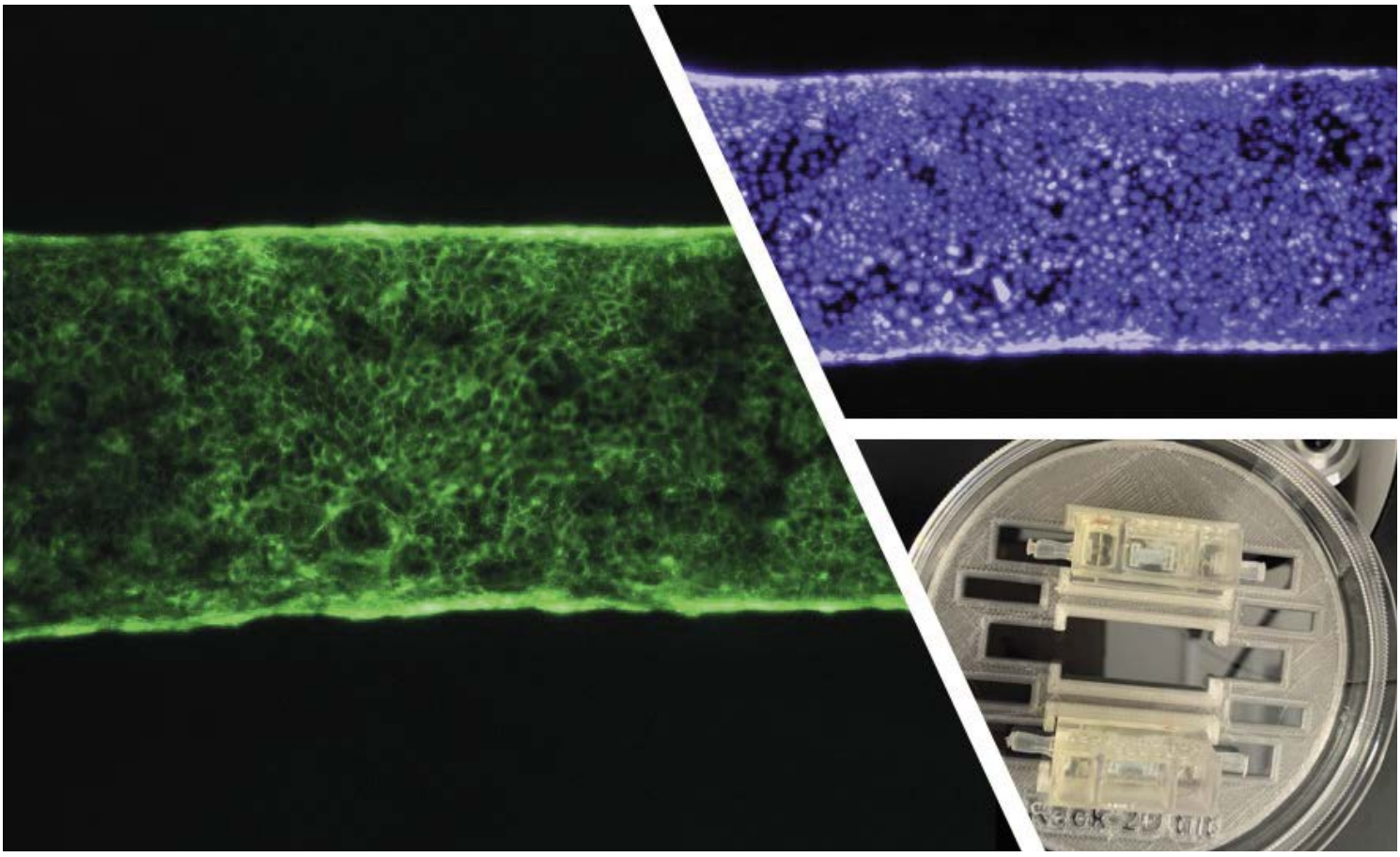
Oslo universitetssykehus



Norwegian PSC Research Center

ANNUAL REPORT 2021

NOPSC

Visit the NoPSC web pages: *www.ous-research.no/nopsc and www.med.uio.no/klinmed/english/research/groups/primary-sclerosing-cholangitis/*

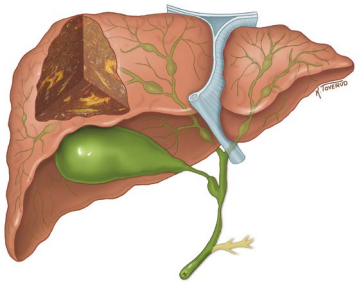
UiO : University of Oslo

Norwegian Primary Sclerosing Cholangitis Research Center (NoPSC)

ANNUAL REPORT 2021

What is PSC?

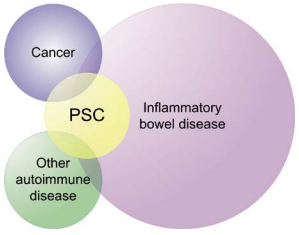
Primary sclerosing cholangitis (PSC) belongs to the group of autoimmune liver diseases.



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

There is an increased risk of cancer of both the bile ducts (160-1500x) and the large bowel (5x). PSC is more common in Northern Europe, where approximately 1:10.000 individuals are affected. 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 often have concurrent inflammatory bowel disease (IBD). Disease course is highly variable, and the time from diagnosis to liver transplantation may thus vary from 10-25 years. Individuals with PSC often suffer from fatigue, itching and repeated bacterial infections.



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

NOPSC
Norwegian PSC Research Center

Content:

NOPSC ANNUAL REPORT 2021

More information at the web pages:
www.ous-research.no/nopsc
www.med.uio.no/klinmed/english/research/groups/primary-sclerosing-cholangitis/

FRONT PAGE: *"3D reconstruction of a bile duct in vitro" E-cadherin and Dapi staining. Photo: Anna Frank*

ILLUSTRATIVE PHOTOS: *Øystein Horgmo UiO*

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SAMPLES: 220

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

Leader´s Corner

The year of 2021 marks a distinct change in orientation of NoPSC, towards clinical utility. The process affiliated with the loss of the governmental "gift reinforcement funds" related to the core Canica grant for the center, and the persistent lack of institutional support for all of our research groups led to a prolonged process of assessing alternatives for going forward by the management group throughout this year. The process was coupled with several significant scientific developments; most notably the *in vitro* opportunities offered by the "bile duct on a chip" (and intermediates) from the experimental group, the clinical interventions made possible by the newest microbiome findings of the genomics group, and the opportunities for clinical trials and biomarker queries opened up by the ScandPSC cohort set up by our clinical groups with the support from the Halloran family foundation.

Translational research takes time. In hepatology, a famous example is that of hepatitis C – and the 30 years journey from the discovery of the virus to the arrival of curative drugs. A fundamental question for us in revising our forward strategy was thus to clarify where we stand within such a journey. To me the most prominent answers after almost 15 years of NoPSC are; a) we have a dedicated team led by a "next generation" of four talented, independent and now senior group leaders, b) we have a world-leading "PSC research machine" with all the necessary components in place – cutting edge methodologies, model systems, patients cohorts and unique biobank collections, c) strong capacity for competitive fundraising, with success evident from all relevant funding bodies at national (e.g. the Norwegian Research Council and Helse Sør-Øst) and international (e.g. EU and National Institutes of Health) level, and d) a top level network of collaborators, all over the world.

In these annual reports we have presented the classical measures of success in science; a rare collection of extremely high-level publications of scientific breakthroughs; successful grant applications with subsequent growth of the center to a staff now counting more than 30; new PhDs; and awards to our researchers as a token of excellence. Working with patients you sometimes wonder about the relevance of these metrics, unless they are also reflected by change in clinical practice. A clear message has thus been provided to our team; looking back 10 years from now – at the next future "checkpoint" - our main criteria of success should be related to the question: what can we do for our patients today, that was not possible 10 years ago? Along the way, we must train and nurture the next generation of PSC researchers – and hopefully discover aspects of biology that will guide a next transformative phase of our research, which ultimately will also have clinical implications.

After 15 years, philantropy is still the backbone of NoPSC, and this warrants some reflections. Despite the success of the center, in publications, in competitive grant achievements, and also in methodological developments important for the broader Oslo research environment (e.g. microbiota assessments), our access to institutional support is still extremely limited. Reasons for this are probably manifold, including the rarity of PSC, but also signify deficits in the flexibility and organization of institutional support mechanisms.

The support from Canica for NoPSC over the years, and more recently from the Halloran family foundation for the ScandPSC network, has been provided with a different mindset than what we unfortunately face within our institutions: a grand vision for change for people with PSC, trust and stability. The stepping up of Canica and Stein Erik Hagen to not only fill-in the gaps left by the cancelled gift-reinforcement, but also add a "super reinforcement" will allow us to take full advantage of our current translational research portfolio. It comes from our side with a clear responsibility to deliver and focus the efforts where they matter the most. We will need to work in new ways, in particular with industry, and most of all, it calls upon us to keep working very hard. We should use the opportunities offered by our unique research platform to take a leap towards the end of the PSC translational journey.

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 research related to basic and clinical aspects of the chronic liver disease Primary Sclerosing Cholangitis.

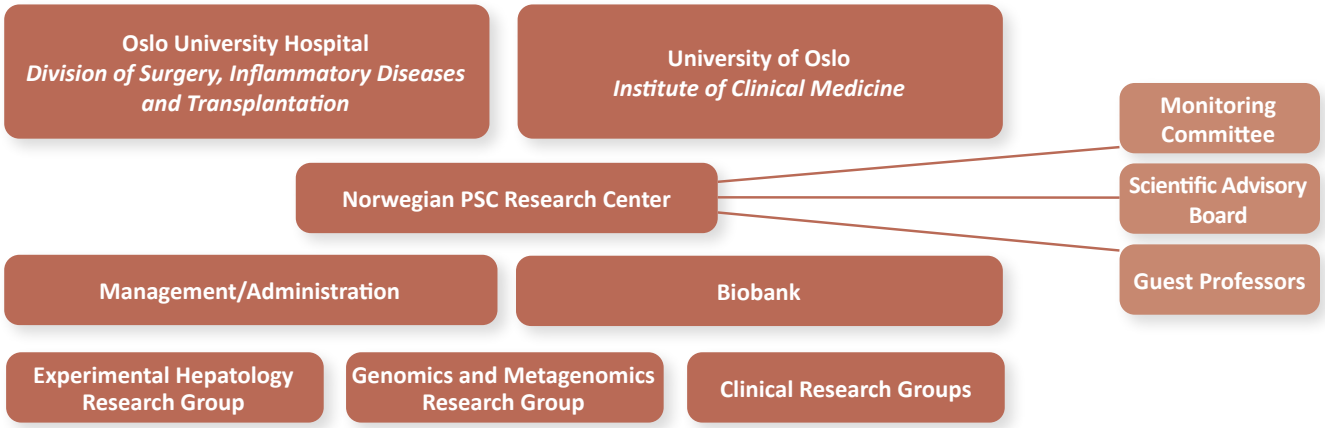
The philantropic funding is made with a grand vision to make a difference for individuals with PSC, and has given the research environment stability to prosperously grow its activity with 10 year horizons for each funding period.

Aims of the NoPSC organization

- Ensure targeted and prudent management of the private donation
- Motivate high-quality PSC research in Norway
- Coordinate and distribute resources for PSC research in Norway
- Establish international collaborations when needed
- Establish and run Biobank and PSC Registry

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, Inflammatory Diseases and Transplantation. 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 Unit for Gastroenterology and Hepatology at the Department of Transplantation Medicine, Oslo University Hospital, and Haraldsplass Deaconess Hospital, Bergen, respectively.



MONITORING BOARD

The Board monitors that the Center is managed according to the Aims. Next year's budget is discussed in the autumn, while the Annual report and the accounting are reviewed at the spring/summer meeting. The scientific activities of the center are also presented at the Monitoring Board meetings.

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Prof. Dag Kvale,
Head of the Institute of Clinical Medicine, University of Oslo

Nina Paulsen
Canica A/S

Dr. Morten Tandberg Eriksen, *Head of Div. of Surgery, Inflammatory Medicine and Transplantation, OUH Rikshospitalet*

Hans Mossin
Director, Faculty of Medicine, University of Oslo

Dr. Daniel Sørli
Canica A/S

Prof. Bente Halvorsen,
Head of the Research Institute of Internal Medicine, OUH Rikshospitalet

Prof. Tom Hemming Karlsen,
Center leader, is also part of the monitoring board.

GUEST PROFESSORS

Ass. Prof. Niklas Björkström
Unit of Gastroentero-logy and Rheumatology, Karolinska University Hospital, Huddinge, Sweden

Prof. Massimo Pinzani,
Institute of Immunity & Transplantation Royal Free Hospital, London, UK

SCIENTIFIC ADVISORY BOARD

The Scientific Advisory Board (SAB) was formally established in 2015 and reviews the center biannually.

Prof. Herbert Tilg
University of Innsbruck, Austria

Prof. Terje Espevik
University of Science and Technology (NTNU), Trondheim, Norway

Prof. Tore Kvien
University of Oslo, Norway

MANAGEMENT

The management has the overall responsibility for the day-to-day work performed at the Center.

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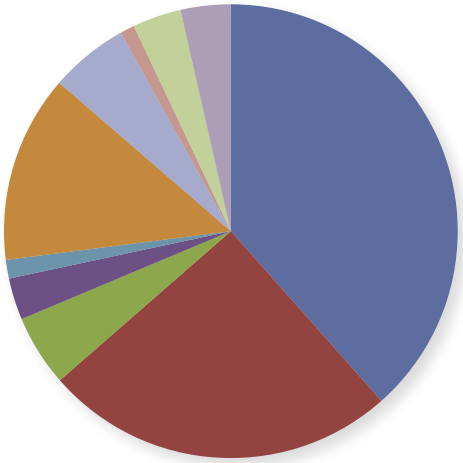
Accounting

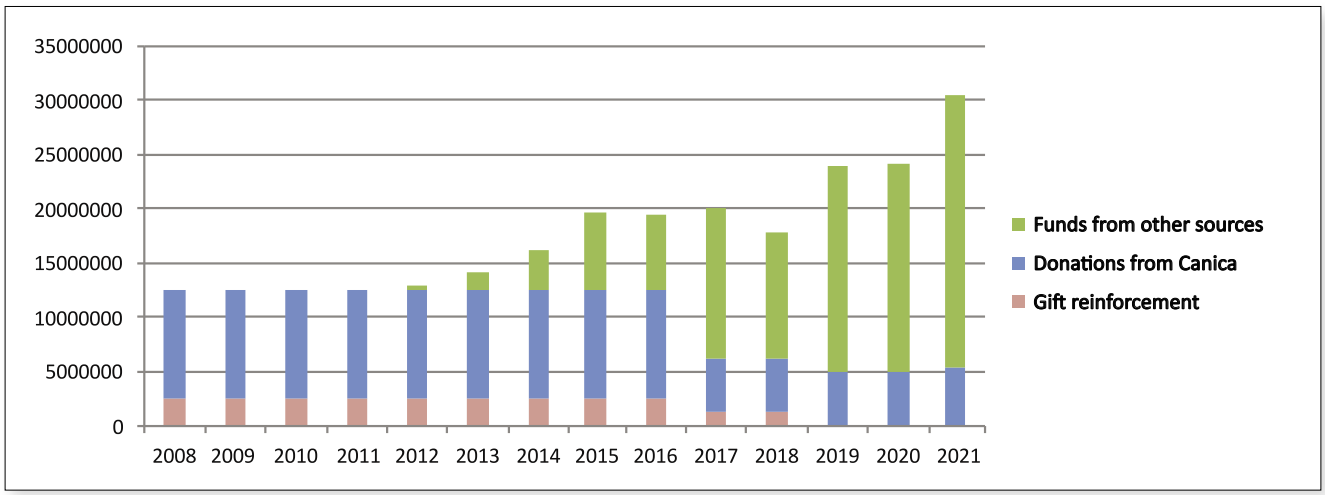
In 2021 the amount of expenditures from Canica funding was NOK 8.244.000,-. Overall the expenditure of all projects within the center amounted to NOK 21.442.000,-, of which NOK 13.198.000,- in 2021 were covered by other independent competitive grants, largely form the South-East Norway Regional Health Authorities and the Norwegian Research Council.

	OSLO UNIVERSITY HOSPITAL		UNIVERSITY OF OSLO	
	INCOME	**EXPENSES**	**INCOME**	**EXPENSES**
TRANSFER FROM 2020	-398 122		6 364 009	
INTEREST				
FROM CANICA			5 000 000	
OTHER INCOME	643 032			
TRANSFER FROM UiO	3 806 564			3 806 564
WAGES		2 933 006		1 215 198
OVERHEAD		324 067		143 140
INFRASTRUCTURE		31 777		
OTHER OPERATING EXPENCES		3 584 187		12 706
TRANFER TO 2022		**-2 821 563**		**6 186 401**

	2021
Canica	8 244
S-E Norway Regional Health Authorithy	5 389
Norwegian Research Council	1 092
University of Oslo	637
Scientia fellow	286
ERC grant	2 867
Strategic support funds OUH	1 200
PSC Partners	219
ScandPSC	745
Other	763
Thousand NOK	**21 442**

This pie chart shows the expenditure distribution between the different funds:





The Lancet Liver Commision History

On November 1st 2017, leader of NoPSC, Tom Hemming Karlsen, at that time Secretary General of the European Association for the Study of the Liver (EASL), met with Chief Editor Richard Horton at Rikshospitalet in Oslo to discuss the possibility of a Lancet commission to delineate problems and solutions for individuals with liver disease in Europe. The decision was to proceed with such a joint project between EASL and the Lancet. After his term on the EASL Governing Board, Tom Hemming Karlsen served as chair for the commission, together with Patrizia Burra from Padova, Italy, and Michael Manns from Hannover, Germany.

A Lancet commission is a scientific review, inquiry, and response to an urgent, and perhaps neglected or understudied, health predicament. It should be data-driven, science-led, include international collaborations, multiple disciplines and aim for transformational change, especially focused on policy or political action. A complex organization of more than 50 contributors across 9 working groups was established to deliver on the project which was structured into five components; a) burden of liver disease in Europe and mapping of relevant policies, b) stigmatization related to liver disease, c) primary care hepatology, d) multi-disciplinary educational opportunities, e) disease specific aspects.

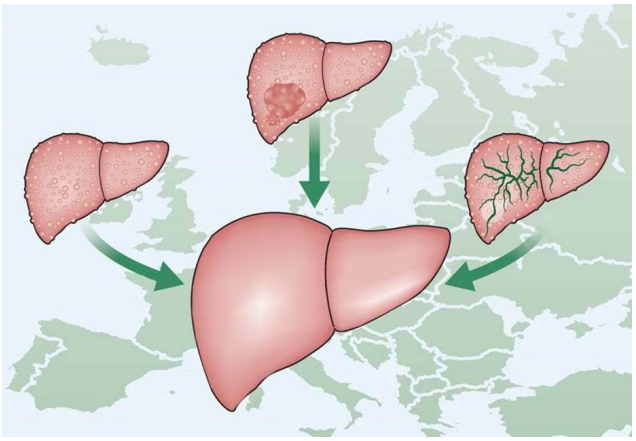
EU president Ursula von der Leyen at The EASL-Lancet Liver Commission lauch December 2nd 2021.

The commission report was launched December 2021, spanning almost 60 pages of a special issue of The Lancet, and was accompanied by three Editorials, one of which reviews the role of Tom Hemming Karlsen in the field of PSC as a background to his contribution as first author to the commission report.

The report achieved massive international attention, and both the EU President Ursula von der Leyen and The Lancet Chief Editor Richard Horton delivered talks at the launching seminar, which had to be done online due to the arrival of the omicron variant of Covid-19 at the time.

A key finding of the report was that liver disease is a major source of mortality and morbidity of young individuals in Europe. Hence, a key emphasis of the report was made to children and young adults. This is particularly relevant to PSC, which was also highlighted in the report, with suffering and substantial health burden (also as measured by health care costs) at young age. Also, a call is made for reducing stigmatization of individuals with liver disease. Stigmatization affects not only individuals with alcohol-related liver disease or hepatitis due to intravenous drug use, but also individuals with autoimmune liver diseases, PSC included, who suffer from the prejudice that all liver disease is self-inflicted. A special article in Aftenposten to this point was written by Tom Hemming Karlsen and Mette Vesterhus from NoPSC.

The commission provided a landscape for follow-up work spread across 10 recommendations, five which are predominantly related to the health care sector and health care providers, and five of which are predominantly oriented to policy and policy makers. Each recommendation is coupled with practical suggestions for action. Many of the recommendations hold strong relevance for PSC, for instance that on the need for systems for early diagnosis and interventions prior to irreversible fibrosis. It is also to hope that with the recommendations on how to reduce stigma for individuals with liver disease, people with PSC will receive better care and be able to talk more openly about their condition.



1. *Karlsen TH, Sheron N, Zelber-Sagi S, Carrieri P, Dusheiko P, Bugianesi E, Pryke R et al. The EASL–Lancet Liver Commission: protecting the next generation of Europeans against liver disease complications and premature mortality. The Lancet 2021;399: 10319*
2. *Cooke GS and Nayagam S. Liver disease: at the heart of public health challenges for Europe in the 21st century. The Lancet 2021; 399:10319*
3. *Kleinert S and Horton R. An urgent challenge for Europe: from tackling liver diseases to protecting liver health. The Lancet 2021; 399: 10319*
4. *Watts G. Tom Hemming Karlsen: hepatologist with a public health message. The Lancet 2021; 399: 10319*

Drugging the bug? A PSC perspective to an institutional research priority area

Johannes R. Hov

The links between the gut microbiota and human diseases are under intense investigation. Many chronic conditions are associated with changes in the gut microbial composition, typically characterized by a reduced diversity and altered relative abundance of multiple microbes. This is also the case in PSC, which is strongly associated with inflammatory bowel disease. There are many unanswered questions in PSC, and a desperate need to develop new tools for treatment and follow-up. Can gut microbiota be a source of such tools?

Key questions in gut microbiota research are a) is it altered in disease, b) does it influence disease course, c) can we measure it in a clinically useful way and d) can we change it to improve disease outcome or even cure diseases? In 2018, we were awarded funding within Oslo University Hospital to establish a so called “Strategic research area” of Personalized microbiota therapy in clinical medicine. The idea of the strategic research area is to gather multi-disciplinary expertise (including gastro-enterology, infectious diseases, microbiology and disease specific groups) across all parts of the hospital to improve clinical care by measuring or treating the gut.

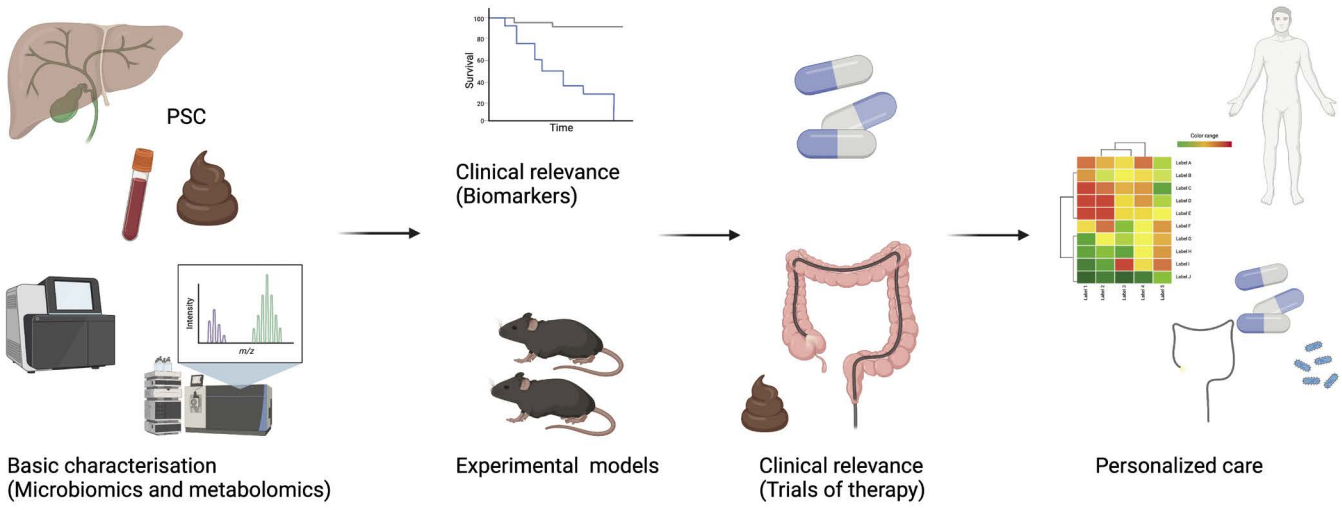
For PSC and question a) we have convincingly shown that there are major alterations in the gut microbiota (1). In a recent study where we sequenced all bacterial genes present, we found strong evidence of altered microbial “metabolic” functions, in particular in the biosynthesis of essential nutrients, like vitamin B6 (2). Low levels of vitamin B6 was found in patient blood and was associated with a more severe disease course, which could mean that vitamin B6 and other microbial metabolites represent potentially clinically relevant measures (biomarkers) of disease, relevant for question c) above, and also indirect evidence of microbial influence on disease.

Stronger evidence would need experimental models. Recent data suggest that mouse models of biliary disease colonized with human PSC microbiota got more severe disease than those colonized with healthy human microbiota (3). We have therefore together with the experimental group established germ-free model systems in a special mouse facility, which enables specific investigation of the gut microbial effects on disease.

One important goal of our concept of "clinical microbiota medicine" is to treat disease. Proof-of-concept trials may both show us new treatment options (question d), but also provide support for the causal link between gut microbiota and disease activity. In PSC (internationally), there are several trials ongoing or in a planning phase related to both antibiotics targeting gut microbes (vancomycin) and fecal microbiota transplantation from healthy donors. At NoPSC, we are now initiating a clinical trial program to start the translation from basic science to clinical utility. The first microbiota-related trial will be for vitamin B6 supplementation to understand its effects on the liver and the gut of people with PSC.

Gut microbiota therapy will likely be relevant in PSC, but since the microbiota differs between individuals, probably in a personalized way. A key step to allow this direction was the establishment of a unit and donor bank for fecal microbiota transplantation. This took place in 2021 in the context of the Strategic research area and with the support and driving force of several other groups at the hospital. This donor bank will initially be the source of "unselected" therapeutic products to fecal transplantation trials run by various groups at the hospital (e.g. C. difficile infection, irritable bowel syndrome, cancer immunotherapy). With increasing understanding of disease mechanisms, the aim will be to understand which microbiota elements are the key targets, and which patients should receive which treatment (or e.g. from which donor), representing a personalized strategy.

To summarize (Figure below), the Strategic research area of Personalized microbiota therapy in clinical medicine represent the final steps of a translational research program starting with basic characterization of the microbiota in a disease (establishing relevance), linking to disease and disease course as biomarkers and experimental models, further studies with proof-of-concept interventions, at the interphase of basic and clinical medicine, and finally personalization, adapting clinical care to the individual patient, both in terms of biomarkers and therapy. The cornerstone of all these developments is our research at NoPSC.



1. *Kummen M, Holm K, Anmarkrud JA, Nygard S, Vesterhus M, Hoivik ML, Troseid M, et al. The gut microbial profile in patients with primary sclerosing cholangitis is distinct from patients with ulcerative colitis without biliary disease and healthy controls. Gut 2017;66:611-619.*
2. *Kummen M, Thingholm LB, Ruhlemann MC, Holm K, Hansen SH, Moitinho-Silva L, Liwinski T, et al. Altered Gut Microbial Metabolism of Essential Nutrients in Primary Sclerosing Cholangitis. Gastroenterology 2021;160:1784-1798 e1780.*
3. *Nakamoto N, Sasaki N, Aoki R, Miyamoto K, Suda W, Teratani T, Suzuki T, et al. Gut pathobionts underlie intestinal barrier dysfunction and liver T helper 17 cell immune response in primary sclerosing cholangitis. Nat Microbiol 2019;4:492-503.*

EXPERIMENTAL LIVER RESEARCH GROUP

From top left: Markus Jördens, Espen Melum, Anna Frank, Enya Amundsen-Isaksen, Kari Otterdal, Katrine Sivertsen Nordhus, Tine Oldereid and Xiaojun Jiang.

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The experimental liver research group is focusing on experimental and translational studies related to primary sclerosing cholangitis (PSC). Our laboratory activities take place at the Research institute of Internal Medicine. In 2021 the group

consisted of the group leader, three senior researchers, three postdocs, five PhD students, the lab manager, one full-time technician and one part-time technician. Following Anne Pharo's retirement, Oda Helgesen Ramberg took over the lab-manager responsibility. The main aim of our research is to understand mechanisms regulating cholangitis with a clear focus on immunology and the interaction of the immune system with the microbiome. In 2021 our use of techniques from regenerative medicine further increased and we also started using sequencing-based methodologies. Together with patient material, animal models and *in vitro* assays these additional techniques give us a comprehensive and complete scientific toolbox for achieving our aims.

During the last years one of our major lines of research has been to clarify the regulatory role of unconventional T-cells in bile duct inflammation and in 2021 we published a report demonstrating the presence of antigens activating natural killer T (NKT)-cells in bile. Similarly, we also demonstrated in another project that antigens for mucosal associated invariant T (MAIT)-cells are also present in bile and are defined by the microbiome. The role of the immune system during cholestasis has been a key interest of the team focusing on NKT-cells and in 2021 we expanded these projects by investigating the temporal and spatial development and specifically the contribution of the immune system using tissue transcriptomics. Another major topic of our immunology studies has been the role of CD100, which we have found to regulate cholangitis in a familiar form of PSC, and in 2021 a large collaborative paper reporting on a novel mutation in CD100 causing disease in mice and humans were published in Science Translational Medicine. In our studies using germ-free animals we have performed a range of large animal experiments to evaluate the effect on bacterial metabolites on immune system development. To aid the characterization of immune cells from these mice we have started using high-dimensional flow-cytometry with 25-colors using the BD Symphony located at the flow-cytometry core facility. The organoid and bile-duct-on-a-chip projects were further strengthened last year by the recruitment of Enya Amundsen-Isaksen as an engineer and the recruitment for the first postdoc in the Research Council of Norway funded project DUCTchip was initiated at the end of the year.

A major event for the group was the excellent defense and celebration of Natalie Lie Berntsen's thesis on June 4th with the title "The role of natural killer T cells in biliary immunology and disease". Professor Ye Oo from the University of Birmingham acted as the first opponent and Professor Susanna Cardell from the University of Gothenburg as the second opponent, and their complementary background in NKT-cells, immunology in general and hepatology led to a very interesting discussion. After being awarded a combined position with research and clinical work from her department, previous PhD student Elisabeth Schrumpf rejoined the group to work on unconventional T-cells in our ongoing projects, while at the same time developing her own research agenda related to unconventional T-cells and skin inflammation. 2021 also marked the well-deserved retirement of lab-manager Anne Pharo, who has been instrumental in establishing all current methods in the group and especially those related to experimental animal models. Although Anne will be greatly missed by all group-members, she leaves a strong and solid foundation for smooth running of the lab that we will build on in the years to come. We wish her a very happy retirement.

In June the INFLAMMABILE grant was funded by the Research Council of Norway grant with 12 mill NOK. In this project we will examine bile duct inflammation in PSC patients and mouse models at different time points using spatial sequencing and 3D immunohistochemistry. The grant was a collaboration with Brian Chung in the genomics group at NoPSC and the grant now funds a senior scientist position in the experimental group that Brian started in, in December. Markus Jördens joined the team working on sequencing based techniques in September as a PhD student funded by the German Cancer Aid foundation and his project will also encompass examination of the spatial transcriptome of cholangiocarcinoma.

GENOMICS AND METAGENOMICS RESEARCH GROUP

From top left: Mikal J. Hole, Sajan Raju, Liv Wenche Thorbjørnsen, Johannes R. Hov, Kristian Holm, Peder Braadland, Petra Hradicka, Hanne Guldsten, Maria Maseng, Beate Vestad, Simen Hyll Hansen, Lise Katrine Engesæter and Brian Chung.

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RESEARCH PROFILE

The projects in the genomics and metagenomics group aim to characterize and understand how the human genome and the gut microbiome influence inflammatory disease. We do this by applying modern genotyping and sequencing technologies, as well as metabolomics. Increasingly, experimental approaches *in vitro* and *in vivo* (mouse models) are also relevant.

Our main interest is primary sclerosing cholangitis, which we study 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, which we use for genetic (microbiome) and/or metabolomic analyses, but we are also establishing animal models for these studies in collaboration with Melum group.

In 2021, the final version of our first study of full metagenome sequencing (i.e. the study of all microbial genes) was published in Gastroenterology. We found evidence that microbial metabolism of essential nutrients is altered in PSC, with deficiency of vitamin B6 potentially of microbial origin as a particularly interesting topic. We follow up on these to establish the clinical impact of vitamin B6 in PSC and we have now received a grant to set up a clinical trial focusing on translational aspects of vitamin B6 supplementation. This represents an example on how we work to identify and potential treat altered microbial functions in PSC, 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 is the underlying idea of the ERC Starting Grant project StopAutoimmunity, which directs many of the priorities in the group. The first data on gut microbiota in this setting will be published in 2022, identifying overlapping features in PSC before and after liver transplantation. With increasing data size and complexity, we increasingly depend on bioinformatics and statistics. In our IBD focused projects, where we have used 2021 to perform microbiota profiling of >1000 samples in collaboration with the Inflammatory Bowel Disease in South-Eastern Norway 3 study, we can now apply more advanced bioinformatics and e.g. artificial intelligence to improve the yield from big data from microbiome or metabolome analyses.

The group also works more disease independent with Clinical microbiota medicine, as part of a Strategic research area at Oslo University Hospital awarded to the group in 2019. Interventions targeting the gut microbiome to treat disease may provide evidence of causal relationships between the gut microbiome and disease. In 2021, MD Cristiane Mayerhofer (co-supervised by group leader Hov) defended her thesis "Targeting the Gut Microbiota to Treat Heart Failure" on this topic. Also in 2021, a unit and donor bank for fecal microbiota transplants was formally established at Department of Transplantation. Finally, the annual National Microbiota conference was a success, this time in a hybrid format.

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 people in the group were in 2021 funded by one ERC Starting Grant, five PhD or postdoc grants and one network grant from Regional Health Authorities of South Eastern Norway, one PhD student following an industrial PhD scheme (funded by Research Council of Norway), one Strategic research area grant in Oslo University Hospital, in addition to Canica, funding one bioinformatician, and Nordforsk. In a collaboration with the Experimental group and partners from the Baltic area (driven from Lithuania) we also received from 2021 funding from the EEA Baltic research funds, which will fund one post doc starting early 2022.

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, the group has been working in the ReMicS network (Regional research network for clinical Microbiota Science), with Hanne Guldsten as administrator. After a digital conference in 2020, we successfully hosted the eight national conference on gut microbiota as a hybrid event in November 2021.

Internationally, we continue strong collaborations both within and outside the International PSC Study Group, with the currently strongest links to Swedish and German groups.

CLINICAL RESEARCH GROUP IN OSLO

From top left: Kirsten Muri Boberg, Merete Tysdahl, Sigurd Skiaker Breder, Kristine Wiencke, Trine Folseraas and Liv Wenche Thorbjørnsen.

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RESEARCH PROFILE

The projects of the clinical PSC research group aim at improving clinical outcomes for PSC patients. Over the last years we have had a particular focus on molecular characterization and identification of early detection markers and treatment targets for PSC-associated cholangiocarcinoma (CCA).

IDENTIFICATION OF EARLY DETECTION MARKERS FOR PSC-ASSOCIATED BILIARY TRACT CANCER

We have several projects ongoing exploring novel markers for early and more accurate detection of biliary tract cancer in PSC. The overall aim of these efforts is to provide PSC patients with meaningful surveillance for CCA and to enable an early and more precise diagnosis of CCA in PSC.

In collaboration with the Epigenetics group at the Department of Cancer Prevention, Institute for Cancer Research at the Norwegian Radium Hospital we have recently identified four DNA methylation markers that provide early and accurate detection of CCA in patients with PSC.

These methylation biomarkers have been analyzed using bile samples collected from more than 300 Norwegian, Swedish and Finnish PSC patients.

Findings strongly suggest that analyzing aberrant DNA methylation utilizing bile as liquid biopsy material may improve and complement current detection methods for CCA. This work was published in Hepatology in 2021 (see section on highlighted publications in 2021). We now plan to use various liquid biopsy materials from PSC patients to prospectively validate these biomarkers and to explore other promising methylation markers derived from an ongoing whole genome DNA methylation sequencing analysis of PSC-CCA tissue.

MOLECULAR CHARACTERIZATION AND IDENTIFICATION OF DRUGGABLE TARGETS IN PSC-ASSOCIATED BILIARY TRACT CANCER

In collaboration with IPSCSG and the Department of Pathology at the University Hospital of Heidelberg, we have established a collection of tissue samples derived from PSC-patients with CCA. Several projects utilizing this valuable tissue collection is now underway. In collaboration with the Department of Pathology at the University Hospital of Heidelberg and the Institute of Clinical Molecular Biology, Christian-Albrechts-University Kiel, we have performed exome sequencing of a high-quality subset of this tissue collective, which has allowed us to detect many new genomic alterations and putative therapeutic targets in PSC-CCA. This may open up for early phase clinical trials of molecular target drugs in PSC-CCA. We anticipate to publish this work by the end of 2022.

CONTINUED SYSTEMATIC BIOBANKING AND REGISTRATION OF CLINICAL DATA ON PSC PATIENTS AND RELATED COLLABORATIONAL PROJECTS

The cross-sectional biobank and database of the Norwegian PSC Research Center is steadily growing (currently including clinical data and biological samples on close to 950 Norwegian PSC patients), and represent a valuable source for PSC research both nationally and internationally.

By contributing patient data to other clinical registries administered by the National network for autoimmune liver diseases and the ScandPSC, the International PSC Study Group and the European Network for the Study of Cholangiocarcinoma, we actively facilitate research on characterization, management and treatment of PSC and biliary tract cancers. In 2021 we have actively contributed to several research articles outgoing from these collaborations.

CLINICAL TRIALS

It is of importance for NoPSC to contribute to drug development in PSC and CCA through the participation in clinical trials. NoPSC is currently involved in a phase III clinical trial for nor-ursodeoxycholic acid.

DEFINING PSC – AN INTERNATIONAL PSC STUDY GROUP (IPSCSG) CONSENSUS PROCESS

The IPSCSG commissioned a consensus process among its experts to issue a set of definitions to aid clinical trialists designing much needed clinical trials. In an extensive consensus process, the group applied a hybrid between a Delphi process and a nominal group process. Kirsten Muri Boberg and Lars Aabakken from the Clinical Research Group in Oslo participated in this project. The results were presented as a comprehensive set of consensus statements and diagnostic criteria for PSC in Gastroenterology 2021 (see p. 29).

KEY COLLABORATORS

- The Department of Pathology, Oslo University Hospital, Rikshospitalet
- 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, Helsinki, Finland
- 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 International PSC Study Group (IPSCSG)
- European Network for the Study of Cholangiocarcinoma

CLINICAL RESEARCH GROUP IN BERGEN

From top left; Mette Vesterhus, Lasse M. Giil, Kristin Kaasen Jørgensen, Guri Fossdal, Anders B. Mjelle, and Holmfridur Helgadottir.

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RESEARCH PROFILE

The projects of the Clinical Research group in Bergen aim to identify, evaluate, and establish prognostic biomarkers and surrogate markers of disease activity and severity in PSC. The ultimate goal is to contribute to the development of tools that are implemented for prognostication in clinical follow-up and for improved patient selection and effect assessment in clinical trials. The establishment of a large, prospective, biobank and a national patient cohort are important strategic aims in order to achieve these goals and to facilitate patient inclusion into clinical trials.

BIOMARKERS OF DISEASE ACTIVITY AND PROGNOSIS

We were the first to identify and validate the ELF®Test as an independent prognostic marker in PSC. Moreover, in a recent paper, we described the annual variation of ELF test compared to ALP and liver stiffness in PSC patients in a prospective panel. Our results indicated that the ELF test may have superior reliability for risk stratification compared with liver stiffness measurements in PSC.

A recent (2021) international guideline from the European Association for the Study of Liver diseases (EASL) now recommends the use of ELF test in the clinical diagnosis and follow-up of patients with PSC based on our research. In Norway, the ELF test is approved based on a Health Technology Assessment report referring our research, and we are promoting its establishment for clinical use in Norway. To this end, we advocated the implementation of ELF test for fibrosis assessment in chronic liver diseases in general, in line with international recommendations, in a paper published in the journal of the Norwegian Medical Association.

In collaboration with corporate partner Nordic Biosciences in Denmark and the Royal Free Hospital (London, UK), we are exploring novel, tailored, and dynamic biomarkers of fibrosis in PSC. In a meta-analysis, we are now exploring a broad biomarker panel reflecting various disease pathways in PSC. Preliminary results presented at the 2021 EASL International Liver Congress indicate that a combination of markers of inflammation, gut microbiota metabolism, and fibrosis increases our ability to capture disease risks and outcomes in patients.

IMAGING AND ARTIFICIAL INTELLIGENCE

Liver stiffness measurements using ultrasound elastography is one of the top candidate prognostic biomarkers in PSC. PhD student Anders B. Mjelle defended his thesis on his project concerned with ultrasound elastography in PSC and the development of normal values for children and adults in 2021.

In a follow-up paper published 2021, we identified larger within-patient variation over time for liver stiffness measurements compared to ALP and ELF test in our prospective panel, warranting further studies to clarify whether this is due to observer variation and what constitutes clinically significant change.

NoPSC is involved in several studies involving artificial intelligence techniques investigating MRI in PSC trough a strategic collaboration with the Mayo Clinic. We are also contributing to ongoing MRI-related studies initiated through the International PSC Study Group (IPSCSG). The 2022 annual meeting of the IPSCSG MRI Working Group planned for Oslo in the fall.

CLINICAL TRIALS AND PATIENT-REPORTED OUTCOME MEASURES

The prospective cohort serves as a recruitment basis for clinical studies. Contribution to drug development for PSC through the participation in clinical trials is an important aim for NoPSC. NoPSC is currently involved in a phase III clinical trial for nor-ursodeoxycholic acid, with patients participating from Bergen, Ahus, and Rikshospitalet. Funded by grants from Helse Vest and the Halloran Family Foundation, we are planning a multicenter, proof-of-concept investigator-initiated clinical trial. In this project, we aim to investigate the effect on parameters reflecting disease severity or pruritus and explore the mechanisms of a novel drug targeting mitochondrial dysfunction and PPAR pathways which are of interest in PSC. Acknowledging the importance of patient-reported outcomes, we aim to contribute to the development of a patient-reported outcome measures (PROM) instrument primarily to assess the effect of treatment in clinical trials. We have translated and are currently pilot testing a PSC-specific PROM instrument. Next, we plan field testing in the large ScandPSC patient panel.

KEY COLLABORATORS

- UCL Institute for Liver and Digestive Health, Royal Free Hospital, London, UK
- Nordic Biosciences, Denmark
- The Mayo Clinic, Rochester, USA
- Karolinska Institutet, Sweden
- International PSC Study Group
- Norwegian Centre of Excellence in Gastrointestinal Ultrasonography, Haukeland University Hospital, Bergen

NATIONAL NETWORK FOR AUTOIMMUNE LIVER DISEASES

The National network for autoimmune liver diseases is a multicenter study including a research registry and a prospective research biobank for non-transplant patients with PSC, PBC or autoimmune hepatitis. The project comprises annual collection of data, imaging, biological samples, and patient-reported outcomes. It is approved for 10 years until 2029.

Four novel centers (Vestre Viken Bærum Hospital, Stavanger University Hospital, Innlandet Hospital Lillehammer, and Vestfold Hospital Tønsberg) started active patient inclusion in 2021. Thus, there are now 8 actively recruiting centers, with 257 PSC patients included. Further expansion is expected in 2022 as the burden on local laboratories and staff posed by the pandemic is reduced.
At the annual meeting of the Norwegian Gastroenterology Society in February 2022, we presented data from the project registry and showed that a large proportion of patients with PSC had normal or low (<1.5 x ULN) ALP, contesting the use of ALP for the diagnosis of PSC or for patient selection to clinical trials.

PROJECT LEADER
Mette Vesterhus, NoPSC

PROJECT COORDINATOR
Kristin K. Jørgensen

BOARD LEADER GROUP
Mette Vesterhus (NoPSC)
Trine Folseraas (NoPSC)

BOARD MEMBERS
Kristin K. Jørgensen (HSØ)
Svein Oskar Frigstad (HSØ)
Lars N. Karlsen (HV)
Åse Kjellmo (FAL, patient representative)

PROJECT AIMS

- To establish a large, population-based patient panel for PSC and other autoimmune liver diseases
- To study prognostic factors, biomarkers of disease activity and prognosis, and patient-reported outcome measures in PSC, PBC and AIH
- To provide a platform for patient recruitment to clinical trials
- To improve diagnostics, therapeutic options and patient follow-up

Strategic Prospective Scandinavian PSC Biobank (ScandPSC)

PROJECT BACKGROUND

Strategic Prospective Scandinavian PSC Biobank (ScandPSC) merges two strong scientific environments in Norway and Sweden with track record for PSC biobanking with more than 30 years of legacy in a collaborative effort to collect a large prospective biological and clinical sample collection. Scandinavia is a geographical "hot-spot" for PSC, with a high willingness of patients to participate in research studies and very good healthcare infrastructures coupled to unique national registries, altogether providing ideal conditions for high-quality, well-powered prospective studies.

MANAGEMENT GROUP

Mette Vesterhus, Associate Professor, MD, PhD
Haraldsplass Deaconess Hospital, Bergen, Norway

Annika Bergquist, Professor, MD, PhD
Karolinska University Hospital, Huddinge, Sweden

Tom Hemming Karlsen, Professor, MD, PhD
Oslo University Hospital, Norway

Niklas Björkström, Associate Professor, MD, PhD
Karolinska University Hospital, Huddinge, Sweden

STEERING COMMITTEE

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

MONITORING BOARD

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

EMPLOYED PROJECT COLLABORATIVE

Kristin K. Jørgensen, MD PhD, Norway

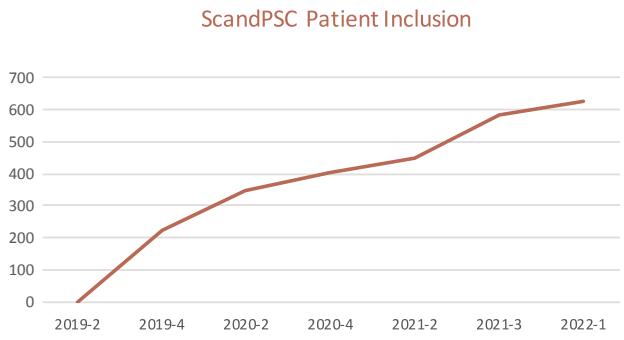
There were 4 ScandPSC Board Meetings (April 8, June 15, November 12 2021; February 18 2022). Annual Meetings for collaborating centers were held in April and May in Norway and Sweden, respectively. All meetings were held virtually.

FUNDING

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

PROJECT STATUS 2021

The prospective cohort includes biobank serum samples from 512 PSC patients (31.12.2021), of which 257 in Norway and 255 in Sweden. The patient panel demonstrates typical demographic characteristics; the patients had a median age of about 45 years at inclusion and the majority are male (ca 2/3) and have IBD (ca 80%). Several novel centers started active patient inclusion in Norway and Sweden in 2021, increasing the number of active centers to 16 (Norway 9, Sweden 7). Other centers have signed collaboration agreements and finalized local preparations and plan for patient inclusion in 2022.



AIMS

ScandPSC aims to establish the world's largest prospective PSC biobank and register with 1300 patients enrolled per 2023, as a platform for clinical trials and biomarker discovery.


Publikumshelten rammet av livstruende sykdom: – Ventetiden og uvissheten er kanskje det verste

STAVANGER (TV 2): Harr trosset smertene han fikk av infeksjonene, bet tennene sammen og ville fortsette fotballkarrieren. Men kroppen ville ikke mer. Viking-helten Johnny Furdal (35) er avhengig av et nytt organ for å overleve.

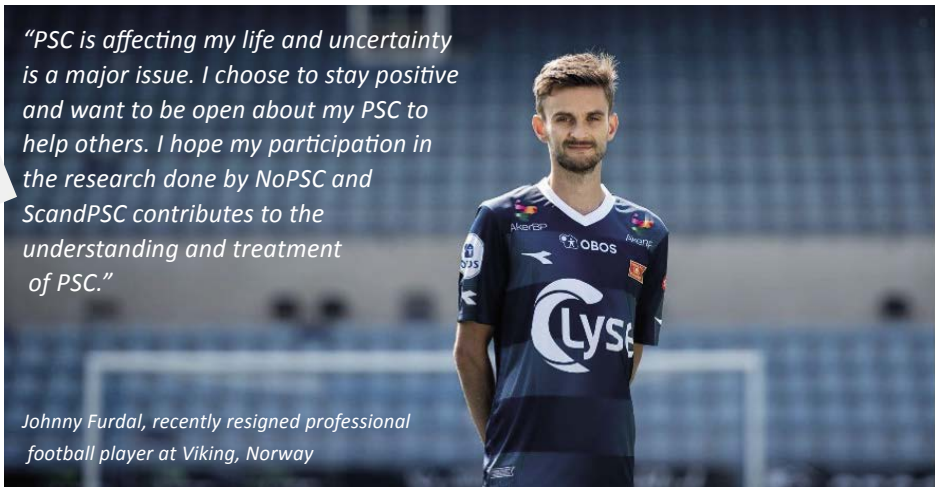


Photo: Jan Inge Haga. Reprint permitted by Stavanger Aftenblad.

ECONOMY

Exspenses 2021		
Norway	Salaries	270 031
	Biobank- and visit-related expenses	190 956
	Travel	2 010
Sweden	Biobank- and visit-related expenses	282 296
SUM Expenses		**745 293**
Donation	Transfered from 2020	-1 559 591
Tranfered to 2022		**-654 878**

EXPANSION PLAN

In Norway, the two university hospitals in Northern Norway as well as several centers in the South-East Health Region are actively preparing to start patient inclusion in 2022. In Sweden, all 7 university hospitals have started data collection and further expansion to other centers is planned. Continued recruitment of additional patients is planned in all existing active centers in Norway and Sweden.

ACTIVELY RECRUITING CENTERS AND PIs

NORWAY	National PI: Mette Vesterhus Coordinator: Kristin Kaasen Jørgensen
Haraldsplass Deaconess Center	Mette Vesterhus
Akershus University Hospital	Kristin Kaasen Jørgensen
Oslo University Hospital Rikshospitalet	Trine Folseraas
Oslo University Hospital Ullevål	Håvard Midgard
Lovisenberg Diaconal Hospital	Hans Lannerstedt
Vestre Viken HF Bærum Hospital	Svein Oskar Frigstad
Stavanger University Hospital	Lars N. Karlsen
Vestfold Hospital	Øystein Rose
Hospital Innlandet HF Lillehammer	Tone Søberg
SWEDEN	**National PI: Annika Bergquist Coordinator: Lina Lindström**
Karolinska University Hospital	Annika Bergquist
Academic Hospital Uppsala	Fredrik Rorsman
Skåne University Hospital	Emma Nilsson
Linköping University Hospital	Stergios Kechagias
Sahlgrenska University Hospital	Hanns-Ulrich Marschall
Örebro University Hospital	Nils Nyhlin
Norrland University Hospital	Mårten Werner

BIOBANK

The biobank constitutes

- Serum
- EDTA blood
- Feces
- Comprehensive biobanking at selected centers

The biobank material is prospectively collected at annual intervals.

The biobank is physically centralized to the fully automated Biobank Haukeland in Bergen for Norway and to a study specific ultra-freezer at Karolinska University Hospital for Sweden. Biobank material is transferred from participating centers at regular intervals.

Highlights 2021

NORWEGIAN GASTROENTEROLOGY ASSOCIATION

Mette Vesterhus was leader of the Norwegian Gastroenterology Association (Norsk Gastroenterologisk Forening, NGF) also in 2021. At the all-digital annual meeting 4-5th of February, our post doctor Peder Braadland received a prize for best presentation within liver/bile/pancreas research for the presentation: “Vitamin B6 deficiency associates with liver transplantation-free survival in primary sclerosing cholangitis.”

MONITORING BOARD MEETINGS

In 2021, the spring Monitoring Board meeting for NoPSC was held as a hybrid meeting on 11th of June. As usual, the accounting and the annual report from last year was presented. The second Monitoring Board meeting was digital only and took place on 10th of December 2021. The budget for 2022 was presented and approved.

IN THE MEDIA

Johannes Hov was interviewed in an article by the Horizon Magazine February 2nd under the title; “Why gut bacteria are becoming key suspects in autoimmune diseases” and also featured in The Times 13th of April 2021 with the headline “Why the future of medicine is all in your gut”. Tom Hemming Karlsen co-authored an article in Norway’s largest newspaper Aftenposten May 5th 2021 on Covid-19 and genetics titled: “Tør vi snakke om Covid-19 og genetikk”, as a follow up on the findings from the large Covid-19 GWAS study in New England Journal of Medicine from 2020. Johannes How was also interviewed in a podcast by PSC partners entitled: “Microbial Metabolism and PSC; A discussion with Dr. Hov”. (1)

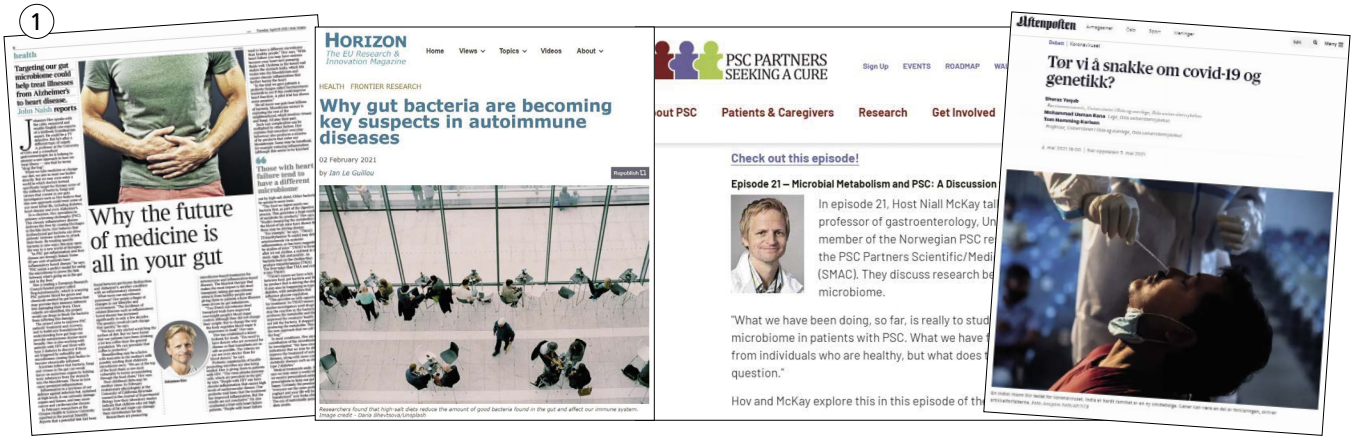
THE INTERNATIONAL LIVER CONFERENCE

In 2021 the annual International Liver Conference organized by EASL was held in a digital format because of the Covid-19 pandemic, and we gathered in one of the hospital auditoriums (with the approved social distance) and watched it together on June 23rd. (2)

PATIENT BOARD

With a strong focus on involving patients as active participants in the planning of research projects, we are grateful for the ongoing collaboration with the patient organization (Foreningen for Autoimmune Leversykdommer). In 2021 the annual meeting to discuss planned research initiatives was held digitally 30th of August.

1



NoPSC RETREAT

In between Covid-19 restrictions, the NoPSCs annual retreat for 2021 was held 13-14th of September at Holmen Fjordhotel. The theme focused around the ongoing research at NoPSC and how can we be resources for each other to develop our scientific platform further. Hence, all scientific personnel presented their projects. The retreat also included workshops and social activities. The opportunity to meet face to face was highly appreciated.

SOCIAL ACTIVITIES

Social activities in 2021 were much reduced because of Covid-19 regulations. All we managed was one outdoor event 14th of October, with mushroom picking and hotdogs on a bonfire. (3)

GLOBAL PSC AWARENESS DAY

The American patient organization, PSC Partners, has promoted 29th of October as a Global PSC awareness day. In connection with this day Johannes Hov was interviewed by the leader of the Norwegian patient organization (Foreningen for Autoimmune Leversykdommer) Espen Bunæs under the headline; “Autoimmune sykdommer i sammenheng”. (4)

Autoimmune sykdommer i sammenheng
Lederen i FAL i samtale med professor Johannes Hov, Rikshospitalet

EIGHTH NATIONAL MICROBIOTA CONFERENCE

The 8th National Microbiota Conference was held as a hybrid digital/in person event on November 11th supported by Regional Health South-East Authority and Oslo University Hospital. NoPSC group leader Johannes R. Hov hosted the event. Our PhD student Mikal Hole presented the topic “New insights from mapping of the mucosal gut microbiota in primary sclerosing cholangitis before and after liver transplantation”.
The event was recorded and can be viewed here; https://microbiota.no/previous-conferences/

THE EASL-LANCET LIVER COMMISSION

The EASL-Lancet Liver Commission was launched online on December 2nd 2021 and Tom Hemming Karlsen was Co-Chair of the event and first author of the commission report. Following this launch an article was published in Aftenposten by Mette Vesterhus and Tom Hemming Karlsen on the 15th of December, with the title: “Leveren har et image-problem”. (5)

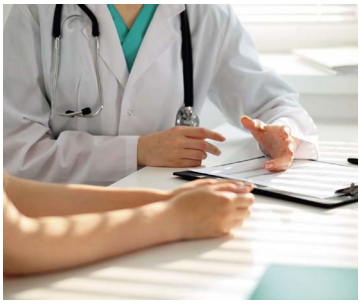
5

Aftenposten Torsdag 16. desember 2021 | 35

Viten

Leveren har et imageproblem

Personer med leversykdom blir stigmatisert. Det resulterer i at liv går tapt.



Viten
Mette Vesterhus
Førstelinjemannskis og overlege ved Haraldsplass Diakonale sykehus

Tom Hemming Karlsen
Professor og overlege ved Oslo universitetssykehus

Leversykdom er nå den andre ledende årsaken til tapte arbeidsår i Europa, kun slått av hjertesykdom.
Det viser tall fra den anerkjente studien «Global Burden of Disease». Samtidig vet vi at mange leversykdommer kan forebygges og behandles. Likevel er leversykdommer i liten grad på agendaen både hos leger og «folk flest».
Hvorfor er det slik?

Forsterker stigmatisering. Stigmatisering av personer med leversykdom er et stort problem. Det viser en rykende ferskrapport fra det ledende medisinske tidsskriftet Lancet.
Mange i risikogruppene oppsøker ikke helsehjelp. Det skyldes til dels moralisme og stigmatisering knyttet til faktorer som mange forbinder med leversykdom (høyt inntak av alkohol og andre rusmidler, samt overvekt og usunn livsstil). Mange oppsøker legehjelp på et stadium av sykdommen der det ikke lenger er mulig å reversere skadene.
Vanlige typer stigma er sosialt stigma (for eksempel stereotypier knyttet til adferd), strukturelt stigma (for eksempel begrensninger i tilgang til bestemte typer behandling) og stigmatisering i helsetjenesten (ofte som et resultat av stereotypier).
Vi leger kan bidra til å forsterke stigmatiseringen gjennom navnene vi gir leversykdommene i medisinsk fagspråk for eksempel «alkoholisk leversykdom» og «fettlever». Vi finner ikke lignende navngivning for sykdommer relatert til nøyking.
Hvem har vel hørt om tobakkslunger?

Skam og mistenkeliggjøring. Stigmatiseringen leder til forsinkelse og diskriminering i helsetjenestene. For dem som lever med leversykdommer, bidrar dette til ulikhet i helse. Flere utvikler alvorlig leversykdom som kunne vært behandlet eller forhindret.
Personer med leversykdommer som ikke er relatert til alkohol eller livsstil, som for eksempel autoimmune leversykdommer, opplever også samme type stigmatisering. De opplever mistenkeliggjøring i forhold til alkoholinntak selv om de ofte er avholdende.
De skammer seg ofte over leversykdommen sin.
Flere leversykdommer rammer sosialt skjevt med økt forekomst i sosioøkonomisk svakere grupper og blant innvandrere. Det bidrar til å forsterke stigmatiseringen.
For mange av disse sykdommene finnes det ingen pasientforeninger. Vi mangler sterke pasientstemmer i samfunnsdebatten sammenlignet med det vi ser for mange andre sykdomsgrupper som kreft og hjertesykdommer.
Leversykdom neglisjeres både av personene som rammes, helsepersonell og samfunnet for øvrig. Et eksempel er personer med diabetes type 2. De kontrolleres regelmessig for ledsagende skader i hjerte, nyrer og øyne. De fleste retningslinjer unnlater å nevne risikoen for leversykdom, som også rammer denne pasientgruppen.

Tiltak virker. Det er mulig å endre måten vi tenker på. Vi må snakke om en sykdom og personer med sykdom. Hiv-viruset som ikke direkte påvirker leveren, er et godt eksempel.
Det har krevd hardt arbeid gjennom flere tiår for å endre oppfatningen av personer som lever med Hiv-infeksjon. Takket være medisinske nyvinninger er de nå ofte beskyttet mot alvorlig sykdomsutvikling.
Stereotypier og skam som preget de første årene etter at hiv-viruset ble oppdaget, er nå nesten borte.
Ordbruken vår er også viktig for både forståelsen og handlingene våre. Enkle grep for å endre omtalen fra «narkoman» til «person som injiserer legemidler», kan øke viljen til testing og behandling for hepatitt C.
På engelsk gjelder «people first»-språk. Man er ikke en diagnose eller først og fremst en sykdom. Man er en person som lever med den, som så mye annet.

Hva bør vi gjøre? Arbeidet mot stigmatisering er møysommelig. Det må rettes mot flere nivåer. Stigmatisering internaliseres som selvstigmatisering. Pasienter opplever skam for adferd og symptomer og unngår å oppsøke helsehjelp.
Vi leger må starte med oss selv. Det er svært uheldig at Verdens helseorganisasjon (WHO) i oppdateringen av medisinsk fagspråk (såkalt ICD 11) som lanseres i 2022, fortsatt snakker om «alkoholisk leversykdom» og «ikke-alkoholisk fettleversykdom».
I Norge har Folkehelseinstituttet (FHI) tatt i bruk god terminologi for rusbrukslidelser, for eksempel «alkoholbruksliddelse». Det er ikke lenger akseptabelt å snakke om alkoholikere i helsevesenet. Begrepet som «ikke-alkoholisk fettleversykdom» bør erstattes med begrep for overvektsrelatert sykdom (eller hvorfor ikke nettopp det?)
Sykelig overvekt må i seg selv betraktes som en sykdom.

Liv går tapt. Likemannsarbeid ved pasientforeninger og pasientstyrking gjennom læringsog mestringskurs kan bidra til å redusere skam og selvstigmatisering.
Tiltak som forbedrer kunnskapene om årsaker og de store mulighetene vi nå har for å forebygge og behandle de vanligste leversykdommene, bør rettes mot lege- og sykepleierstudenter så vel som alle som allerede arbeider i primær- og sekundærhelsetjenesten.
Både helsemyndigheter og leger bør oppmuntre og legge til rette for testing for leversykdom i grupper med høy risiko for leversykdom.
For personer som lever med leversykdom, uavhengig av årsak, er det viktig at stigmatiseringen opphører. Det må være like greit å si at man har leversykdom, som at man har kreft eller hjerte- og karsykdom. For øyeblikket fører stigmatisering til forsinkelser.
Det resulterer i at liv går tapt.

Det må være like greit å si at man har leversykdom som at man har kreft eller hjerte- og karsykdom.

Man er ikke en diagnose eller først og fremst en sykdom. Man er en person som lever med den, som så mye annet.

Mange leversykdommer kan forebygges og behandles. Likevel er leversykdommer i liten grad på agendaen både hos leger og «folk flest», skriver innleggsforfatterne.
Foto: Shutterstock/NTB

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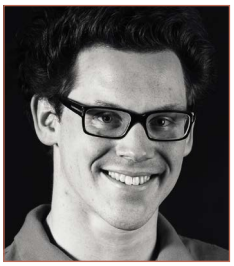
New employees

Elisabeth Schrumpf, MD, PhD
Researcher
Interested in mucosal and skin immunology. Doing research makes me a better clinician.
ESCHRUM@ous-hf.no



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Kristin Kaasen Jørgensen, MD, PhD
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Retired

Anne Pharo, BSc, Laboratory Manager 2015-2021
I would like to express my gratitude for having had the opportunity to work as a lab manager in the Experimental Group at the NoPSC center from January 2015 until I retired in July 2021. It has been a privilege to have had such an inspiring job and good colleagues at the end of my working career. The friendly working environment at the center has made it nice and easy to be at work. The feeling that people trust in you, believe in you and want you to succeed inspires and gives you the energy to move on even when the results are not what you hoped for.

When I started as a lab manager in 2015, after more than 25 years of experience, I was ready for new challenges and wanted to learn new techniques, and NoPSC really gave me that opportunity. Under the good and steady leadership of Espen, I was introduced to animal experiments, which for me was a new world. Working with animals is very different from regular lab work, and requires completely different skills, which I found both inspiring and challenging, in a positive way.

I wish you all great success with your projects and hope that you will succeed in finding a treatment for the PSC patients. Keep up the good work and the positive working spirit.

Networks and collaborations

KEY LOCAL COLLABORATORS

Research Institute for Internal Medicine (RIIM)
The Institute is headed by Prof. Bente Halvorsen and the research groups led by Espen Melum and Johannes E.R. Hov respectively are located at RIIM. Several collaborative projects are established with the groups of, among others, Dr. Børre Fevang, Dr. Thor Ueland and Prof. Bente Halvorsen.

Department of Transplantation Medicine
Department Head, Prof. Pål-Dag Line, Dr. Einar Martin Aandahl and Dr. Bjarte Fosby collaborate with NoPSC on projects related to liver transplantation in PSC and induced murine models of cholangitis.

Department of Rheumatology, Dermatology and Infectious diseases
Ass. Prof. Marius Trøseid is a key collaborator for NoPSC on microbiome studies. Rheumatologists Prof. Øyvind Molberg and Dr. Anna-Maria Hoffmann-Vold also collaborate on immunology and microbiome studies.

Department of Pathology
Dr. Peter Jebsen, Prof. Tor J. Eide, Dr. Henrik Reims and Dr. Krzysztof Grzyb are 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 at Ullevål
Prof. Bjørn Moum, department Head Dr. Asle Medhus and Ass. Prof. Marte Lie Høivik are important collaborators on multiple projects including the original IBSEN and the new IBSEN III study.

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 Cardiology
Prof. Lars Gullestad is an important collaborator on microbiome of statins and cardiovascular disease.

Center for Clinical Heart Research
Prof. Ingebjørg Seljeflot is a collaborator on circulating biomarkers of the gut barrier.

Department of Infectious Diseases
Dr. Dag-Henrik Reikvam is another key collaborator on gut microbiome studies.

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. The Norwegian Sequencing Center hosts the NoPSC MiSeq next generation sequencing machine.

Institute of Immunology
NoPSC has a longstanding collaboration with the Institute of Immunology in our functional genetic projects. In particular the good collaborations with Section of Transplantation Immunology, led by Prof. Torstein Egeland and Prof. John Torgils Vaage, and the research group of Dr. Fridtjof Lund-Johansen, are important for the activities of NoPSC.

Department of Medical Biochemistry
In conjunction with the establishment of the NoPSC Biobank quality control project the collaboration with Dr. Yngve Thomas Bliksrud is highly appreciated.

Institute for Cancer Research
A collaboration with Prof. Guro Lind, Department of Molecular Oncology at Radiumhospitalet, 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. Knut Brabrand, and Gunter Kemmerich for their active contributions. (Ida Bjørk,

Department of Paediatric Research
Department head Ass. Prof. Runar Almaas is an important collaborator on our liver transplantion research and Dr. Gareth Sullivan on regenerative medicine.

KEY NATIONAL COLLABORATORS

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

The IBSEN study group
The biological material collected by Prof. Morten Vatn, Prof. Bjørn Moum and several other co-workers of the IBSEN study group is still important for several of the basic genetic and metagenomic studies at NoPSC.

Akershus University Hospital
The collaboration with Dr. Kristin Kaasen Jørgensen regarding the regional network for Autoimmune Liver Diseases is ongoing and will continue for many years to come. Prof Jørgen Jahnsen's group at Department of Gastroenterology and Dr. Anne Nergård and Dr. Aida Kapic Lunder at the Department of Radiology are important contributors and collaborators in MRI studies in both the IBSEN study and the new IBSEN III study.

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. For the bile acid and microbiota projects, Prof. Rolf Berge at the University of Bergen provides the serum lipid measurements.

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
Our leader for the clinical group in Bergen, Mette Vesterhus, has a permanent position at Haraldsplass Deaconess Hospital, hence we have a strong collaboration there too.

KEY INTERNATIONAL COLLABORATORS

The Nordic Liver Transplant Group
Collaborators in Helsinki (Dr. Arne Nordin), Stockholm (Prof. Bo-Göran Ericzon and Dr. Carl Jorns), Gothenburg (Prof. William Bennet) and Copenhagen (Dr. Allan Rasmussen) are involved in several projects where data from the Nordic Liver Transplant Registry are required. Ilse Duus Weinreich at the Scandiatransplant office is a key person ensuring smooth operation of the registry.

Karolinska University Hospital, Stockholm, Sweden
Prof. Annika Bergquist is a close collaborator on clinical projects in PSC and has also participated in the genetics studies. Ass. Prof. Niklas Björkström (Guest Professor at NoPSC) is involved in projects relating to human immunology in PSC. They are both a part of the management group of the Strategic Perospektive Scandinavian PSC Biobank (ScandPSC)

Molecular and Clinical Medicine, Wallenberg Laboratory, University of Gothenburg, Sweden
Prof. Fredrik Bäckhed and Prof. Hanns-Ulrich Marschall have been collaborators related to the gut microbiota axis for several years. Bäckhed is an expert on gut microbiota, metabolism and gnotobiotic animals and has been an advisor and collaborator on gut microbiota studies in mice, while hepatologist Hanns-Ulrich Marschall contributes with bile acids expertise.

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, and collaborates with NoPSC 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.

Universitätsklinikum Dresden, Germany
There is a growing collaborative activity with Prof. Jochen Hampe and Prof. Marino Zerial in Dresden.

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

Department of Internal Medicine I, University of Bonn, Germany
Dr. Tobias J. Weismüller is leading the International PSC Study Group (IPSCSG) database project comprising more than 8000 PSC patients and is an important collaborator within the IPSCSG. His collaborator, Dr. Taotao Zhou will from 2022 be the main contact in Bonn.

Netherlands, IPSCSG
The secretariat of the IPSCSG has been located in Amsterdam, The Netherlands, since 2018, in the capable hands of Prof. Cyriel Ponsioen and Prof. Ulrich Beuers at the University of Amsterdam's Faculty of Medicine.

Cambridge Institute for Medical Research, UK
An ongoing collaboration with Dr. Fotis Sampaziotis at Cambridge Biorepository for Translational Medicine and Prof. Ludovic Vallier at the Wellcome - MRC Cambridge Stem Cell Institute has proved extremely valuable regarding organoids and regenerative medicine.

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 was funded within the Scientia Fellows' program of the University of Oslo through 2018 and further by the Regional Health South-East Health Authority in Norway and involves postdoc Georg Schneditz and Dr. Nicole Kaneider-Kaser.

University of Birmingham, UK
Prof. David Adams (former Guest Professor at NoPSC) at the Center for Liver Research at the
Institute of Biomedical Research, University of Birmingham, collaborate on several projects related to the further characterization of the HLA related immune response in PSC.

Royal Free Hospital London, UK
Prof. Massimo Pinzani (Guest Professor at NoPSC), director of the Institute for Liver and Digestive Health at University College London and the Royal Free Hospital in London, and Dr. Douglas Thorburn at the same institutions, collaborate with NoPSC on projects related to the characterization of fibrosis and the development of novel targeted PSC-specific fibrosis markers as prognostic tools in PSC in a tri-party collaboration with Nordic BioScience.

Medical University of Vienna and Medical University of Graz, Austria
In collaboration with Prof. Michael Trauner and Prof. Peter Fickert, ongoing projects aim at crossvalidating findings in mouse models of PSC with human data. Prof. Michael Trauner (former Guest Professor at NoPSC) has extensive experience in animal models of PSC and serves as an important collaborator related to the development of a bile duct specific Cre mouse.

Sapienza, Università di Roma, Italy
Prof. Eugenio Gaudio, Domenico Alvaro and coworkers are experts on biliary tree stemcells, and material from the NoPSC Biobank is 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
Dr. 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 lead by Maria Reig, is world leading on hepatocellular carcinoma research. Key collaborating researcher is Marco Sanduzzi-Zamparelli, who visited NoPSC for 3 months during the autumn 2020.

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 and Dr. Lewis Roberts at the Mayo Clinic in Rochester has been ongoing 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.

Brigham and Women's Hospital, Harvard Medical School, Boston, USA
Prof. Richard Blumberg is an important collaborator in Dr. Espen Melum's projects related to NKT cells. We are also collaborating with Dr. Joshua Korzenik on various aspects of PSC pathogenesis.

Lithuanian University of Health Sciences, Vilnius, Lithuania
In 2020 we were awarded 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". This project is chaired from Lithuania, where Gediminas Kiudelis is PI, and the project partners include both Latvian (Latvian Biomedical Research and Study Centre) and Estonian (University of Tarty) institutions. The project will run 2021-2023 and involve both the Hov and Melum groups.

New grants awarded in 2021

Research group	Source	Project	Duration	Total amount
Clinical, Oslo	University of Oslo	Clinical PhD student	5 years	NOK 3 000 000
Clinical, Bergen	Western Norway Regional Health Authority	New plasma biomarkers for mitochondrial function in cholestatic liver diseases: A proof-of-concept clinical trial	3 years	NOK 2 450 000
	Halloran Family Foundation	Additional funding; New plasma biomarkers for mitochondrial function in cholestatic liver diseases: A proof-of-concept clinical trial	3 years	NOK 3 900 000
Genomics and Metagenomics	BioMe/The Research Council of Norway	PhD student	3 years	NOK 2 700 000
	South-Eastern Norway Regional Health Authority	MicroBLiver - Clinical impact of gut Microbial B vitamin metabolism in Liver disease	3 years	NOK 9 000 000
		Targeting GPR35 and mast cells to treat cholangitis and liver fibrosis	3 years	NOK 9 000 000
	PSC Partners	Taragеting GPR 35 to treat cholaniocarcinoma	2years	NOK 550 000
Eksperimental Hepatology	Health South-East	Microbial drivers of immune-mediated cholestatic liver disease	3 years	NOK 3 561 000
	German Cancer Aid	PhD student	2 years	NOK 2 000 000
	The Research Council of Norway	Multiomic 4-dimensional identification of novel treatment targets for bile duct inflammation	4 years	NOK 12 000 000
	PSC partners	Defining the interactome of bile duct inflammation in PSC	2 years	NOK 550 000
		Overall		**NOK 48 711 000**

Awards

- Peder Braadland received the award for best abstract within liver/bile/pancreatic research for his work entitled: Vitamin D6 deficiency associates with liver transplantation-free survival primary sclerosing cholangitis at the Norsk Gastroenterologisk Forening annual meeting in 4-5 February 2021.

- Twice a year Oslo University Hospital awards outstanding research articles with important findings, high quality and international impact. The prize for the first half of 2021 was awarded to the research article “A heterozygous germline CD100 mutation in a family with primary sclerosing cholangitis” authored by Xiaojun Jiang et al, published in Science Translational Medicine.

  The comittee states:
  An original work with high scientific value, international impact and a clear clinical relevance with a focus on primary sclerosing cholangitis. The study combines in depth studies of genetically causes of disease with well controlled animal studies. A new pathogenic gene variant was identified and coupled to PSC, and injection of healthy t-cells to genetically engineered mice gave them protection against bile duct disease. This might be translated to cell-therapy in humans with PSC and the results from this study has identified potential new treatment options that may be relevant for all PSC patients.

Xiaojun Jiang recieving the price at a ceremony at Oslo University Hospital.

Dissertation

June 4th 2021 Cand.med. Natalie Lie Berntsen defended her thesis "The role of natural killer T cells in biliary immunology and disease" for the degree of PhD (Philosophiae Doctor).

Natalie Lie Berntsen

The etiology and pathophysiology of cholangiopathies are mostly unknown and their disease courses are often chronic and progressive due to limited treatment options. The biliary anatomy limits the accessibility to the bile ducts in experimental models and complicates study of biliary immunopathology. The purpose of this thesis was to study the regulatory mechanisms in biliary inflammation, with an emphasis on the role of natural killer T (NKT) cells and the role of lipid antigen presentation in the bile ducts.

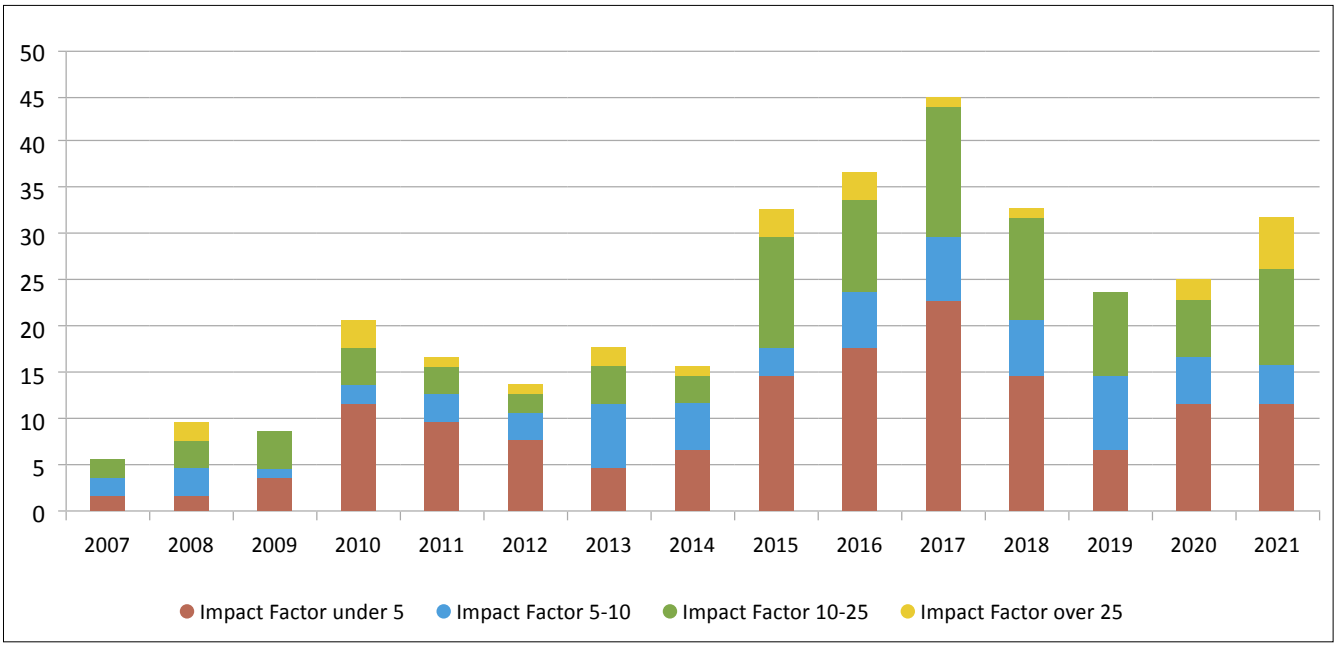
We first established a novel bile duct injection model in mice to access the bile ducts for *in vivo* study of biliary immunopathology. This model may be valuable in future studies of normal biliary physiology and different pathophysiological disease mechanisms as it was well tolerated and easily reproducible.

NKT cells are activated by lipid antigen presentation by the CD1d-molecule. Cholangiocytes function as antigen presenting cells (APCs) with CD1d-dependent activation of NKT cells *in vitro* and we hypothesized that this immunoregulatory pathway is important in the bile ducts. To explore this, we first demonstrated that intrabiliary injection of the NKT cell-activating agent oxazolone in wild type mice caused an acute cholangitis with activation of NKT cells. $Cd1d^{-/-}$ mice that lack NKT cells and wild type mice pretreated with antibody blocking of CD1d were protected from disease. These findings implicate that cells in the bile ducts function as APCs in vivo and activate NKT cells in a CD1d-restricted manner.

Finally, we demonstrated the presence of NKT cell-activating antigens in bile from patients with various liver diseases. This may be of importance in biliary immunopathology.

As NKT cells are potent immunomodulators that can act both protective and detrimental in disease, future studies should aim to elucidate this biliary immune pathway as it may expose potentially new therapeutic approaches in cholangiopathies.

Publications NoPSC 2007-2021



Publications 2021

Primary articles marked with an asterix

HIGHLIGHTED PUBLICATIONS

Vedeld HM#, **Grimsrud MM#**, Andresen K, Pharo HD, von Seth E, **Karlsen TH**, Honne H, Paulsen V, Färkkilä MA, Bergquist A, Jeanmougin M, Aabakken L, **Boberg KM, Folseraas T**, Lind GE (2021) #- shared first authorship
***Early and accurate detection of cholangiocarcinoma in patients with primary sclerosing cholangitis by methylation markers in bile**
Hepatology, 75 (1), 59-73

Patients with primary sclerosing cholangitis (PSC) are at increased risk of developing cancer in the bile ducts (cholangiocarcinoma (CCA). Currently available detection methods for CCA in PSC are inaccurate, consequently CCA is often identified too late for curative resection or liver transplantation. In the present study, we aimed at establishing robust DNA methylation biomarkers in bile for early and accurate diagnosis of CCA in PSC.
Droplet digital PCR (ddPCR) was used to analyze large panel of bile samples (n=344) from patients with sporadic and PSC-associated CCA, PSC, and other nonmalignant liver diseases for promoter methylation in four genes. We showed that CCA in PSC was accurately detected also at an early stage by measuring and combining four DNA methylation biomarkers in bile. Although these results should be validated in a prospective effort, we believe that these epigenetic biomarkers can be used to complement current detection methods for CCA and to monitor cancer development in patients with PSC.

Jiang X, Bergquist A, Löscher BS, Venkatesh G, Mold JE, **Holm K**, Laerdahl JK, Skånland SS, Maleki KT, Cornillet M, Taskén K, Franke A, **Karlsen TH**, Björkström NK, **Melum E** (2021)
***A heterozygous germline CD100 mutation in a family with primary sclerosing cholangitis**
Sci Transl Med, 13 (582)

Genetic factors contribute to primary sclerosing cholangitis (PSC) pathogenesis, but so far, no causative mutation has been found. A key paper this year was therefore a long-awaited first family study for PSC, in which we performed whole-exome sequencing for the first-to-date known PSC family and identified a plausible causal mutation in SEMA4D, encoding a K849T variant of CD100. In the study, we comprehensively examined the functional consequences of this mutation and surprisingly found it alters the function of T cells, a central player in the immune system. We also generated mice with the homologous mutation using the CRISPR-Cas9 system, a cutting-edge technique for gene-editing, and observed clear disease susceptibility in these mice when subjected to experimental cholangitis. Importantly, adoptive transfer of normal T cells attenuated disease in mice. Thus, our findings suggest a protective role for T cells in PSC that might be used therapeutically. The project was conducted in Espen Melum's group with senior researcher Xiaojun Jiang as the frontrunner, in close collaboration with our friends in Stockholm and Kiel.

Fossdal G, Mjelle AB, **Wiencke K**, Bjørk I, Gilja OH, **Folseraas T**, **Karlsen TH**, Rosenberg W, Giil LM, **Vesterhus M** (2021)
***Fluctuating biomarkers in primary sclerosing cholangitis: A longitudinal comparison of alkaline phosphatase, liver stiffness, and ELF**
JHEP Rep, 3 (5), 100328

Here, we characterize the annual variation of alkaline phosphatase (ALP), the serum-based ELF test, and liver stiffness by ultrasound in PSC patients in a prospective panel. Our results demonstrated differences regarding within- and between-patient effects, indicating that the ELF test may have superior reliability for risk stratification compared with liver stiffness measurements in PSC. ELF and liver stiffness showed a significant increase over time only in patients with ≥1.5 x ULN, supporting this as a relevant cut-off level for risk stratification. Interestingly, up to 13% of patients with ALP ≥1.5 x ULN at baseline experienced ≥40% ALP reduction (a commonly used primary outcome in clinical trials) at any time point whereas none of the patients with lower ALP showed ALP reduction of this magnitude. Furthermore, at each follow-up visit, about 10% of patients featured a concomitant reduction in all of ALP, ELF, and liver stiffness. Our findings are relevant for clinical trials design and raise the question of whether fibrosis level or disease severity may regress in PSC.

ADDITIONAL RESEARCH ARTICLES

Karlsen TH, Sheron N, Zelber-Sagi S, Carrieri P, Dusheiko G, Bugianesi E, Pryke R, Hutchinson SJ, Sangro B, Martin NK, Cecchini M, Dirac MA, Belloni A, Serra-Burriel M, Ponsioen CY, Sheena B, Lerouge A, Devaux M, Scott N, Hellard M, Verkade HJ, Sturm E, Marchesini G, Yki-Järvinen H, Byrne CD, Targher G, Tur-Sinai A, Barrett D, Ninburg M, Reic T, Taylor A, Rhodes T, Treloar C, Petersen C, Schramm C, Flisiak R, Simonova MY, Pares A, Johnson P, Cucchetti A, Graupera I, Lionis C, Pose E, Fabrellas N, Ma AT, Mendive JM, Mazzaferro V, Rutter H, Cortez-Pinto H, Kelly D, Burton R, Lazarus JV, Ginès P, Buti M, Newsome PN, Burra P, Manns MP (2021)
***The EASL-Lancet Liver Commission: protecting the next generation of Europeans against liver disease complications and premature mortality**
Lancet 399 (10319), 61-116

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