to focus on risk prediction markers, accurate early diagnostic markers, and molecular characterization of PSC-associated CCA, is to provide PSC patients with meaningful surveillance and earlier diagnosis of CCA.

In 2024, we published results from a long-term collaboration with the Department of Pathology at the University Hospital of Heidelberg and the Institute of Clinical Molecular Biology, Christian-Albrechts-University Kiel, where we performed whole exome sequencing and copy number variation analysis of PSC-associated CCA (see highlighted papers for details).

Collaborating with the Biodonostia Institute, Donostia University Hospital, San Sebastian, Spain, we have analysed the protein content of extracellular vesicles from bile samples derived from the NoPSC biobank from PSC and/or CCA patients. We identified promising protein biomarkers for predicting and accurately diagnosing CCA in PSC patients. This manuscript is expected to be finalized by 2025.

In another long-term collaboration with the Epigenetics group at the Institute for Cancer Research at the Norwegian Radium Hospital, we have applied whole-genome methylome sequencing on fresh frozen liver tissue from PSC and PSC-CCA patients to detect candidate markers for early diagnosis of CCA.

Liver transplantation in PSC

In collaboration with Annika Bergquist's research group at Karolinska Institutet, Stockholm, Sweden, we have conducted retrospective studies on a cohort of over 500 PSC patients who underwent liver transplantation. We have evaluated diagnosis, selection, and outcomes for individuals with PSC treated with liver transplantation due to suspected biliary dysplasia or CCA. The results from these studies will be published in 2025. We are expanding this cohort and pursuing further projects to investigate other important topics related to liver transplantation in PSC.

Industry- and investigator initiated clinical trials

Contributing to drug development in PSC through clinical trials is a priority for NoPSC. In 2024, we participated in the phase III clinical trial and extension phase for nor-ursodeoxycholic acid. Additionally, we are involved in an investigator-initiated trial led by NoPSC, assessing the efficacy of vitamin B6 supplementation in PSC. The prospective PSC patient cohort, followed by our group at Rikshospitalet since 2013, provides a crucial recruitment base for these clinical trials.

KEY COLLABORATORS

- **The Department of Pathology, Oslo University Hospital, Rikshospitalet, Norway**
- **The Epigenetics Group at the Department of Cancer Prevention, Institute for Cancer Research, the Norwegian Radium Hospital, Norway**
- **Karolinska University Hospital, Stockholm, Sweden**
- **Helsinki University Hospital, Finland**
- **Biotech Research and Innovation Centre, Department of Health and Medical Sciences, University of Copenhagen, Denmark**
- **Institute of Clinical Molecular Biology, Christian-Albrechts-University, Kiel, Germany**
- **The Department of Pathology at the University Hospital of Heidelberg, Germany**
- **Biodonostia Institute, Donostia University Hospital, San Sebastian, Spain**
- **The Mayo Clinic, Rochester, USA**
- **The IPSCR, Amsterdam AMC, the Netherlands**
- **The International PSC Study Group (IPSCSG)**
- **European Network for the Study of Cholangiocarcinoma (ENSCCA)**
- **COST Action CA22125: Precision medicine in biliary tract cancer**

CLINICAL LIVER RESEARCH GROUP, BERGEN

Photo: Private

From left; Holmfridur Helgadottir; Mette Vesterhus, Karen Rønneberg and Cesilie Dahll.

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RESEARCH PROFILE

The projects of the Clinical Research group in Bergen aim to identify and evaluate prognostic biomarkers and surrogate markers of disease activity and severity in PSC. We are also engaged in developing instruments to reliably measure quality of life and symptoms in PSC. The outcomes of our research may improve patients' lives by allowing tailored, personalized clinical follow-up, and improving clinical trials design. To achieve these goals, we have established a large, prospective, Scandinavian biobank (ScandPSC) and National network for autoimmune liver diseases.

BIOMARKERS OF DISEASE ACTIVITY AND PROGNOSIS

Since we identified and validated the ELF test as a strong prognostic marker in PSC, our continued research has contributed to the accumulation of sufficient data to support recommendations by current EASL guidelines to use the

ELF test in PSC to assess prognosis and disease progression. In August 2024, ELF test was made clinically available in Norway. We are continuing our studies of the ELF test in collaboration with international partners with the goal of achieving regulatory (FDA, EMA) approval for ELF test as a surrogate marker in clinical trials in PSC. Through a long-standing collaboration, we are pursuing studies of tailored and dynamic biomarkers of fibrosis (e.g. PRO-C3) in PSC with similar goals in collaboration with corporate partner Nordic Biosciences in Denmark.

LARGE INTERNATIONAL STUDIES

Recognizing that PSC is a complex disease, we hypothesize that a multimarker panel, combining biomarkers of various components of PSC pathogenesis, may perform better than single biomarkers to capture disease risks and outcomes in people with PSC. With the aim of identifying a multimarker prognostic panel, we have collected a large patient panel from Scandinavia and the Mayo Clinic for which we are now exploring a broad range of biomarkers reflecting various disease pathways in PSC. With over 900 patients, this will be one of the largest biomarker studies performed in PSC. In the frames of an IPSCG flagship project, we have initiated and lead the FICUS biomarker project seeking to further characterize ELF test as well as a range of other proposed biomarkers.

PROSPECTIVE COHORTS AND CLINICAL TRIALS

We manage and monitor the national AIL-study and the prospective ScandPSC biobank. Out of the over 800 included PSC patients, we have contributed 20%. Clinical and imaging data from our patients have contributed to NoPSC-initiated and international studies. We have contributed to the phase II and III NUC studies and aim to participate in upcoming clinical trials.

PRURITUS AND PROMS

Pruritus may significantly reduce the quality of life in PSC. In an ongoing study, coordinated by postdoc Helgadottir, we combine targeted proof-of-concept analyses of candidate pruritogens and hypothesis-free global metabolomics to identify the cause or pathways of cholestatic itch and identify therapeutic targets. Reliable evaluation of patient-reported outcomes (PROM) is important. We participate in the international validation and development studies of two different PROM instruments: SCCS and the UK quality-of-life measure for PSC. Postdoc Helgadottir serves a leading role in NoPSC's engagement.

THE AIL-STUDY AND SCANDPSC

The National network for autoimmune liver diseases (AIL-study) is a multicenter, observational cohort study established 2019 and collecting clinical and PROM data as well as biological samples at annual study visits. Through the effort of dedicated local study teams, the AIL-study recruits participants from 24 centers across all Norwegian health regions, currently including over 800 people with non-transplant PSC. As the AIL-study was established as an extension and expansion of a previous prospective cohort study dating back to 2013, a proportion of the patients now have over 10 years of prospective follow-up.

Important activities in 2024 have been to revise the data collection tool and prepare a robust data monitoring plan in collaboration with the other clinical groups. Adherence to the biobanking protocol and documentation is being reviewed. PROM studies and clinical trials are recruiting participants from the patient cohort. In preparation for increased utilization of the data registry and biobank, we are working to streamline the workflow for extraction of data and biological samples. All participants of the AIL-study who have PSC are also included in the ScandPSC biobank (page 22).

KEY COLLABORATORS

- The Mayo Clinic, Rochester, USA
- Karolinska University Hospital, Stockholm, Sweden
- Nordic Biosciences, Herlev, Denmark
- IPSCR, Amsterdam AMC, the Netherlands
- Helsinki University Hospital, Helsinki, Finland
- UCL Institute for Liver and Digestive Health, Royal Free Hospital, London, UK
- Bevital, Bergen, Norway
- International PSC Study Group (IPSCSG)
- Norwegian Centre of Excellence in Gastrointestinal Ultrasonography, Bergen, Norway

CLINICAL LIVER RESEARCH GROUP, AKERSHUS UNIVERSITY HOSPITAL (AHUS)

Photo: Stian Ødegård, Ahus.

From left: Ragnhild S Bergheim, Narcisa M Lupu, Aida K Lunder, Anne Negård, Kristin K Jørgensen, Stine Dommersnes, Mari Vingdal and Usha Tharmathas.

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RESEARCH PROFILE

The Clinical Liver Research Group at Ahus focus on developing new knowledge in terms of surrogate endpoints and novel therapies for PSC through both investigator-initiated and industry-initiated clinical trials. At Ahus, an investigator initiated clinical trial unit is being established to investigate new therapeutic options for PSC. This will be achieved by implementing appropriate study designs, suitable

study and control groups, valid biomarkers and relevant study endpoints.

PROJECTS

INVESTIGATOR-INITIATED CLINICAL STUDIES

Novel clinical trials

We are in the process of establishing a clinical liver trial unit at Ahus, with the objective of recruiting individuals with PSC into high-level, multicenter clinical trials implementing valid biomarkers and study endpoints. Our aim is to explore new therapeutic options for PSC, an area that is under-explored hence no medical therapy for PSC is currently available.

AIL and ScandPSC

Our research group participates in the National Network for Autoimmune Liver Diseases (AIL-study) in Norway. This large multicenter observational study follows around 800 PSC patients annually, with our included patients comprising nearly one fifth of the cohort. The collaboration also includes work in a parallel Swedish initiative, jointly comprising the ScandPSC cohort (see page 22 for more details).

Pyridoxine Treatment in Primary Sclerosing Cholangitis (the PiPSC study)

This multicentre, phase II, double-blinded, randomized controlled cross-over study compares pyridoxine supplementation to a placebo (refer to page 20 for more details). Our centre is participating in the trial, with PhD candidate Tharmathas responsible for screening, inclusion, and follow-up of patients. The study results concerning exploratory biomarkers for efficacy assessments will be included in her thesis.

IBSEN III: Liver disease in inflammatory bowel disease (IBD)

We participate in the IBSEN III study led by Prof. Marte L Høyvik at Oslo University Hospital. This prospective, observational trial consists of a large, population-based inception cohort including all incident IBD patients in the South-Eastern Health Region of Norway over a three-year period (2017-2019). In particular, we contribute to the PSC-screening branch of the study by performing liver MRIs in all included patients at Ahus in conjunction with the five-year follow-up, with the aim of exploring the incidence and type of liver pathology in a large cohort of Norwegian IBD-patients.

We also engage in international PSC study initiatives and have contributed to several research articles from these collaborations (see publication list for details).

INDUSTRY-INITIATED CLINICAL STUDIES

Our study group participates in multiple phase 2 and 3 industry initiated, randomized, controlled clinical trials in autoimmune liver diseases (PSC and primary biliary cholangitis), evaluating treatment with norucholic acid (NCA), obeticholic acid, and bezafibrate. We are involved in the NUC-5/PSC phase 3 study comparing NCA with placebo over 96 weeks, proceeded by an additional double-blind phase and lastly an open-label extension phase. We are also participating in the NUC-11/BIO phase 1 study on the pharmacokinetics of NCA in PSC patients and the NUT-22/PSC phase 3 open-label study investigating the efficacy and safety of NCA in PSC. Our group also provides scientific advice to the industry on drug development for autoimmune liver diseases.

KEY COLLABORATORS

- Dr. Falk Pharma
- The IBSEN III (IBD in South-Eastern Norway) study group, Ullevål University Hospital, Oslo, Norway
- Karolinska University Hospital, Dept. of Gastroenterology and Dept. of Radiology, Stockholm, Sweden.
- Nordic Bioscience A/S, Herlev, Denmark
- Mayo Clinic, Dept of Radiology and Division of Gastroenterology & Hepatology, Minnesota, USA
- The IPSCR, Amsterdam AMC, the Netherlands
- The International PSC Study Group (IPSCSG)
- Hannover Medical School, Department of Diagnostic and Interventional Radiology, Germany.

EXPERIMENTAL HEPATOLOGY RESEARCH GROUP

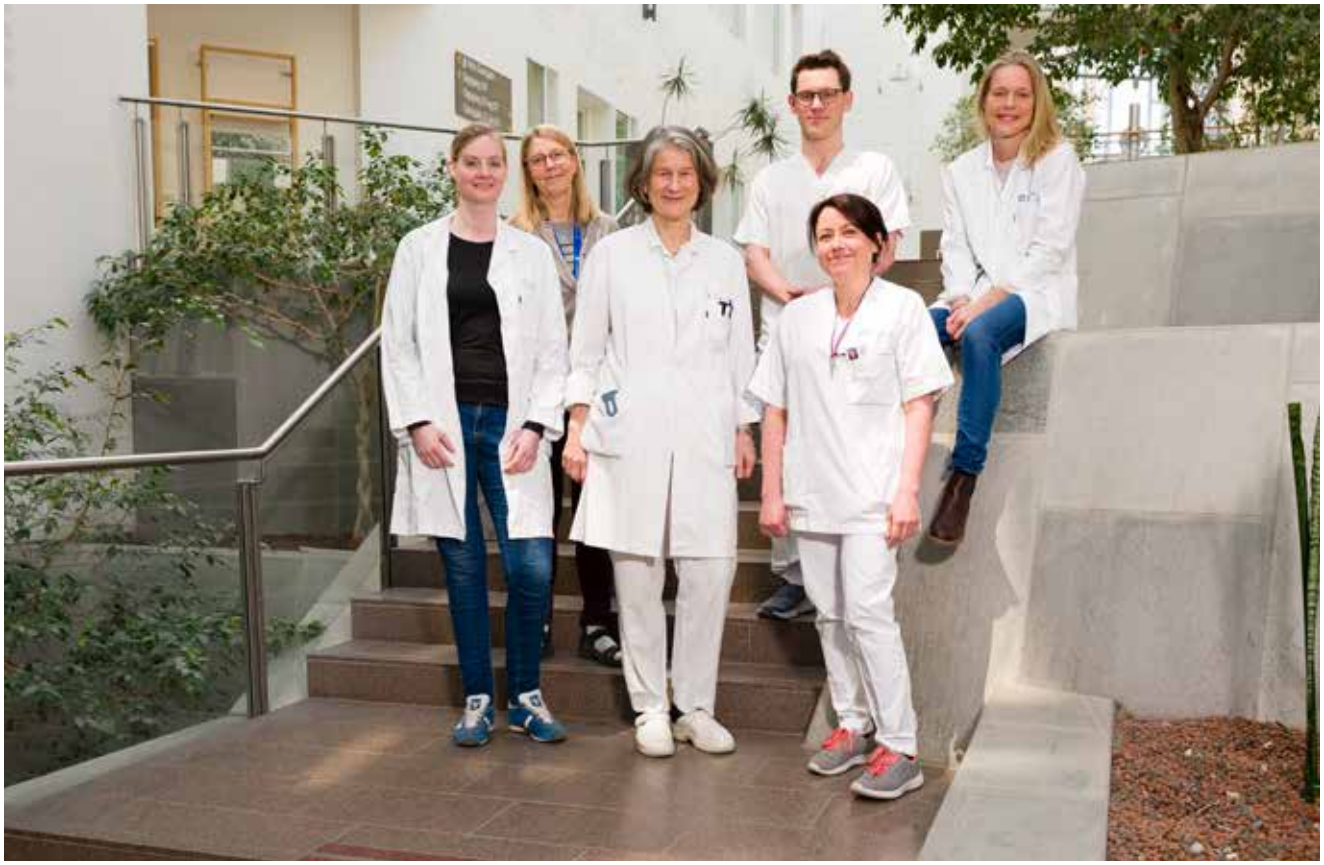

Photo Øystein H. Horgmo, University of Oslo

From back left; Brian Chung, Sarah Peisl, Lisa Brynjulfsen, Jonas Øgaard, Marie-Christin Röcklinger, Elisabeth Schrumpf, Jeremy (Wen Jie) Yeoh, Henry W. Hoyle, Anna Frank, Oda Ramberg and Kathrine Nordhus
From front left: Oline Hovland, Espen Melum and Enya Amundsen-Isaksen

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RESEARCH PROFILE

The experimental liver research group is one of the three NoPSC research groups based in Oslo and focuses on experimental and translational studies related to primary sclerosing cholangitis (PSC). Our laboratory activities take place at the Research institute of Internal Medicine. In 2024 the group consisted of the group leader, four senior researchers, four postdocs, four PhD students, the lab manager, one researcher and two technicians. The overarching topic in the group is to understand mechanisms regulating cholangitis with a clear focus on immunology and the interaction of the immune system with the microbiome and the role of cholangiocytes in propagation of inflammatory processes. A key aspect is to establish new methods for characterizing and modelling PSC.

Our strong collaboration with the Hybrid-technology-hub on the bile-duct-on-a-chip is crucial for the project-team working on the chip. As part of our participation in the University of Oslo's SPARK program for commercialization we further develop the innovative aspect of the chip and submitted a patent for the original design which we now call version 1 of the chip. In parallel with this we develop version 2 of the chip where we will integrate the immune system. This task will be central for Dr. Wen Jie (Jeremy) Yeoh who joined the group as a postdoc in October 2024. Jeremy received his masters from Imperial College in London and then trained in immunology at the University of Bern where he defended his PhD thesis giving him an ideal background for taking on this task. Our collaboration with Novartis in Basel continued in 2024 and the team was strengthened with the recruitment of Dr. Marie-Christin Röcklinger who will have the main responsibility for conducting the drug-screen in Basel and the follow-up functional experiments in Oslo. Prior to joining NoPSC Marie finished her masters and PhD in Vienna where she worked on developmental biology. Access to healthy tissue for research is important and organoid technology open up new opportunities for propagating collected tissue. After approval from the regional ethics committee, we have started to generate organoids from organ donors. This was made possible by an institutional grant for biobanks that enabled us to hire Oline Øie Hovland who established our 'Living biobank' in 2024.

In our joint project with the Seoul National University, SINTEF and OsloMet that was funded through the National Research Foundation of Korea we had one workshop in Seoul, Korea and a project meeting in Oslo. Based on this collaboration a tool evaluating the PSC literature using artificial intelligence has been developed. In the CD100 project we have, based on our previous finding that the CD100 mutation contributes to pathogenic Th17 differentiation at the cholangiocyte-immune interface, performed targeted analysis of known Th17-driving factors that unexpectedly revealed strong additional pathogenic concepts, highlighting potential novel tissue-specific targets for treating biliary inflammation in PSC.
The group also completed several projects using spatial transcriptomics and single-cell sequencing to characterize human and murine bile duct inflammation in 2024. Papers based on two of these projects were submitted towards the end of 2024. Three additional projects were presented at the EASL congress as abstracts and final additional analyses were completed in 2024. The process of recruiting a new postdoc who will extend these findings and integrate the multiomic datasets with protein based data was started towards the end of the year.

In 2024 we published two papers using germ-free mice and we started the process of developing the gnotobiotic mouse facility further in collaboration with our close partner Henrik Rasmussen who is heading the OUS animal facility and the group of Johannes Hov at NoPSC. The next years will include a significant expansion in terms of technical equipment that will enable us to perform more advanced projects.

After consistently demonstrating a functional loss of CD1d on cholangiocytes from mice with a conditional deletion of CD1d in the bile ducts using organoid technology we were in 2024 able to in-detail characterize the role of CD1d on the biliary epithelium *in vivo*. This was done both in the setting of cholestasis using the bile duct ligation technique and antigen driven natural killer T-cell activation by injecting oxazolone.

GENOMICS AND METAGENOMICS RESEARCH GROUP

Photo: Åsne Rambøl Hillestad, University of Oslo

From back left: Simen Hyll-Hansen, Kristian Holm, Peder Braadland, Petra Hanzely, Jørgen Rønneberg, Sara Tjønnfjord and Hanne Lyche Alme. Front: Isma Sohail, Johannes Hov, Beate Vestad and Hanne Guldsten.

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RESEARCH PROFILE

The genomics and metagenomics group aim to characterize and understand how the human genome and the gut microbiome influence inflammatory disease, and how this knowledge can be applied clinically. Our general approach is to use unbiased discovery tools like nontargeted high-throughput omics (e.g. sequencing and metabolomics), followed by targeted hypothesis-driven methods, supported by bioinformatics and biostatistics including machine-learning.

We study primary sclerosing cholangitis both before and after liver transplantation (with or without recurrence) together with healthy individuals and patients with inflammatory bowel disease. Our main human materials are blood and fecal samples, but we are also establishing methodology for microbiota profiling in low-biomass material (blood, tissue, bile), while our experimental agenda involves germ-free, gnotobiotic and conventional mice with induced biliary or intestinal disease as well as advanced in vitro/ex vivo models (organoid systems), in collaboration with the Experimental Hepatology group.

Our current main working hypothesis is that biochemical footprints of microbial activity is driving disease. We aim to define altered functional microbial changes using metagenome sequencing (i.e. the study of all microbial genes) and metabolomics. Our first interesting finding was that altered microbial metabolism of essential nutrients is altered in PSC, with deficiency of vitamin B6 as a potential disease-modifying factor caused by microbiome changes. A clinical trial focusing on translational aspects of vitamin B6 supplementation is ongoing and aims to complete recruitment in 2025 (Pyridoxine in primary sclerosing cholangitis, PiPSC). This represents an example on how we work to identify and potentially treat altered microbial functions, defining their clinical impact as biomarkers or in therapy.

Recurrence of PSC after liver transplantation is a significant clinical problem, and our work to describe it in detail (clinically) in the Norwegian population is in its final phase. An important question is whether PSC and recurrent PSC represent the same disease, which would make recurrence useful as a "human model" of disease. This was the underlying idea of the ERC Starting Grant project *StopAutoimmunity*, which was formally completed in 2024, where we among other observations have identified overlapping features in PSC before and after liver transplantation (Hepatology 2023). Multiple other studies are in their final phase following this project. Importantly, Hov was awarded a new ERC grant in 2024 – the Consolidator grant *FatVersusBile*, which will commence in 2025 and focus on intestinal drivers of liver health.

With growing data size and complexity, we increasingly depend on bioinformatics and statistics. In our IBD focused projects, now comprising thousands of samples, in collaboration with the Inflammatory Bowel Disease in South-Eastern Norway 3 study, we now apply more advanced bioinformatics and artificial intelligence to improve the yield from big data from microbiome or metabolome analyses.

The groups also work more disease independent with *Clinical microbiota medicine*, as part of a Strategic research area at Oslo University Hospital funded from 2019-2024. In 2023 and 2024, one important focus was to increase the activity and capacity of the donor bank for fecal microbiota transplants. After following ten years of annual National Microbiota conferences in Norway, the first Nordic Microbitoa conference was successfully organized in Copenhagen in 2024 and will onwards remain a Nordic event.
Finally, we continue our agenda on the targets of autoimmunity in PSC - does it originate in the gut? And further studies of GPR35 in inflammatory disease are also ongoing, supported by funding to the center leader Karlsen and post doc Georg Schneditz.

FUNDING

The group leader was awarded an ERC Consolidator grant at the end of 2024 to the project "FatVersusBile", which will be very important in the group activities until 2030. In addition, the group is funded by multiple grants from the Regional Health Authorities of South-Eastern Norway, as well as Canica, and one UIO funded postdoc.

KEY NATIONAL AND INTERNATIONAL COLLABORATORS

- Locally, the group has extensive collaborations ongoing within NoPSC and the Research Institute of Internal Medicine, multiple clinical research groups (including in particular the IBD group at the Ullevål campus) as well as pathology and radiology.
- Regionally and nationally, the group has been working in the ReMicS network (Regional research network for clinical Microbiota Science), with Hanne Guldsten as administrator.
- Internationally, we have strong collaborations both within and outside the International PSC Study Group, with the currently strongest links to Swedish groups in Stockholm, Gothenburg and Uppsala, in addition to US groups (Brigham, Mayo clinic) and Germany (Kiel).

Strategic Prospective Scandinavian PSC Biobank (ScandPSC)

ScandPSC merges two strong scientific environments in Norway and Sweden in a collaborate effort to collect a large prospective biological and clinical sample collection. In Scandinavia, a PSC "hot-spot", high willingness in patients to participate in research studies and limited loss to follow-up coupled to unique national registries, provide ideal conditions for high-quality, well-powered prospective studies.

AIMS

ScandPSC aims to establish the world's largest prospective PSC biobank and register, and use this as a platform for clinical trials and biomarker discovery.

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Kristin Kaasen Jørgensen, Professor, MD, PhD
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Lina Lindstöm, MD, PhD
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Martin Cornillet, MSc, PhD
Karolinska University Hospital, Sweden

STEERING COMMITTEE

National PI Annika Bergquist (Sweden) and Mette Vesterhus (Norway). Lead physicians from collaborating centers (CI) in Norway and Sweden.

MONITORING BOARD

The Monitoring Board of the Norwegian PSC Research Center (NoPSC) will oversee the management of the funds.

Employed Project Coordinator

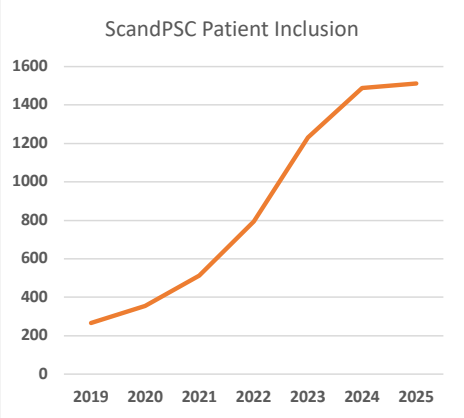
Kristin K. Jørgensen, MD PhD, Norway.

FUNDING

The project is funded by a generous donation from the Halloran family foundation.

PROJECT STATUS 2024

The initial goal of including 1300 individuals was passed in May 2024. By 31.12.2024, the prospective cohort included biobank serum samples from 1488 people with PSC (a 21% increase from 1230 in 2023), of which 788 in Norway and 700 in Sweden. By 31.03.2025, ScandPSC included data and biobank samples from an estimated > 4000 study visits for 1512 individuals recruited at 34 active centers (Norway 24, Sweden 10). Almost 400 have 5 years of follow-up in the study. Study participants exhibit typical demographic characteristics: median age of about 37 years at inclusion; the majority are male (63%) and have IBD (ca 80%); about 10% have PSC-AIH and 7% have smallduct disease.



ECONOMY

Expenses 2024		
Norway	Salaries	434 502
	Biobank- and visit-related expenses	1 185 933
	Meetings	25 821
	VAT, compensated	-306 889
Sweden	Biobank- and visit-related expenses	1 228 023
Total expenses 2024		**2 567 389**
Income	From 2022 and new donation	-5 912 215
Transfered to 2025		**-3 344 826**

PRIORITIES FOR 2025

As the primary goal for participant inclusions has been achieved, the main priority has shifted from study expansion to the running, refining, and utilizing of the ScandPSC prospective data registry and biobank. New participants may still be recruited, but emphasis is put on securing follow-up visits. In 2024, limited baseline clinical characteristics and demographics of the ScandPSC cohort were presented at international conferences. The data collection tool has been updated, and a robust monitoring plan was developed and will be implemented in 2025, securing “regulatory quality” of collected data. Important priorities in 2025 will be monitoring of data quality and streamlining the workflow for extraction of data and biological samples in order to prepare for scientific utilization of this huge resource. When the data quality and workflow are satisfactory, the ScandPSC data and biobank will be open for applications from the scientific community, and information will be made available via a new website that will be published soon.

Photo: Private

HIGH-QUALITY BIOBANK

The ScandPCS Biobanking follows a common Standard Operating Procedure (SOP). Biological sampling is decentralized at active canters, but sample storage is centralized. In Norway the samples are stored centrally in the fully automated, high-security Biobank Haukeland in Bergen.

The fully automated biobank facility at Haukeland is demonstrated for the ScandPSC PI’s.

Brief annual report IPSCSG 2024

In 2024, the International PSC Study Group (IPSCSG) made progress in advancing research and fostering collaboration in the realm of Primary Sclerosing Cholangitis (PSC), defined by different events and an updated leadership team, which reinforced our commitment to better understand and manage PSC.

Photo: Private

IPSCSG biennial meeting in Stockholm, Sweden, September 9th-10th 2024.

One of the significant changes in 2024 was the formation of a new steering committee, composed of a diverse group of experts from around the world: David Assis (New Haven, USA), Nora Cazzagon (Padova, Italy), Aliya Gulamhusein (Toronto, Canada), Cara Mack (Wisconsin, USA), Bregje Mol (Amsterdam, The Netherlands), Palak Trivedi (Birmingham, UK), and Mette Vesterhus (Bergen, Norway). September 9th-10th 2024 we held our biennial IPSCSG meeting in collaboration with the Karolinska Institutet and Karolinska University Hospital in Stockholm, Sweden. Special thanks to Annika Bergquist and Niklas Björkström for organising this meeting. This gathering provided a valuable opportunity for researchers to present their work, share insights, and discuss common challenges in the field, for more than 120 participants.

At the meeting Dr. Tobias Poch received the IPSCSG Award for his excellent contributions to research on primary sclerosing cholangitis (PSC), in particular the efforts related to defining the role of T cells in immune pathogenesis.

A prominent highlight of the year was the Young Investigator Workshop, which took place on December 16th-17th in Birmingham, United Kingdom excellently organised by Palak Trivedi and Sarah Al-Shakhshir. The workshop brought together 27 emerging researchers focused on clinical and translational research in PSC and related autoimmune and cholestatic liver diseases. Participants had the chance to network with

IPSCSG includes members from cities and countries all over the world, as illustrated here.

established experts while addressing crucial topics, such as disease epidemiology, designing effective clinical trials for rare conditions, and developing risk scores and biomarkers that improve patient management. This event emphasized the importance of incorporating patient-reported outcomes into research to ensure that studies address the real needs of those affected by PSC.

Throughout the year, the IPSCSG remained actively engaged at key liver conferences, including the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD). These conferences offered additional avenues for dialogue about recent findings and opportunities to strengthen our global network.

As we look to the future, the IPSCSG is dedicated to continuing our work in PSC research through collaboration and education. We want to express our gratitude to all our members for their hard work and passion. With your support, we're excited about what lies ahead for the group and the progress we can create together in the years to come.

Photo: Private

Young Investigator Workshop in Birmingham, UK, December 16th-17th 2024.

On behalf of the IPSCSG secretariat at University Medical Centre Hamburg-Eppendorf, Germany

Highlights

Norwegian Gastroenterology Association

Sigurd Breder contributed as board member in the Norwegian Gastroenterology Association (Norsk Gastroenterologisk Forening, NGF) also in 2024. Kristin Kaasen Jørgensen was leader and Trine Folseraas board member in the NGF Interest group for Liver Disease and Espen Melum in charge of NGF's research funds. At NGF's annual meeting 8-10th of February 2024 at Lillehammer; Sara Tjønnfjord received the NGF research grant.
NoPSC also contributed with an article in the NGF news magazine (NGF-nytt) in 2024; Håvard Midgard and Mette Vesterhus with «Faglig veileder for utredning og oppfølging av leverfibrose».

In the media

UiO, Faculty of Medicine, featured researcher Xiaojun Jiang from NoPSC on their website news feed in January 2024 under the headline «New insight into severe liver disease". The article highlights the key pints from the publication in the journal Gastroenterology entitled "Cholangiocytes Modulate CD100 Expression in the Liver and Facilitate Pathogenic T-Helper 17 Cell Differentiation". UiO also featured Tom Hemming Karlsen receiving the EASL honorary award acknowledging his major scientific contributions in Hepatology.

NoPSC scientific retreat

In 2024 the NoPSC retreat was held at Oscarsborg April 29th to 30th.
The program consisted of several PSC research topic sessions and workshops, with speakers from NoPSC and invited speakers and

collaborators from the newly formed Resnek Family Center for PSC Research in Boston, Josh Korzenic and Erik Hasenoehrl (photo), aiming to strengthen interactions between two strong PSC research centers.

Guest professor meeting

The 2024 guest professor meeting took place 21st to 22nd of October, with Dr. Fotios Sampaziotis and Dr. Jan Tchorz. The meeting included sessions with groups and individuals for discussions and supervision.

Mayo collaboration

Our collaboration with Professor Konstantinos Lazaridis and coworkers at the Mayo Clinic continued in 2024 with regular "Lab Retreats"; meetings with short presentations from the Mayo and NoPSC groups on Zoom, focused on potential collaborative projects.

Monitoring board meetings

On the 20th of June the spring Monitoring Board meeting for NoPSC was held. NoPSC leader Tom Hemming Karlsen presented the accounting and the annual report from last year and Henry W. Hoyle presented "Status of the Bile-ducton-a-chip project".
The second Monitoring Board meeting in 2024 took place on 14th of December. The budget for 2024 was presented and approved and MD and PhD student Lise Katrine Engesæter presented the following; "Residiv av Primær skleroserende cholangitt".

IPSCSG

The biannual IPSCS meeting was held in Stockholm 9-10th of September 2024. NoPSC attending with many participants and presenters; Usha Tharamathas, Henry Hoyle, Johannes Hov, Mette Vesterhus and Lise Katrine Engesæter. In addition, Trine Folseraas and Espen Melum served as chairs. Short IPSCSG meetings was as usual arranged at the "International Liver Conference" by EASL in Milan, Italy in June and at "The Liver Meetings" by AASLD in San Diego, USA in November. In addition, Young Investigator Workshop 2024 (focusing on Clinical and Translational Research) was arranged 16-17th of December in Birmingham, UK. Holmfridur Helgadottir and Usha Tharamathas participated from NoPSC.

Visiting scientist

In 2024 we had two "Visiting scientist" meetings. Prof. Annalisa Berzigotti and Dr. Mirjam Kolev from University Hospital of Berg, Switzerland was here May 28th. And Dr. Jesus Banales and Dr. Ainhoa Lapitz Dambolena visited on September 24th, giving us days of fruitful discussion with research experts from other institutions.

The Norwegian Liver Meeting

At the annual Norwegian/National Liver Meeting 18th of September 2024 in Oslo, conducted by the Interest group for liver disease in Norway. Many NoPSC members were present, Johannes Hov had a presentation and

Kristin Kaasen Jørgensen and Trine Folaseras served as chairs.

The International Liver Congress

The annual International Liver Congress organized by the European Association for Study of the Liver (EASL) was in Milan, Italy, 5-8th of June 2024. NoPSC had several posters (Jonas Øgaard, Sigurd Breder, Markus Jördens and Lisa Brynjulfsen) and oral presentations (Henry Hoyle, Sigurd Breder, Markus Jördens and Johannes Hov). Every year at the annual EASL Congress, EASL acknowledges major and longstanding scientific contributions made by scientists in the field of liver research, and in 2024 Tom Hemming Karlsen received this acknowledgement (photo).

PSC Partners Annual Conference

The conference in 2024 was held October 18-20th in Phoenix, Arizona USA. Tom Karlsen co-organized the event with Ricky Safer from PSC Partners. Karlsen and Johannes Hov contributed with lectures and in the pre-meeting discussions of the International Collaborative Research Network.

Collaborative research seminar Norway/Japan

On September 11th, the Norwegian PSC research center hosted 8 PSC researchers from leading universities in Tokyo and Kyoto to establish new collaborations and develop research topics of common interest (photo).

The Liver Meeting

The American Association for Study of the Liver Diseases (AASLD) annual meeting “The Liver Meeting” was held in San Diego, USA 15-19th of November 2024. From NoPSC Sara Tjønnfjord presented a poster and Lise Kathrine Engesæter had an oral presentation.

Foreningen for Autoimmune Leversykdommer (FAL)

The ongoing collaboration with the patient organization FAL is both useful and enjoyable, and we are very pleased to involve patients as active participants in reviewing new and ongoing research projects. In 2024 our meeting with FAL on the October 8th at Rikshospitalet focused on presenting several grant applications by Espen, Melum, Johannes Hov, Sheraz Yaqub, Trine Folseraas and Kristoffer Lassen. FAL held their biannual conference November 8th in Oslo. Both Katrine Engesæter and Kristin Kaasen Jørgensen contributed with presentations.

The Biomedical alliance in Europe

The Biomedical Alliance in Europe (BioMed Alliance) is a unique initiative of leading European medical societies that aim to facilitate and improve biomedical research in Europe. Tom Hemming Karlsen is on the Board of Directors in the BioMed Alliance, as a President-Elect.

European Network for the Study of Cholangiocarcinoma

NoPSC is a member of the European Network for the Study of Cholangiocarcinoma (ENS-CCA) which constitutes of research groups located in 13 European countries and represents CCA interests from basic, translational and clinical research. The network is organized into 7 Working Groups dealing with interrelated aspects of CCA, and Trine Folseraas is vice leader for the Molecular profiling Working Group.

Online educational course at UEG

In 2024, an online course on Primary Sclerosing Cholangitis was developed by Trine Folseraas and Johannes Hov and published as part of the United European Gastroenterology educational services to European gastroenterologists and gastroenterologists in training.

Grants and Awards

GRANTS

Group leader Trine Folseraas received a PhD grant of NOK 3.882.000 for 3 years for the project: “Bringing next generation diagnostics and risk prediction tools for cholangiocarcinoma to the clinic”. MD Ina Marie Andersen was engaged as a PhD student in November 2024 in this project.

The prestigious ERC Consolidator Grant was in 2024 awarded to Johannes Hov. The grant amounts to 2 million Euros over five years starting in May 2025 for the project “Fatty liver versus autoimmunity of the bile ducts - defining the gut signals driving steatosis and inflammatory disease of the gut-liver axis (FatVersusBile)”.

Johannes Hov also received a donation from PSC partners for $ 60.000 over 2 years to support «Research toward treatments and a cure for PSC and closely associated diseases».

AWARDS

NoPSC leader Tom Hemming Karlsen was given an Award from EASL which acknowledges major scientific contributions made by scientists in the field of liver research. The award was presented at the International Liver Conference in June in Milan.

The “Thirty-Eight Annual Gerald Klatskin Lectureship” was awarded to Tom Hemming Karlsen at Yale School of Medicine/ Yale Liver Center April 24th, 2024.

Senior researcher Xiaojun Jiang received the Oslo University Hospital award for best article published in the second part of 2023. The prize was awarded in a ceremony June 7th, 2024.

At Norsk Gastroenterologisk Forening (NGF) annual meeting February 2024 at Lillehammer, PhD student Sara Tjønnfjord received NGF’s research grant of NOK 40.000 for the project “Colon-dependent microbial drivers of primary sclerosing cholangitis”.

New employees

Usha Tharmathas MD
PhD student

«Passionate about hepatology – unlocking PSC through biomarker science»

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Engineer

«You’ll find me in the cell lab»

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Marie-Christin Röcklinger MSc,
PhD Postdoctor

«Turning tiny PSC organoids into big drug-screens»

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Wen Jie (Jeremy) Yeoh MSc, PhD
Postdoctor

«Immunologist by trade, cake enthusiast by nature - passionate about immunology and disease»

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Ina Marie Andersen MD
PhD student

«Passionate about making elaborate to-do lists and providing patients with the best possible care»

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Networks and Collaborations

KEY LOCAL COLLABORATORS AT OSLO UNIVERSITY HOSPITAL

Research Institute for Internal Medicine (RIIM)

The research groups led by Espen Melum and Johannes E.R. Hov respectively are located at RIIM and several collaborative projects are established with the groups of, among others, Prof. Marius Trøseid, Prof. Thor Ueland and Prof. Bente Halvorsen.

Department of Transplantation Medicine

Prof. Pål-Dag Line and Dr. Bjarte Fosby collaborate with NoPSC on projects related to liver transplantation in PSC and induced murine models of cholangitis.

Department of Gastrointestinal and Child Surgery

Ass. Prof. Sheraz Yaqub, Prof. Knut-Jørgen Labori and other co-workers in the Section of hepatobiliary and pancreatic surgery, are valuable collaborators relating to cholangiocarcinom projects.

Department of Rheumatology, Dermatology and Infectious diseases

Rheumatologists Prof. Øyvind Molberg and Dr. Anna-Maria Hoffmann-Vold collaborate with NoPSC on immunology and microbiome studies.

Department of Pathology

Dr. Henrik Reims and Dr. Krzysztof Grzyb are both involved in the histological and immunohistochemical evaluation of tissue samples from PSC patients and samples from experimental mouse models. Prof. Frode Jahnsen is a collaborator on microbiome studies.

Department of Gastroenterology

IBD research group leader Prof. Marte Lie Høivik is an important collaborator on IBD related projects together with Department Head Associate prof. Vendel Kristensen and Prof. Asle Medhus (leader of the Division of Medicine at OUH).

Department of Comparative Medicine

For many years, NoPSC has had a close and productive collaboration with the Department Head Ass. Prof. Henrik Rasmussen and the staff at the animal facility.

Department of Medical Genetics

The Immunogenetics group, led by Prof. Benedicte A. Lie is involved in several projects related to the further characterization of the HLA association in PSC.

Institute for Cancer Research

A collaboration with Prof. Guro Lind, Department of Molecular Oncology is the basis for epigenetics-centered projects on early diagnosis of cholangiocarcinoma in PSC.

Department of Radiology

The involvement of the Department of Radiology at Rikshospitalet in the prospective follow-up of PSC patients has been crucial for the success of the initiative. We are particularly grateful to Dr. Andreas Abildgaard, Dr. Gunter Kemmerich and Dr. Ida Björk for their active contributions.

Department of Paediatric Research

Department head Prof. Runar Almaas is an important collaborator on liver transplant research and pediatric PSC, and Dr. Gareth Sullivan on regenerative medicine.

Hybrid Technology Hub at University of Oslo

Recent work on organ on a chip includes a close collaboration with Prof. Hanne Scholz and Center director Prof. Stefan Krauss at the Center of Excellence Hybrid Technology Hub.

KEY NATIONAL COLLABORATORS

Foreningen for Autoimmune Leversykdommer (FAL)

The ongoing collaboration with the Norwegian organisation for people with PSC, and it's leader Espen Bunæs is very valuable and appreciated.

Akershus University Hospital

NoPSC group leader Prof. Kristin K Jørgensen is affiliated with the Department of Gastroenterology at Akershus University Hospital. Prof. Anne Negård and Dr. Aida Kapic Lunder at the Department of Radiology are important contributors and collaborators in MRI studies.

Haukeland University Hospital and University of Bergen

For the prospective PSC cohort and advanced imaging modalities there is a close collaboration with Prof. Odd Helge Gilja and several other researchers at the Section for Gastroenterology and the Norwegian Centre of Excellence in Gastrointestinal Ultrasonography, at the Medical Department at Haukeland University Hospital in Bergen.

BEVITAL AS

Prof. Per Magne Ueland and co-workers at BEVITAL are important collaborators in projects related to metabolomic biomarkers, including biomarkers of microbial function.

Haraldsplass Deaconess Hospital, Bergen

The NoPSC Clinical Research Group in Bergen, led by Prof. Mette Vesterhus, is located here. This encompasses also other strong collaborations at Haraldsplass Deaconess Hospital.

KEY INTERNATIONAL COLLABORATORS

The Nordic Liver Transplant Group
Collaborators in Helsinki (Dr. Arno Nordin), Stockholm (Dr. Carl Jorns), Gothenburg (Ass. Prof. William Bennet) and Copenhagen (Dr. Allan Rasmussen) are involved in several projects where data from the Nordic Liver Transplant Registry are required.

Karolinska University Hospital, Stockholm, Sweden
Prof. Annika Bergquist is a close collaborator on clinical projects in PSC and is also participating in our genetics studies. Annika Bergquist is also a part of the management group of the Strategic Prospective Scandinavian PSC Biobank.
Prof. Niklas Björkström (former Guest Professor at NoPSC) is involved in projects relating to human immunology in PSC.

Molecular and Clinical Medicine, Wallenberg Laboratory, University of Gothenburg, Sweden
Prof. Fredrik Bäckhed is an expert on gut microbiota, metabolism and gnotobiotic animals and has for several years been an advisor and collaborator on gut microbiota studies in mice. Antonio Molinaro is a close collaborator as new group leader within clinical and experimental hepatology.

Uppsala University, Sweden
Associate prof. Daniel Globisch is an import collaborator, providing unique expertise on the biochemistry of microbial metabolites. Shared Uppsala/NoPSC postdoc Alejandro Chinillach works on joint projects in the Globisch lab.

Nordic BioScience, Denmark
Morten Karsdal, CEO of Nordic Biosciences in Denmark, has focused his research on the discovery and development of novel biochemical markers of fibrosis. NoPSC collaborates with Nordic BioScience on several projects related to the characterization of fibrosis and the development of new, targeted, PSC-specific fibrosis markers as prognostic tools in PSC.

Institute for Clinical and Molecular Biology, Christian-Albrechts University, Kiel, Germany
Prof. Stefan Schreiber and Prof. Andre Franke's groups in the German excellence cluster "Inflammation at interfaces" are involved in technically advanced projects within the genetic and metagenomic projects. We also have a fruitful ongoing collaboration with Dr. Hesham El Abd and Dr. Aya Mahdy.

University Hospital Heidelberg, Germany
Prof. Peter Schirmacher, Head of Pathology at the University Hospital Heidelberg, represent a world-leading center in hepato-biliary pathology. Together with Dr. Benjamin Goeppert he provides pathology expertise to collaborative projects related to genomic profiling of PSC-associated biliary tract cancers. We also have a strong collaboration in projects related to circulating biomarkers in PSC.

Department of Internal Medicine, Vivantes Humboldt Hospital, Berlin, Germany
Dr. Tobias J. Weismüller is an important collaborator within the IPSCSG, particularly regarding the International PSC Study Group database project comprising more than 8000 PSC patients.

University Medical Center Hamburg, IPSCSG
From 2023 the administration of IPSCSG (International PSC study Group) has been in the capable hands of Prof. Christoph Schramm and Prof. Ansgar Lohse at University Medical Center Hamburg, Germany.
Amsterdam medical Center, Netherlands, IPSCR
We have a close collaboration with Prof. Cyriel Ponsioen and Prof. Ulrich Beuers at the University of Amsterdam's Faculty of Medicine, among other related to projects outgoing from the International PSC registry (IPSCR) initiative led by Prof. Cyriel Ponsioen.

University of Cambridge, Addenbrookes's Hospital, UK
Prof. Arthur Kaser (former Guest Professor at NoPSC), Head of the Division of Gastroenterology and Hepatology at Addenbrooke's Hospital, Cambridge, UK, is still involved in one of the main translational work packages related to the functional characterization of one of the PSC risk genes; GPR35. This project is funded by the Regional Health South-East Health Authority in Norway and involves postdoc Georg Schneditz and Dr. Nicole Kaneider-Kaser. Ongoing collaboration with Dr. Fotis Sampaziotis (Guest Professor at NoPSC) at Cambridge Biorepository for Translational Medicine at the Wellcome - MRC Cambridge Stem Cell Institute has proved extremely valuable regarding organoids and regenerative medicine.

Sapienza, Università di Roma, Italy
Prof. Eugenio Gaudio, Domenico Alvaro and coworkers are experts on biliary tree stem cells, and material from the NoPSC Biobank are being used to explore these cells in PSC patients. In addition, we have a close collaboration with the COST-Action European Cholangiocarcinoma Network where Prof. Vincenzo Cardinale serves as COST-Action chair.

Biodonostia Research Institute, Donostia University Hospital, San Sebastian, Spain
Prof. Jesus M. Banales is the Head of the Liver Diseases Group at the Biodonostia Research Institute and the coordinator of the European Network for the study of Cholangiocarcinoma. Dr. Banales serves as an important collaborator

on projects related to PSC-associated biliary tract cancers.

Hospital Clinic of Barcelona, Spain
In 2020 we established collaboration with the Barcelona Clinic Liver Cancer (BCLC) group. This center, now led by Maria Reig, is world leading on hepatocellular carcinoma research. Key collaborating researcher is Marco Sanduzzi-Zamparelli.

University of Bern, Switzerland
The collaboration with Annalisa Berzigotti at the Department of BioMedical Research in Bern has intensified with her visit to NoPSC in Oslo and MD and PhD student Sarah Peisl coming to Oslo to work in our labs.

Lithuanian University of Health Sciences, Vilnius, Lithuania
After a grant from the EEA Baltic research funds to the project "Gut-blood-liver axis: Circulating microbiome as non-invasive biomarker for Inflammatory Bowel Disease (IBD) and Primary Sclerosing Cholangitis", chaired from Lithuania. We still collaborate with the PI Gediminas Kiudelis and other project partners from Latvian Biomedical Research and Study Centre and University of Tartu, Estonia The project involved both the Hov and Melum groups.

Toronto Centre for Liver Disease, Toronto General Hospital, Canada
Dr. Gideon Hirschfield (former Birmingham, UK) continues the collaboration with NoPSC regarding characterization of the HLA related immune response in PSC from Toronto Centre for Liver Disease, Toronto General Hospital, Canada. Biostatistician Bettina E. Hansen is leading the statistical analyses of clinical data collected in the International PSC Study Group (IPSCSG) database project, assisted by Dr. Aliya Gulamhusein at the same institution.

The Mayo Clinic, Rochester, USA
Collaboration with Dr. Konstantinos Lazaridis at the Mayo Clinic in Rochester has been very valuable regarding our projects on the genetics of PSC. Via infrastructure at the Mayo Clinic, DNA from PSC patients in USA and Canada are collected and utilized in local projects as well as for verification of findings in genetic studies at NoPSC. We also collaborate with Dr. John Eaton and his research environment on imaging studies.

Brigham and Women's Hospital, Harvard Medical School, Boston, USA
Prof. Richard Blumberg is an important collaborator on Dr. Espen Melum's projects related to NKT cells. In addition, multiple projects in collaboration with Dr. Joshua Korzenik on PSC pathogenesis have been initiated in the context of the Resnek Family Center for PSC Research. A center which is dedicated to discovering what causes PSC and developing and testing new therapies for this disease.

Japan
From 2024 we have intensified our collaboration with Janapese researcher; Prof. Atsushi Tanaka at Teikyo University School of Medicine, Ass. Prof. Nobuhiro Nakamoto and Dr. Haruka Nakaharu at Keio University School of Medicine, Tokyo and Dr. Sachiko Kanai from University of Tokyo. In addition, collaborations with Dr. Masahiro Shiokawa at Kyoto University on antibodies in PSC have been initiated.

Publications 2024

HIGHLIGHTED PUBLICATIONS

Frank AK, **Chung BK**, De Novales MLL, **Engesæter LK**, **Hoyle HW**, **Øgaard J**, Heslop J, **Karlsen TH**, Tysoe O, Brevini T, Tchorz JS, Vallier L, Mohorianu I, Sampaziotis F, **Melum E** (2024) **Single-Cell Transcriptomic Profiling of Cholangiocyte Organoids Derived from Bile Ducts of Primary Sclerosing Cholangitis Patients** Dig Dis Sci, 69 (10), 3810-3823

We have previously established a method for culturing and expanding cholangiocytes from the bile ducts of PSC patients *in vitro*, in form of three-dimensional organoids. In the current study, we investigated whether those PSC patient-derived organoids retained disease-relevant features when expanded over several passages *in vitro*. We thus isolated cholangiocytes from PSC and non-PSC patients undergoing routine ERCP, expanded the cells over several passages in form of organoids, and performed single cell sequencing of the resulting cells. Comparison of cells derived from PSC vs. non-PSC disease controls shows that cholangiocytes, derived from the damaged area within the bile ducts of PSC patients, are largely similar to control organoids after extended organoid culture and do not display any functional or genetic disease-related features. We however found a differential regulation of cancer-associated genes in cells derived from patients that at a later timepoint developed dysplasia, highlighting the potential of organoids for discovering new biomarkers for diagnostic purposes

Grimsrud MM, Forster M, Goeppert B, Hemmrich-Stanisak G, Sax I, Grzyb K, **Braadland PR**, Charbel A, Metzger C, Albrecht T, Steiert TA, Schlesner M, Manns MP, Vogel A, Yaqub S, **Karlsen TH**, Schirmacher P, **Boberg KM**, Franke A, Roessler S, **Folseraas T** (2024) **Whole-exome sequencing reveals novel cancer genes and actionable targets in biliary tract cancers in primary sclerosing cholangitis** Hepatol Commun, 8 (7)

This paper presents the largest and most comprehensive assessment of mutational characteristics of biliary tract cancer (BTC) in PSC to date, finalizing a long-term effort to describe the genomic landscape of BTC in PSC. It follows a more limited, targeted sequencing effort published in Hepatology in 2020. We collected tissue samples from 52 PSC patients with BTC, covering all anatomical locations. Through extensive histomorphological characterization, exome DNA sequencing, and whole genome copy number variation analysis, we revealed multiple novel candidate cancer genes, prognostic markers, and potential therapeutic targets. These findings enhance our understanding of BTC development in PSC and could serve as a platform for developing personalized treatment approaches.

Oldereid TS, **Jiang X**, **Øgaard J**, **Schrumpf E**, Bjørnholt JV, Rasmussen H, **Melum E** (2024) **Microbial exposure during early life regulates development of bile duct inflammation** Scand J Gastroenterol, 59 (2), 192-201

Through a range of studies, the importance of the microbiome in PSC has been established and we have previously also demonstrated that this is the case in animal models of PSC. In this paper we utilized the NOD.c3c4 model with spontaneous inflammation in the bile ducts to examine the temporal association with exposure to the microbiome. We used germ-free animals and introduced the mice to a microbiome at birth or weaning compared to mice born and raised in a regular animal facility. Exposure to bacteria at birth gave similar bile duct inflammation as mice born in the regular facility while later introduction of a microbiome delayed the development of bile duct inflammation.

OTHER RESEARCH ARTICLES FROM NoPSC

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Indole 3-acetate and response to therapy in borderline resectable or locally advanced pancreatic cancer
Front Oncol, 14, 1488749

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Medical treatment of primary sclerosing cholangitis: What have we learned and where are we going?
Hepatology (in press)

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Nat Rev Gastroenterol Hepatol, 21 (12), 869-884

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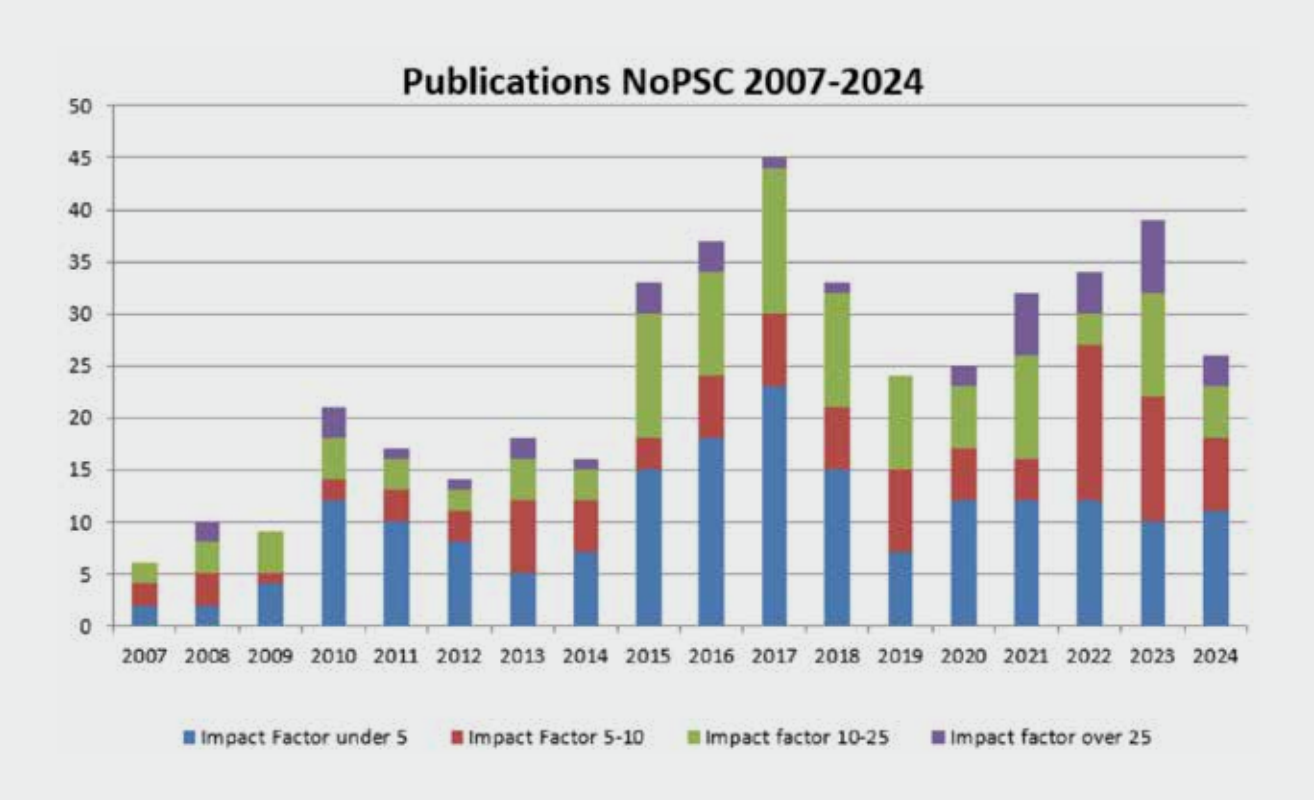


NOPSC

Photo: Private

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UiO : University of Oslo