K.G. Jebsen
Colorectal Cancer Research Centre
Mid-term report 2016

Cancer prevention and precision medicine


Op-stue 10

CONTENTS

Editor: Anette Sørensen, Administrative coordinator | Design: Millimeterpress | Photo: Terje Heiestad | Print: Grøset Trykk | Paper: 150/300 Profimatt | Circulation: 200

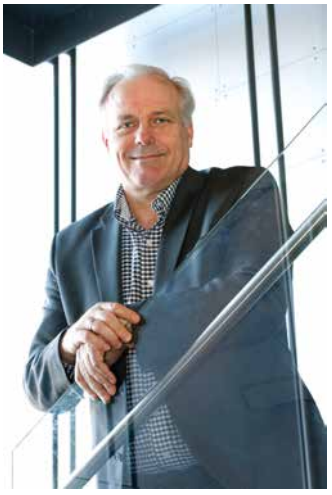
Foreword

Colorectal cancer (CRC) is common in Norway and cancer deaths from CRC are second only to lung cancer deaths. Although mainly a disease in the elder, CRC also affects a substantial number of patients < 50 years at diagnosis. We therefore have a need for more effective prevention to reduce the incidence and for improved treatment to increase survival for the patients.

The clinical pathway for colorectal patients is a multidisciplinary task involving several departments, and the delivery of high quality care is dependent on a well-coordinated approach by these units. The K. G. Jebsen Colorectal Cancer Research Centre is organized according to the same multidisciplinary principle and has a comprehensive approach spanning from laboratory research to clinical trials and screening. The Centre covers all stages of the disease from pre-neoplastic lesions to overt metastatic disease.

Precision medicine is only to a small extent implemented in today's standard treatment of CRC. We need more detailed biological mapping of the patients to identify patients at risk, who may benefit and who will not benefit from a specific treatment, leading to improved cost-efficient use of resources. The leadership of the Centre has been able to gather the leading clinicians and scientists within CRC management and research at the University hospital. Together they have a cutting edge clinical competence and hands-on experience in advanced technologies and analyses that enable the Centre to conduct international competitive translational research. These technologies include multilevel clin-omics (detailed clinical analyses beyond standard procedures integrated with advanced genomics) and an advanced drug screening program. The Centre has demonstrated the ability to develop biological hypotheses based on experimental results on biomarkers and tumor heterogeneity, validated in preclinical models and to be tested in clinical trials to optimize treatment for selected CRC patient groups.

Oslo University Hospital has the ambition to be a leading comprehensive cancer center in Europe. Frontline research that covers the major tumor groups is mandatory to achieve this ambition. The K. G. Jebsen Colorectal Cancer Research Centre is an example and an inspiration for other scientists and research groups working with other malignancies to join forces and add synergy in a comprehensive model to gain knowledge and optimize management of our patients.



Professor Sigbjørn Smeland

Head of Division of Cancer Medicine
Oslo University Hospital

Hosting the K. G. Jebsen Colorectal Cancer Research Centre in cooperation with the Institute for Clinical Medicine, University of Oslo

Comments by the directors

Colorectal cancer (CRC) is a global health burden. Due to non-specific symptoms, increasing population age, variable quality in health systems and low compliance in screening programs CRC remains one of the most common malignancies with high mortality rate.

CLINICAL CHALLENGES AND RESEARCH QUESTIONS

Prevention/early detection

CRC is in principle a preventable disease, since the vast majority arise in benign precursor lesions, polyps. Removal of these will prevent the development of a carcinoma at this site. Colonoscopy remains the gold standard for detection of polyps, but several questions remain unanswered: Who should undergo endoscopy screening and how often taking into account efficacy and resources? May the current classification of high risk vs low risk adenoma be improved? Are alternative screening methods as safe and efficient as endoscopy? Can polyp classification be improved with biomarkers, and can blood based biomarker assays replace screening?

Management

Despite huge research efforts and clinical studies, the disease stage (I-IV; see "Facts about CRC") at diagnosis remains the best prognostic factor deciding the choice of treatment. CRC patients receive mostly traditional treatments as surgery and chemotherapy and/or radiation dependent on disease stage and tumor location. However, preoperative staging is not always correct resulting in over- and under- treatment of many patients. About 25% have disseminated disease with metastases in the liver, lung or other sites at time of diagnosis. Approximately one third are offered surgical resection, but only a proportion benefit from this treatment, while the remaining will die of new metastases within a rather short period of time. Most of these patients receive palliative chemotherapy and a subgroup is offered targeted drugs. The choice of drugs is mostly done without information from predictive biomarkers, meaning the patient's expected response is unknown.

How can we best identify the patients that need aggressive treatment beyond surgery? How do we select the patients that will benefit from liver surgery? To what degree is the intrinsic biology of the primary tumor reflected in the metastases? Will unraveling of genomic tumor heterogeneity guide new management strategies? Will integrative tumor genome- and ex vivo drug screen- data from the individual patient be the future precision medicine tools? Can we improve monitoring of response to novel and combination treatments?

The consensus opinion for multidisciplinary and multimodality approaches to management of colorectal cancer patients underlines the need for translational research. An important goal is to improve the prognostic stratification and establish more homogenous patient groups as guide for the dynamic process through pre- and/or postoperative treatment.

RESEARCH IN THE K.G. JEBSEN CENTRE

In our Centre, we make an effort to truly integrate competence from several disciplines in Life sciences with focus on colorectal cancer. With interest the clinicians and scientists have established a high quality research logistics ranging from screening protocols to treatment of advance disease, system-

The PI group (from left): Rolf I. Skotheim, Arild Nesbakken, Marianne G. Guren, Ragnhild A. Lothe, Kjell Magne Tveit, and Michael Bretthauer

atic biobanking of tissue and body fluids from the patients and building corresponding comprehensive clinical databases.

Our vision is to reduce incidence and mortality of CRC, and improve quality of life of patients living with disease. Importantly, several of the projects aim to provide population representative data – often a limitation of clinical trials and in the scientific literature since many investigations are based on highly selected patient groups.

Clinical studies

During the first two years of the Centre PI - Michael Bretthauer, an international opinion leader in the field of screening and surveillance trials, has published several articles in prime medical and gastroenterology journals together with his team and collaborators. In May this year they launched the EPoS European polyp surveillance study randomizing 30 000 patients from seven countries to different surveillance colonoscopy intervals after polypectomy to investigate the most effective and cost-effective surveillance strategy.

A phase II clinical trial in geriatric oncology has been initiated in the Centre and patient inclusion started in May 2016. PI - Marianne Guren is the coordinator for the trial that aims to conclude on tolerance for 5FU based chemotherapy among elderly, > 75 years, with stage III disease. The study was approved by the Regional Ethical Committee based on evidence of large regional differences in adjuvant treatment of this patient group.

Among rare malignancies in the GI tract, we contribute to a study of anal cancer in which the primary objective is patient outcome in relation to a strict combination of precise chemo-radiotherapy volume and doses. The willingness of the patients to allow biopsies prior to radiation is highly appreciated and the technical challenge with this procedure has been established by prof Arild Nesbakken, ensuring fresh material for parallel advanced genomic studies.

Tumor heterogeneity/Cutting edge technologies

Intra-tumor heterogeneity and clonal evolution play a pivotal role in cancer progression. The –omics technologies and in particular the next generation

sequencing have reopened the investigations on genetic tumor heterogeneity. One of the core projects in the Centre is multilevel clin-omics (detailed clinical analyses beyond standard procedures integrated with advanced genomics) investigations of the primary tumor and liver metastases from individual patients. Hands-on competence in genomics is found in the Lothe and Skotheim groups. Recently, we have shown that patients with multiple liver metastases and a low level of genetic heterogeneity have a more than four times longer progression free survival than patients with a high level of heterogeneity.

By detailed radiological examinations of several liver metastases per patient using MRI (AI - Andreas Abildgård) striking lesional heterogeneity in response to preoperative therapy is found and the exciting relationship to molecular data is expected to be presented next year.

The liver surgical team (AIs - Bjørn Atle Bjørnbeth/Bård Røsok) has included patients undergoing liver surgery and up to 5 separate metastases are biobanked for molecular investigations in the SMART - CRC project, a focus research area of the hospital, and overlapping with the Centre projects and PIs/AIs. By molecular investigations of individual metastatic foci we have found disagreements with the diagnostic KRAS assay which has been performed on the corresponding primary cancer and guided the treatment decision (EGFR-antibody). Such data underline the importance of taking into account the heterogenous nature of tumor in metastatic patients

Clinical biomarkers

There are many challenges in the Research & Development of biomarkers, from identification of the medical unmet needs to changes in clinical practice. Thus it is imperative that all steps are done with high quality and without bias and that existing guidelines are followed. We believe the scientists in the Centre are aware of and practice such quality, and together with international collaborators we may also achieve large enough series of patients to identify small subgroups for which specific biomarkers will make a difference in prognosis or choice of treatment. This summer we published a joint European Multi-Centre study on Polymerase E mutations, which identify a 1-4% subgroup of CRC with particular features and good prognosis. We have also during this first period established a very interesting collaboration with the SAGE bionetwork and the Oslo series are included with thousands of stage II/III patients in an international consortium investigation of prognostication beyond the TNM staging, on request by the American joint cancer committee.

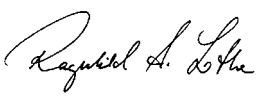
Patient advisory board

We are grateful to the patients and their next of kin who have agreed to join our recently established patient advisory board. We really foresee a fruitful interaction with the board for discussions and advices on several aspects of a clinical science program, in agreement with the hospital strategy as well as with the health authority politics emphasizing the important role of patient participation not only in decisions regarding their own disease but also in implementation of research.

Future promises

During these first two years we are pleased with the success of the transdisciplinary collaborations and efforts within the hospital, supported by our host institution, the Cancer Clinic and head professor Sigbjørn Smeland. The interest and enthusiasm we have experienced from the trial unit and our AI – Tormod Guren is highly appreciated, and increased future focus on CRC clinical trials founded in biological hypotheses is a joint goal. We are proud of the success of the many young scientists and new PhDs. The promise for continued high level research is also seen in the several external grants received by the scientists of the Centre and we acknowledge all our financial sources. Last but not least we are grateful to all our international collaborators including the new cooperation with researchers at the Vall d'Hebron Institute of Oncology with whom several collaborative projects are ongoing, hopefully resulting in joint research success for the benefit of future patients.

Centre leadership, professors



Ragnhild A. Lothe

Arild Nesbakken

Facts about colorectal cancer and research on this malignancy

- **High incidence.** The 3rd most common cancer disease in the world with 1.36 mill new cases each year. More than 4200 new cases each year in Norway alone

- **High mortality** rate. About 50% survive 5 years after diagnosis. The mortality rate depends on the health system and survival varies among countries. In Norway, 5-year cancer specific survival is about 60%.

- Strikes **both genders**.

- The incidence **increases with age**. The median age at diagnosis is 71 years. However, 5-10% of all new cases are found among individuals younger than 50 years. About 250 Norwegians between 20-50 years are diagnosed each year.

- **Genetic predisposition** to CRC caused by a single gene mutation, inherited from one of the parents or acquired early in embryogenesis, includes less than 5% of all CRC patients. The most common of such familial syndromes are Familial adenomatous polyposis which comprises 1% of new CRC, and nearly all develop CRC before the age of 30 years, and Lynch syndrome which comprises about 3% of new CRC, and about 80% develop CRC at a median age of 45 years. Multifactorial genetic risk for CRC is suggested to contribute to development of up to 25% of new cases.

- Most patients have no known genetic predisposition, but develop a **sporadic cancer**. The etiology is not known, but it seems clear that lifestyle and diet play a role; high intake of red meat and fat, overweight and inactivity increase risk.

  Studies aiming to lower a person's **risk profile** include changes in diet and life style and the use of drugs. Aspirin intake reduces the risk for CRC, possibly also reducing the risk of recurrence after an apparently curative resection, but may have side effects. Ongoing studies aim at clarifying the effectiveness and safety of Aspirin prophylaxis before and after the development of CRC. Similar studies that identify subgroups of patients where benefits outweigh side effect risks of drugs are warranted.

- CRC develops through precursor lesions, polyps, and a several years long "window of opportunity" for **detection and removal of precursor lesions** as well as early cancers. Large research efforts are ongoing to identify circulating biomarkers that may replace colonoscopy for sensitive detection of high risk adenomas and early cancers. Optimization of screening programs for detection of adenomas and surveillance after removal remains a worldwide interest.

- At diagnosis CRC is classified into four stages, I-IV. **Stage I-II:** localized in the bowel wall and assumed cured with surgery alone, and thus the patients are not offered adjuvant therapy although 20-25% will experience a recurrence.

Stage III: spreading of tumor to the regional (mesenteric) lymph nodes is associated with higher risk of recurrence and fit patients are offered adjuvant chemotherapy. However, about 50% are cured with surgery alone and for these patients chemotherapy represents over treatment with side-effects. Furthermore, the benefit for elderly (>75 years) remains an open question. **Stage IV:** spread of cancer to distant organs.

There is a great need for better prognostication using biomarkers in addition to clinicopathological staging to optimize treatment.

- Multiple gene expression tests for **recurrence risk** after primary surgery are published and even commercially available tests exist. However, these are not optimal, not available in routine labs and costly. The international consensus **molecular classification** opens a new avenue of patient risk stratification and identification of predictive molecular markers for novel treatments and treatment combinations.

- **Liver metastases** is the main cause of death from CRC, and 20% have synchronous liver metastases at the time of diagnosis (stage IV), while another 20% develop metachronous metastases during disease progression.

- About 20% of patients with liver metastases are offered **surgical resection of the metastases**. However, only one third has a long term survival benefit from this procedure, and about another third has poor prognosis despite liver resection. An open question remains unsolved: how can these patients be identified prior to surgery?

- Patients with liver metastases may have multiple deposits. Currently, international researchers are applying genomics technologies to investigate how intra-organ molecular **tumor heterogeneity** influences response to therapy and survival, and how therapy after primary surgery influences the development of aggressive clones in the liver.

- Response evaluation after drug treatment of metastatic disease is performed according to RECIST criteria, providing an average evaluation of all intra-organ metastatic deposits. However, great variation is seen among individual lesions in one patient. **Radiological heterogeneity** profiles should be assessed together with molecular characterisation of the individual lesions to design improved precision management.

- The possibility of recapitulation of molecular tumor marker signatures in the peripheral blood is another hot research area aiming to develop assays for early detection of drug resistance and of relapse.

Centre activities

Diagnosis; colonoscopy

Staging; radiology

Treatment decisions

Chemoradiotherapy before or after surgery: decision made in a multidisciplinary team. Palliative chemoradiotherapy for advanced disease: decision oncologist team.
Photo: PI-Marianne Guren

Treatment
Primary cancer

Surgery of the primary cancer. Photo: PI-Arild Nesbakken

Follow-up
Control visits

Treatment
Metastases

Surgery of liver metastases. Photo: AI-Bjørn Atle Bjørnbeth.

PATIENT HOSPITAL VISITS & RESEARCH

Quality at all levels in the hospital and project protocols beyond standard routines: a necessity for competitive translational research and improved precision medicine.

Study design and approval of research projects. Inclusion of patients

The scientists ensure biological know-how and hands on competence in cutting edge technologies and analyses. Photo: PI-Rolf I Skotheim, AI-Guro E Lind, PI-Ragnhild A. Lothe.

Patient samples collected to research biobank. Registration of clinical data: building a comprehensive database of disease course.

Biobank handling, experimental work and large scale data analyses are done in-lab. Photo:Researcher-Anita Sveen.

Biobanking from resected liver metastases.
Photo: Study nurse-Magdalena M. Kowalewska

- Integration of biological and clinical data
- Clinical trials
- Publications from the K. G. Jebsen CRC research centre portfolio.

Patient advisory board

A patient advisory board for the Centre was established recently. The members have own experience with the disease or are next of kin. Their experience and opinions will contribute in the design, conduct and evaluation of ongoing and new projects, and in dissemination of the need for and the results obtained in colorectal cancer research. The members will give valuable input when designing easily understandable information to patients before inclusion in a project and advice to researchers in difficult ethical aspects related to the projects.

The Centre PIs are grateful to the board members for their willingness to share and publically expose their private experiences with this disease, and we believe this initiative will be beneficial to all parties involved. User involvement in clinical research is a pronounced strategy from the Norwegian health authorities and our hospital.

BOARD MEMBERS:

- Marianne Guriby, 31 years, teacher, previous large bowel cancer patient
- Thorvald Stoltenberg, 85 years, retired politician, previous large bowel cancer patient
- Jack Waitz, 71 years, athlete coach, next of kin of large bowel cancer patient
- 2 more members will be recruited

RAGNHILD A. LOTHE
Professor, Group leader, PhD
Department of Molecular Oncology
Oslo University Hospital

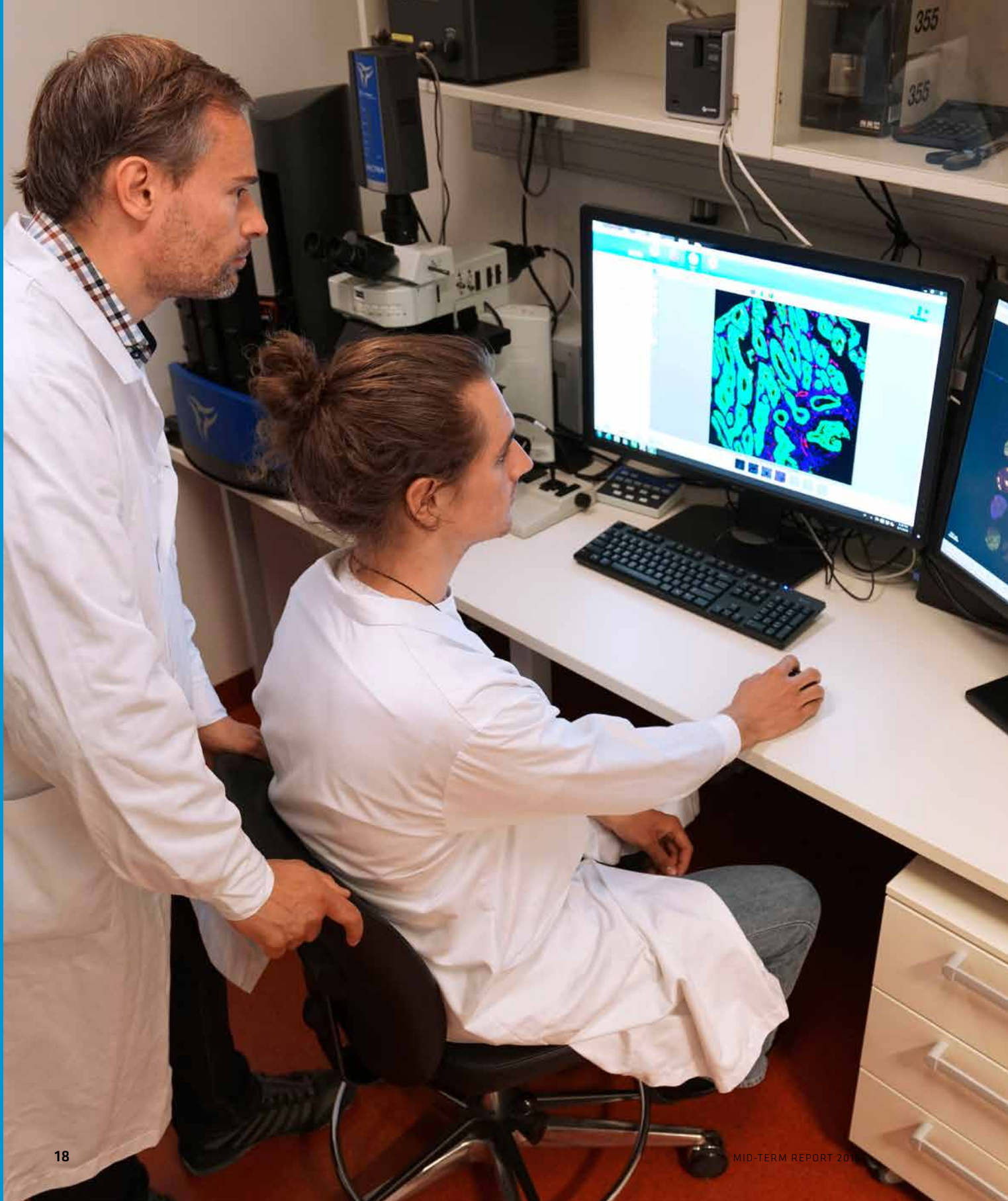
Genetics Group

A new era in cancer genetics has emerged with the development of high-throughput technologies and next generation sequencing – which is highly beneficial for discovery and validation of new and better cancer biomarkers. The current prognostic assessment and prediction of treatment response in colorectal cancer (CRC) are primarily based on clinicopathological factors which lack sufficient precision, resulting in over- and under-treatment of patients.

Our research group combines multilevel genomics, genetics, immunohistochemistry and cell biology to i) discover and develop novel biomarkers and ii) better understand the molecular heterogeneity and mechanisms that promote development and metastasis of CRC. Our overarching goal is to translate novel biomedical knowledge into improved and stratified treatment of CRC.

In the K.G. Jebsen Centre we are studying genomic heterogeneity in primary CRCs and liver metastases, with particular attention to clonal evolution in disease progression and in response to drug treatment. We have identified intra-patient heterogeneity among liver metastatic deposits as a marker of poor prognosis after liver resection. Four consensus molecular subtypes (CMS) of primary CRC have been shown to be associated with distinct clinical features and represent a new framework for exploration of prognostic and predictive biomarkers. We have identified specific drug sensitivities in distinct CMS based on analyses of primary CRCs and drug screening of cell lines and for in vivo validation, xenotrials are in progress at collaborative institution. For identification of effective treatments in individual patients, we are setting up ex vivo drug screening protocols of the patients' own tumor cells in a clinical setting, combined with genomic analyses for identification of predictive markers.

Novel cancer treatment strategies – tumor heterogeneity modeling and ex vivo drug screening



Cancer genomics – clinical and functional biomarkers for improved cancer management

MICHAEL BRETTHAUER
Professor, MD
Clinical Effectiveness Research Group
University of Oslo and
Oslo University Hospital

Clinical Effectiveness Research Group

The history of cancer screening shows that the desire to reduce cancer burden sometimes has resulted in screening programs that are not effective, or even harmful. Therefore, a more scientific approach to cancer screening is needed, especially in our era of fast development of new screening tests, such as imaging techniques, genetic testing and molecular markers.

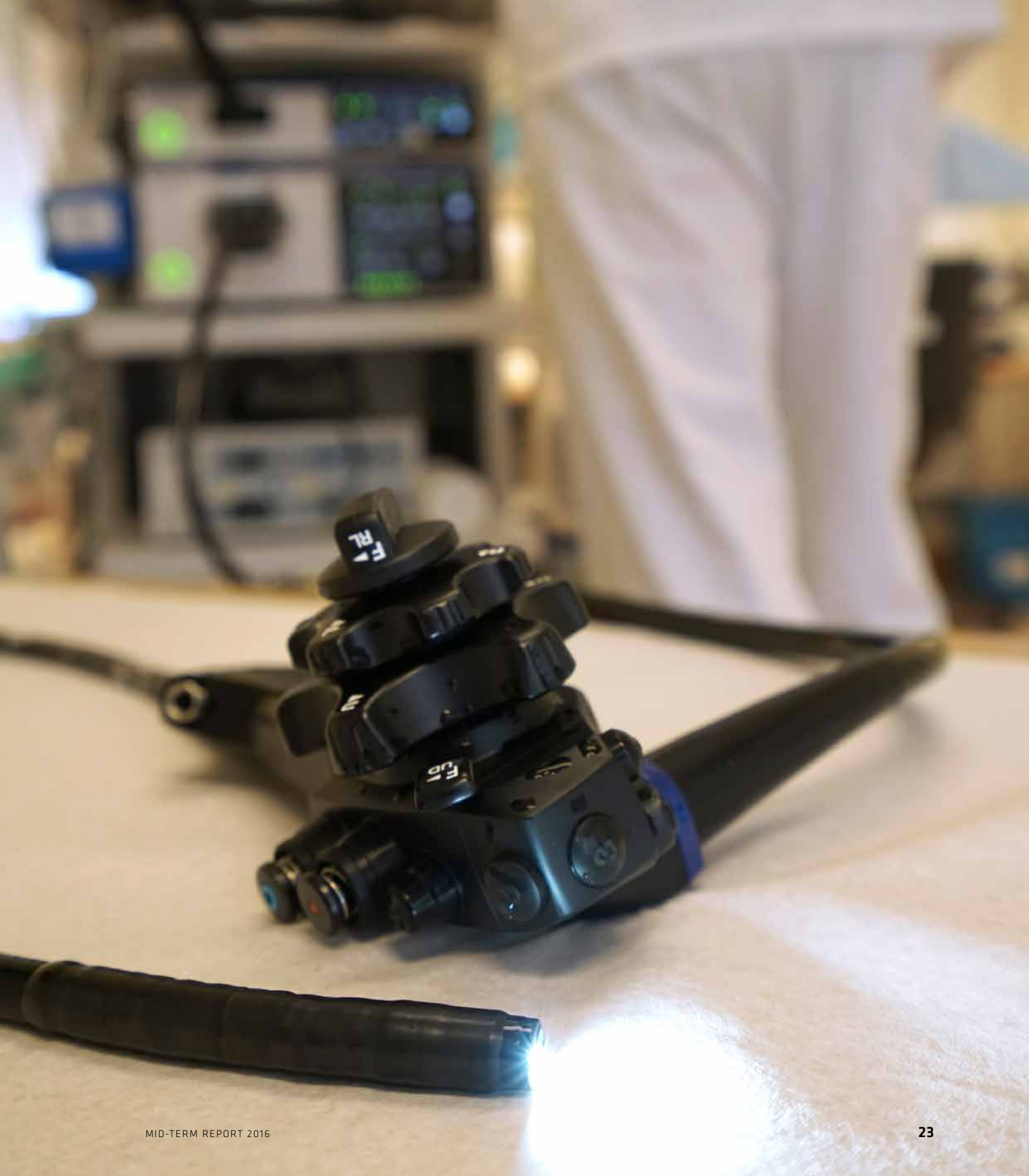
The Clinical Effectiveness Research group was founded in 2012, bringing together experts in clinical trial research and clinical epidemiology in cancer screening to tackle these challenges. Since its inauguration, the group has developed a unique portfolio of large-scale clinical trials and observational studies in cancer screening, with colorectal cancer as a main focus. Our colorectal cancer studies are large, long-term trials which aim at closing important gaps in current knowledge in colorectal cancer screening, surveillance and prevention.

In addition to the EPoS study (see page 46), main projects include:
The **NordICC** (Nordic-European Initiative on Colorectal Cancer) trial, a randomized trial including 95,000 individuals from Norway, Sweden, Netherlands, and Poland. NordICC is the first randomized trial worldwide to disentangle the effect of colonoscopy screening versus no-screening on colorectal cancer incidence and mortality. The trial started in 2009 and has ended recruitment in 2014. First results have been published in 2016 and final results will be available in 2029

NORCCAP (Norwegian Colorectal Cancer Prevention) is a randomized trial with 100,000 participants from Telemark and Oslo, Norway, evaluating the effect of flexible sigmoidoscopy screening on colorectal cancer incidence and mortality. The screening examinations were performed from 1999 to 2001, and interim results were published in 2009 and 2014. The next analysis is planned in 2017.

Finding the best screening test for colorectal cancer

Closing the knowledge gaps in colorectal cancer prevention and surveillance



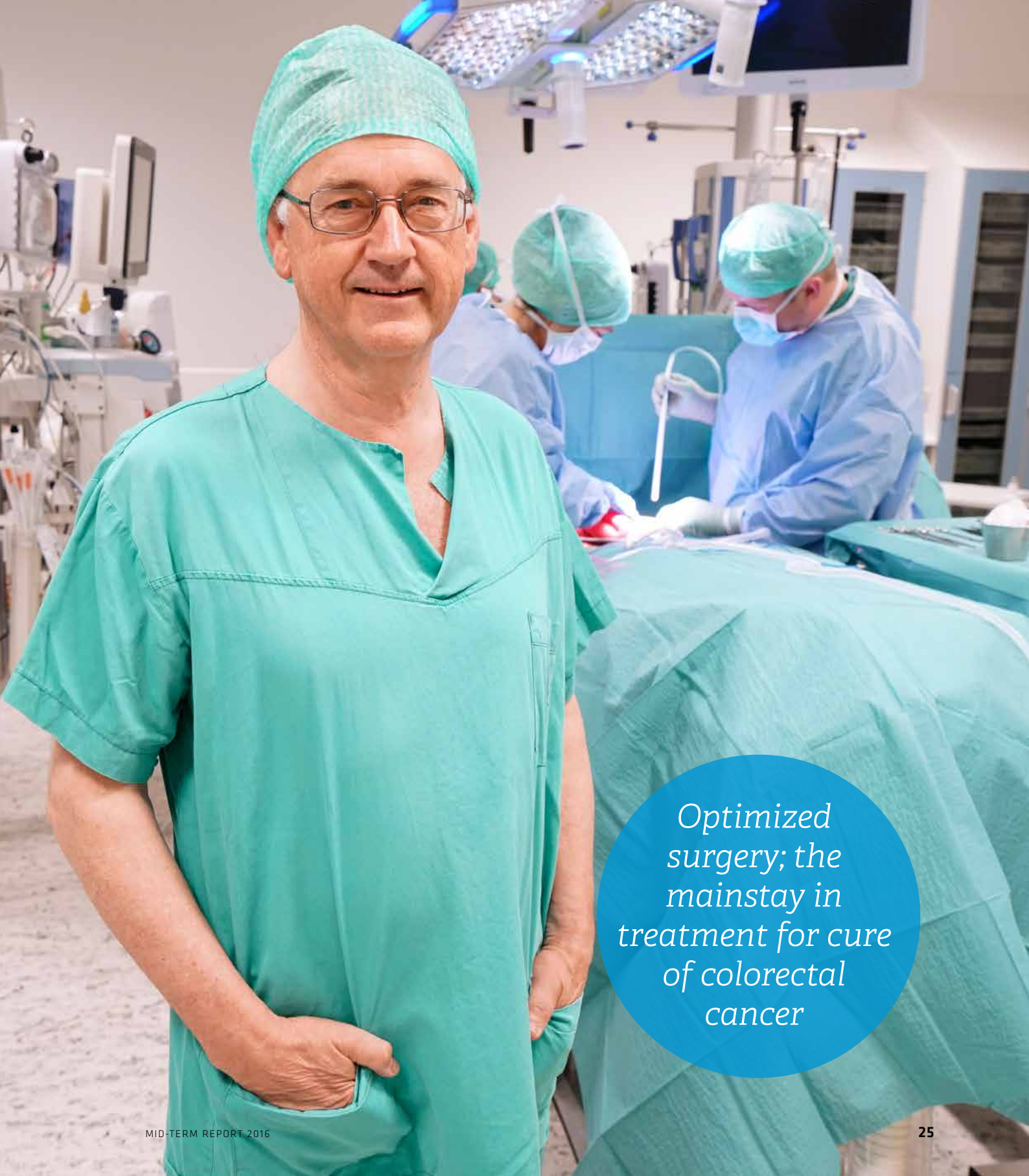
ARILD NESBAKKEN
Professor, MD, Senior Consultant
Department of Gastrointestinal Surgery
Oslo University Hospital

Gastrointestinal Surgery

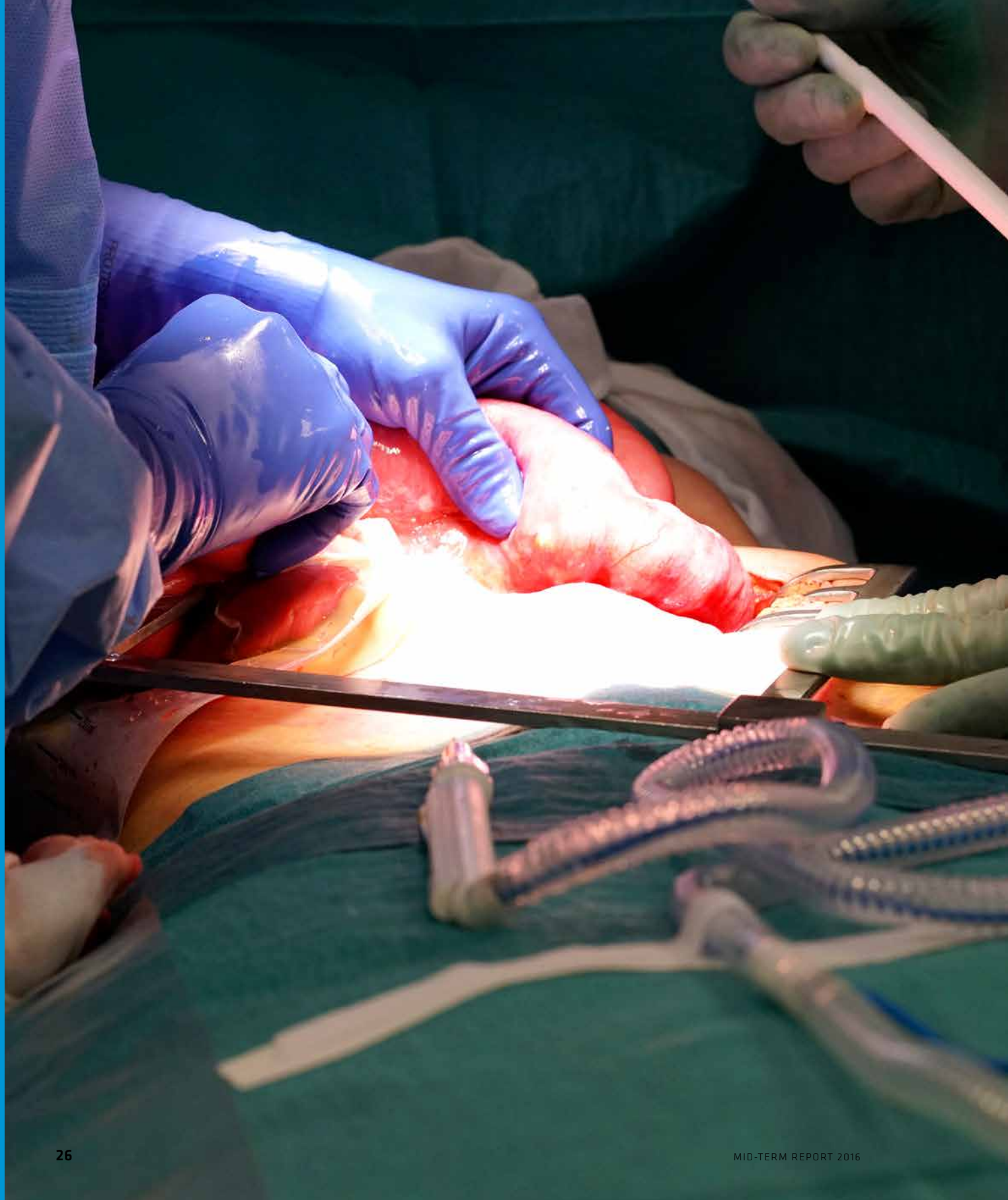
The life-time risk of developing a colorectal cancer is close to 7 % in the Norwegian population. The mainstay of treatment is surgical resection of the bowel segment with the primary tumor and regional lymph nodes, sometimes even resection of metastases in the liver and lung.

Our clinical research projects focus on safety and efficacy of the surgical treatment, especially the outcome after minimally invasive surgery: Laparoscopic approach for major resection of the colon and rectum securing fast recovery after surgery, and transanal endoscopic microsurgery of large polyps and early cancer in the rectum, whereby a permanent stoma can be avoided.

Our translational research is aimed at detection of new and better molecular biomarkers which may simplify detection, prognostication, drug effect prediction and monitoring of the disease. In these efforts high quality registration of clinico-pathological features, high quality sampling of tumor tissue and blood for biobank, and inclusion of a large number of non-selected patients are essential. If we succeed, the result could be a great improvement in screening and treatment of this common cancer, which would be more personalized and tailored to the characteristics of the tumor in the individual patient.

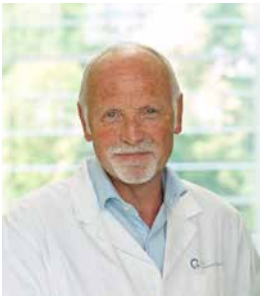


Optimized surgery; the mainstay in treatment for cure of colorectal cancer




Optimized biobanking and detailed clinical annotations – the foundation for translational research

MARIANNE GRØNLIE GUREN
MD, PhD, Oncologist
Department of Oncology
Oslo University Hospital



KJELL MAGNE TVEIT
Professor, MD, PhD
Department of Oncology
Oslo University Hospital

Oncologic Treatment and Research

Oncologic treatment of colorectal cancer includes treatment with chemotherapy and radiotherapy as part of multidisciplinary patient care. Treatment intent can be curative or palliative depending upon disease stage. Adjuvant and neoadjuvant chemotherapy is given to increase the cure rates, and radiotherapy to reduce recurrence rates. Palliative chemotherapy prolongs survival and relieves symptoms, maintaining quality of life.

The Department of Oncology at Oslo University Hospital treats a large number of patients with colorectal cancer from Oslo and the health region. It is a goal to offer more patients inclusion in clinical trials.

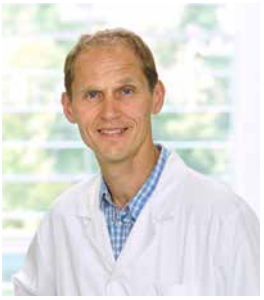
The research projects of the oncology research group include epidemiology, clinical trials to determine the best treatment for patient groups, clinical trials testing the efficacy of new drugs, prognostic and predictive biomarkers, patient-reported outcomes, palliation, and late effects. Through the close collaboration and fruitful discussions within the K.G. Jebsen Colorectal Cancer Centre, the research focus on the clinical impact of molecular oncology has been particularly strengthened.

The overarching goal of the colorectal cancer oncology group is to improve therapy, to provide evidence-based knowledge of the best personalised cancer therapy, and thereby improve survival and quality of life for colorectal cancer patients.

The oncology group participates in the multidisciplinary SMART project, investigating the heterogeneity of colorectal liver metastases. The K.G. Jebsen group has designed the trial "Adjuvant Chemotherapy in Elderly with colon cancer stage III – geriatric assessment and prognostic gene signatures", a randomised phase II study, which has recently started inclusion.


Cutting edge drug combinations to improve survival and quality of life

Molecular medicine in early clinical trials – advancing precision treatment



ROLF I. SKOTHEIM
Associate Professor,
Group leader, Dr.Philos
Department of Molecular Oncology
Oslo University Hospital

Genome Biology Group

The Genome Biology group investigates cancer genomes by integrated computational and laboratory based approaches. The aim is to identify genes that are critically involved in the development of cancer. Such genes may serve as diagnostic or prognostic biomarkers and as targets for molecularly tailored therapy.

The group has had success in discovery and characterization of fusion genes in cancer, including from colorectal cancer. Cross-disciplinary competences in cancer biomedicine, genome technologies, and informatics were enabling these discoveries. The group will now work on large-scale RNA-sequencing data obtained in collaboration with the Lothe and Nesbakken groups. The intention is to identify and develop cancer-specific RNA molecules (transcripts) into clinically useful biomarkers. Cancer-specific transcripts may be detectable from blood, either themselves or their encoded proteins. The search is carried out on the RNA-level since it is currently not feasible to screen the proteome with similar precision and efficiency. Cancer-specific transcripts represent a direct source of detection biomarkers, potentially with prognostic and predictive information. One possibility for therapeutic targeting of the RNA-variants is through immune therapy. The prediction of cancer neoantigens from DNA mutations alone has clear limitations, and identification of which cancer specific variants are actually expressed is of major importance in prediction of true positive neoantigens. Discoveries of cancer-specific variants will also provide new knowledge on the cancer biology.

In the K.G. Jebsen Centre the focus of the Genome Biology group on the cancer transcriptome will add to and be integrated with the interdisciplinary acquisition of multilevel molecular and clinical data from CRC patients, contributing to solve the many clinical challenges we still face for this patient group.


New cancer biomarkers are revealed by cross-disciplinary research


MiniSeq

Synergy between state-of-the-art genome technologies and high-quality clinical biobanks

GURO E. LIND
Professor, Group leader, Dr.Philos
Department of Molecular Oncology
Oslo University Hospital

Group of Epigenetics

Cancer is the result of an accumulation of genetic as well as epigenetic changes. In the group of Epigenetics we are focusing our research on DNA methylation alterations. Our overall aim is to identify methylation biomarkers with clinical impact, including markers for prognostication and monitoring of cancer. Simultaneously, we aim at analyzing and understanding the underlying biology of these aberrations and how they affect the cancer development.

DNA methylation is a likely, but severely understudied, contributor in stratification of colorectal cancers. In collaborative studies within the K.G. Jebsen Colorectal Cancer Research Centre we are focusing on the extremities: cancers with exceptionally frequent- and exceptionally rare-DNA methylation. The first group, comprising 15-20%, is associated with a poor prognosis, but is poorly defined. The second group may represent an intriguing novel, but rare (<5%), subtype with a defect in the DNA methylation machinery, of yet unknown clinical impact. They are currently subjected to basic studies. The methylome pattern in both groups will be addressed by sequencing and integrated in multilevel heterogeneity analyses and stratification of consensus molecular subtypes.


Epigenetic sub-stratification may contribute to improved personalized cancer treatment

TORMOD KYRRE GUREN
MD, PhD, Oncologist
Clinical Cancer Research Unit
Oslo University Hospital

Clinical Cancer Research Unit

The Clinical Cancer Research Unit (CRU), located at The Norwegian Radium Hospital, is a leading center for phase I and early phase II clinical trials in oncology in Norway, and through collaboration between laboratory-based and clinical teams at the hospital, as well as networks nationally and internationally, the CRU aims to provide a pathway from preclinical drug discovery to tumor-specific evaluation of novel treatments.

The CRU has a long-standing experience of cancer immunotherapy as well as targeted therapies where treatments are matched to the particular molecular features of a patient's tumor.

The collaboration with K.G. Jebsen Colorectal Cancer Research Centre involves clinical trials and translational projects in colorectal cancer. In particular, to increase the likelihood that patients will benefit from their treatment, there is a trial in progress where treatment will be stratified based on the molecular signature of a patient's tumor combined with results from high throughput drug sensitivity screening of cancer cells, from cell lines and primary cultures.


Innovative clinical trial designs for the benefit of current and future patients

The Cancer Registry of Norway - active partners in the K.G. Jebsen Centre:

THOMAS DE LANGE
Dr.Med.
Section for Bowel Cancer Screening

GEIR HOFF
Dr.Med.
Section for Bowel Cancer Screening

BJØRN MØLLER
Cand. Scient, Dr.Philos.
Department of Registration

Section for Bowel Cancer Screening

The Cancer Registry of Norway is a leading Institute for Population-based Cancer Research since the 1950ies. The Bowel Cancer Screening section leads a pilot on a national colorectal cancer (CRC) screening program. This randomized comparative effectiveness trial invites 140,000 persons age 50-74 years and compares the effect of flexible sigmoidoscopy and faecal immunochemical test. Both aim to detect premalignant precursor lesions (polyps) and CRC to reduce the incidence and mortality of CRC. The section is also participating in research regarding the development of new screening methods and is collaborating with laboratory, clinical and computer scientist teams. The section has networks nationally and internationally.

The collaboration with K.G. Jebsen Colorectal Cancer Research Centre involves trials for the development of biomarkers for colorectal cancer screening, in particular to develop less invasive screening methods. There is a trial in progress to discover biomarkers in buffered faeces samples.


Discovering less invasive screening methods to reduce the incidence of colorectal cancer

BJØRN ATLE BJØRNBETH
MD, Head of Department
Gastrointestinal and Paediatric Surgery
Oslo University Hospital

BÅRD RØSOK
MD, PhD
Gastrointestinal and Paediatric Surgery
Oslo University Hospital

Liver and Pancreatic Surgery

We are a regional unit serving approximately 3 million people with HPB surgery (hepato, pancreatic and biliary surgery).

Our unit performed 340 liver resections and 170 pancreatic resections in 2015.

We run quality registries for both liver and pancreatic surgery. We systematically report all our complications into the NorGast registry. We are organized together with transplantation -, radiology- and gastromedical- teams ensuring ability to resolve most technical challenges.

The unit is heavily engaged in clinical and translational research. We are engaged in trials comparing liver surgery techniques; comparing open and laparoscopic liver surgery as well as comparing portal vein ligation and ALPPS, two techniques for expanding future liver remnant by extended liver resections.

The SMART project/K.G. Jebsen Centre project is a major project currently running in the department. The clinical research logistics was set up in 2013 and is truly an interdisciplinary effort. By now more than 200 patients (>1000 samples) are included in this major task to unravel molecular tumor heterogeneity and its impact on prognosis and effect of treatment.

Will new discoveries in molecular tumor heterogeneity and colorectal cancer liver metastases lead to new surgical strategies?

ANDREAS ABILDGAARD
MD, PhD, Radiologist

VANJA CENGIJA
MD, Radiologist

Division of Radiology
and Nuclear Medicine
Oslo University Hospital

Unit for Abdominal Imaging

Liver imaging is one of the main focus areas of the unit for Abdominal imaging at Rikshospitalet, OUS. Magnetic Resonance Imaging (MRI) and Computed Tomography (CT) are essential techniques for diagnosing colorectal liver metastases and for evaluation of anti-tumor treatment.

Through our collaboration with the K. G. Jebsen centre we are focusing on new methods for evaluation of liver metastases before and after different therapy protocols. Traditionally, size measurements have been used for therapy response evaluation after chemotherapy, although it is well known that size reduction is a slow and somewhat unpredictable therapy response. Comprehensive MR-evaluation of liver metastasis includes a number of techniques that reflect different aspects and properties of the tumors. This includes the use of liver-specific contrast media which selectively enhance the signal from liver cells, as well as diffusion MRI which provides a semi-quantitative measure of the thermal motion of water molecules in the tissues.

In the interdisciplinary effort of the K.G. Jebsen Centre we seek a better understanding of how molecular tumor properties and patient therapy response are associated with intra-organ multiparametric MR-information of each metastatic lesion.

Radiological liver imaging: towards a non-invasive, multiparametric characterization of tissue properties.

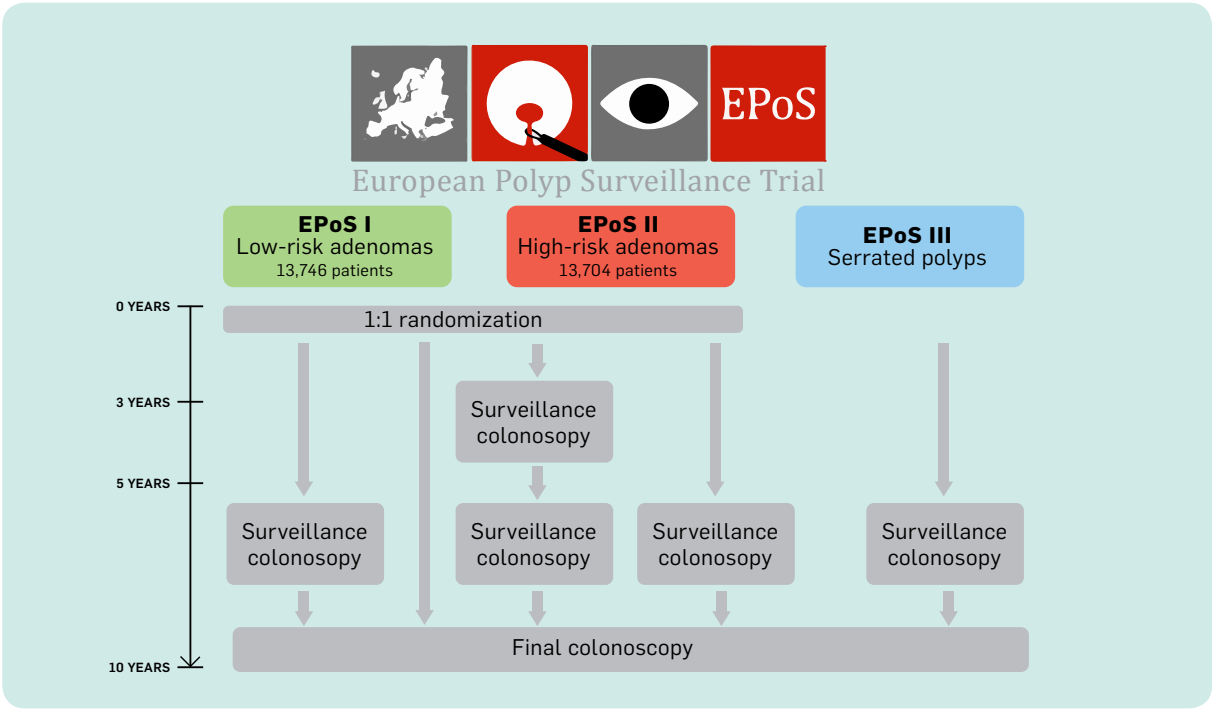
Clinical studies

EPoS – European Polyp Surveillance trials

EPoS is a portfolio of large clinical trials, including more than 30,000 participants from different European countries under Norwegian leadership; Sweden, Denmark, Spain, Poland, Netherlands, Italy, Portugal.

The aim of EPoS is to develop evidence-based guidance for surveillance of patients with colorectal polyps. These patients are today subjected to frequent surveillance colonoscopy, resulting in a significant burden for the patients and the society. If such surveillance is necessary is unclear. EPoS randomized patients after removal of polyps to different surveillance intervals, and the hypothesis is that longer intervals will be non-inferior to shorter intervals. Thus, the EPoS trials will address one of the most challenging and timely questions in colorectal cancer screening and surveillance today.

Many countries are facing a serious overload of colonoscopy demands, mainly because of the large number of patients which are recommended surveillance after screening with polypectomy. This workload has led to long waiting lists in many countries, and is jeopardizing the clinical colonoscopy service. EPoS aims at informing more sustainable guidelines for polyp surveillance, with less waste of resources for the society, and less burden for the individual patient.



Adjuvant chemotherapy in elderly with colon cancer stage III – geriatric assessment and prognostic gene signatures

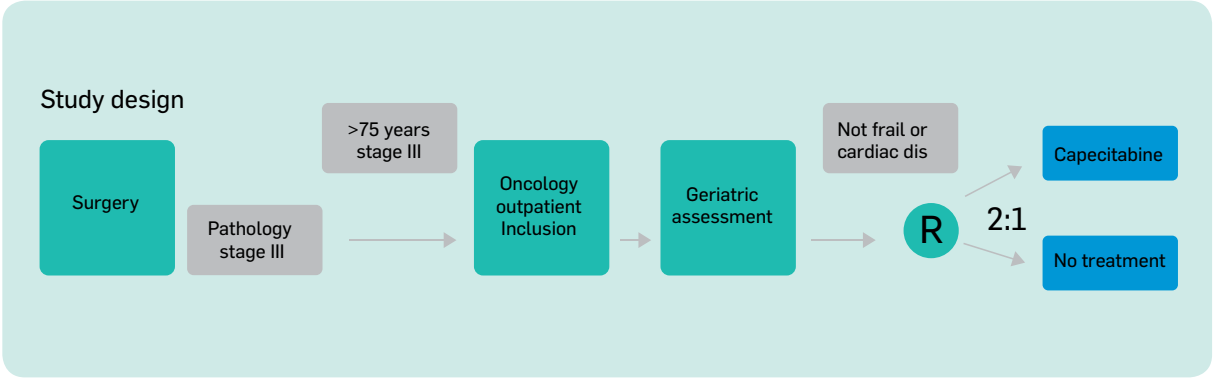
Colon cancer incidence increases significantly with age. After surgery, adjuvant chemotherapy is recommended for patients with regional lymph node metastases. In patients ≥75 years, individual consideration based on functional status, performance status, and comorbidity is recommended.

Elderly are rarely included in clinical studies, and few actually receive chemotherapy. It is expected that chemotherapy has good efficacy provided right patient selection. There is a need for prospective studies in elderly investigating tolerability and efficacy of chemotherapy. Prognostic biomarkers are available, but need validation before use for treatment decisions.

The aim of the study is to investigate the tolerance of adjuvant chemotherapy, measured by functional decline, in elderly patients with colon cancer. Secondary aims are disease-free survival, toxicity, late functional outcome, quality of life, to establish a geriatric assessment, and to examine the prognostic value of molecular biomarkers.

Patients ≥75 years operated for colon cancer stage III are eligible for this randomised phase 2 study. A geriatric assessment is perfomed. Patients classified as fit or intermediate, without significant cardiovascular disease, are randomised 2:1 to either capecitabine for 6 months or no chemotherapy. The primary endpoint is determined by geriatric assessment after 1 year. The multi-centre study plans to include 170 patients, and is open for inclusion.

This study has been designed by a multidisciplinary research group within the K.G. Jebsen Colorectal Cancer Research Centre, including specialists in oncology, gastrointestinal surgery, geriatric medicine, and molecular biology.



External funding

Centre PIs substantially supported through the TOPPFORSK grant from the Norwegian Research Council

Professors Ragnhild A. Lothe and Michael Bretthauer were granted the *FRIPRO Toppforsk projects:

"Modeling tumor heterogeneity in colorectal cancer management" and "COLOSS - COLOn Screening and Surveillance: Comparative Effectiveness of Colorectal Cancer Screening and Surveillance" respectively.

The financial support to these two project is a shared venture between the Research Council and the University of Oslo.

*The Research Council of Norway and Norway's research institutions are providing a total of NOK 1 billion to 46 FRIPRO Toppforsk projects (FRIPRO – "Frie prosjektmidler"). Each project will receive NOK 15–25 million over a four-to-five-year period. FRIPRO is an open competitive arena for all research areas and disciplines, where there are no thematic guidelines and no requirements relating to the applicability or immediate utility of the research.

Prizes and awards

Honors received by members of the K.G. Jebsen Centre:

Early Career Award 2014 from Oslo University Hospital to **EDWARD LEITHE**

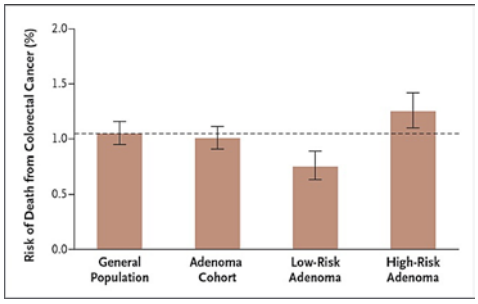
Ragnar Mørk legacy prize 2015 to **GURO E. LIND**

Excellent article award 2016 from Oslo University Hospital to **JARLE BRUUN**

Selected publications June 2014 - June 2016

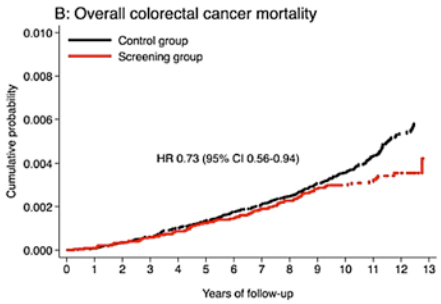
2014

Long-term colorectal-cancer mortality after adenoma removal
Løberg M, Kalager M, Holme Ø, Hoff G, Adami HO, Bretthauer M.
N Engl J Med. 2014 Aug 28;371(9):799-807.



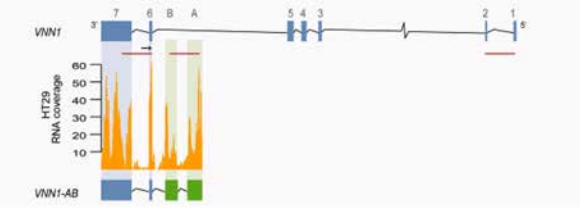
Colorectal-Cancer Mortality in a Cohort of Patients Who Underwent Removal of Adenomas and in the General Population.
The graph shows the risk of death from colorectal cancer after a median follow-up of 7.7 years (maximum, 19) in the general population (dashed line) and in the cohort of patients with adenomas that were removed, which included patients who had high-risk adenomas and those who had low-risk adenomas. I bars indicate 95% confidence intervals.

Effect of flexible sigmoidoscopy screening on colorectal cancer incidence and mortality: a randomized clinical trial
Holme Ø, Løberg M, Kalager M, Bretthauer M, Hernan MA, Aas E, Eide TJ, Skovlund E, Schneede J, Tveit KM, Hoff G.
JAMA 2014;312(6):606-15.



In Norway, once-only flexible sigmoidoscopy screening or flexible sigmoidoscopy and FOBT reduced colorectal cancer incidence and mortality on a population level compared with no screening. Screening was effective both in the 50–54 and the 55–64 year age-group.

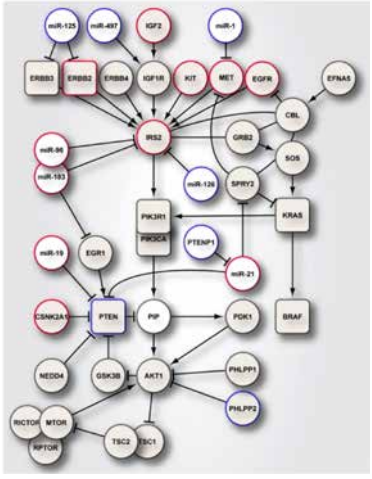
A novel transcript, VNN1-AB, as a biomarker for colorectal cancer
Løvf M, Nome T, Bruun J, Eknæs M, Bakken AC, Mpindi JP, Kilpinen S, Rognum TO, Nesbakken A, Kallioniemi O, Lothe RA, and Skotheim RI.
Int J Cancer. 2014 Nov 1;135(9):2077-84.



Identification of a novel transcript of the VNN1 gene, VNN1-AB,with an organ-confined complete specificity for colorectal neoplasia. VNN1-AB was not present in any of the 43 normal colorectal tissue samples investigated, but in 5 of the 6 polyps, and 102 of the 136 (75%) colorectal cancers.

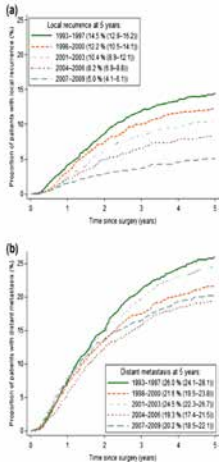
2015

Portrait of the PI3K/AKT pathway in colorectal cancer
Danielsen SA, Eide PW, Nesbakken A, Guren T, Leithe E, Lothe RA.
Biochim Biophys Acta – Reviews on Cancer. 2015 Jan;1855(1):104-121.



The PI3K/AKT pathway with components and alterations. Blue color represents copy number loss and/or downregulation, whereas red color symbolizes amplification and/or overexpression. Rounded squares are genes frequently mutated in colorectal cancer. Arrows and T-shaped lines indicate positive and negative interactions, respectively.

Nationwide improvement of rectal cancer treatment outcomes in Norway, 1993–2010
Guren MG, Kørner H, Pfeffer F, Myklebust TÅ, Eriksen MT, Edna TH, Larsen SG, Knudsen KO, Nesbakken A, Wasmuth HH, Vonen B, Hofsli E, Færden AE, Brændengen M, Dahl O, Steigen SE, Johansen MJ, Lindsetmo RO, Drolsum A, Tollåli G, Dørum LM, Møller B, Wibe A.
Acta Oncologica 2015 Nov;54 (10):1714-1722.



Long-term outcomes from a national population-based rectal cancer registry are presented. Improvements in rectal cancer treatment have led to decreased recurrence rates of 5% and increased survival on a national level.

A review of the evolution of systemic chemotherapy in the management of colorectal cancer.
Gustavsson B, Carlsson G, Machover D, Petrelli N, Roth A, Schmoll HJ, Tveit KM, Gibson F.
Clin Colorectal Cancer 2015 Mar;14(1):1-10.

Modeling and validating the cost and clinical pathway of colorectal cancer
Joranger P, Nesbakken A, Hoff G, Sorbye H, Oshaug A, Aas E.
Med Decis Making. 2015 Feb;35(2):255-65.

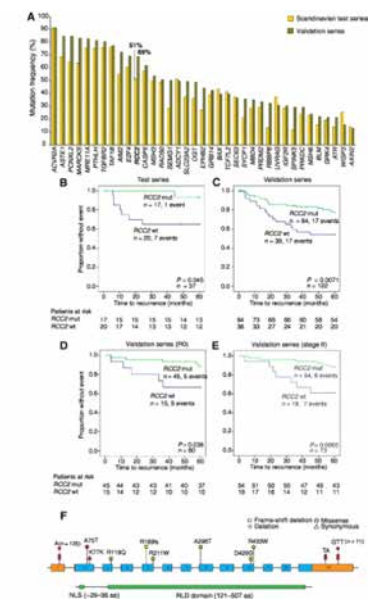
A randomized phase II/III study of Dalotuzumab in combination with Cetuximab and Irinotecan in chemorefractory, KRAS wild-type, metastatic colorectal cancer
Sclafani F, Kim TY, Cunningham D, Kim TW, Tabernero J, Schmoll HJ, Roh JK, Kim SY, Park YS, Guren TK, Hawkes E, Clarke SJ, Ferry D, Frödin JE, Ayers M, Nebozhyn M, Peckitt C, Loboda A, Mauro DJ, Watkins DJ.
J Natl Cancer Inst. 2015 Sep 23;107(12):djv258.

The novel colorectal cancer biomarkers CDO1, ZSCAN18 and ZNF331 are frequently methylated across gastrointestinal cancers

Vedeld HM, Andresen K, Eilertsen IA, Nesbakken A, Seruca R, Gladhaug IP, Thiis-Evensen E, Rognum TO, Boberg KM, Lind GE.
Int J Cancer. 2015 Feb 15;136(4):844-53

Regulator of chromosome condensation 2 identifies high-risk patients within both major phenotypes of colorectal cancer

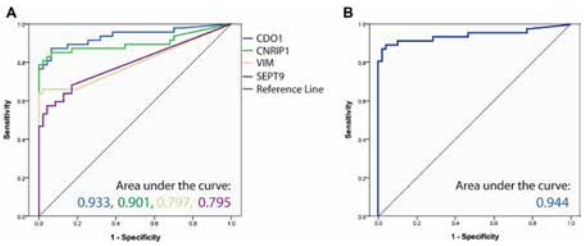
Bruun J, Kolberg M, Ahlquist TC, Røyrvik EC, Nome T, Leithe E, Lind GE, Merok MA, Rognum TO, Bjørkøy G, Johansen T, Lindblom A, Sun XF, Svindland A, Liestøl K, Nesbakken A, Skotheim RI, Lothe RA.
Clin Cancer Res. 2015 Aug 15;21(16):3759-70.



Microsatellite mutations in the 5′ UTR of RCC2 are associated with improved outcome for patients with colorectal cancers of the MSI phenotype. Microsatellite mutation frequencies for MSI target genes in the compiled Scandinavian series and Norwegian validation series (A). Kaplan–Meier TTR analysis (log-rank test) for colorectal cancer patients with MSI tumors stratified by the RCC2 5′ UTR mutation in the test series (B) and the validation series (C), and patients from the validation series with complete resection (R0, no evidence of residual tumor), right-sided tumors, and follow-up data of more than 36 months (D). Subgroup analysis for patients with stage II colorectal cancer (E). Nucleotide-level somatic mutation data in colorectal cancer from the complete length of RCC2 (F).

Four DNA methylation biomarkers in biliary brush samples accurately identify the presence of cholangiocarcinoma

Andresen K, Boberg KM, Vedeld HM, Honne H, Jebsen P, Hektoen M, Wadsworth CA, Clausen OP, Lundin KE, Paulsen V, Foss A, Mathisen Ø, Aabakken L, Schrumpf E, Lothe RA, Lind GE.
Hepatology. 2015 May;61(5):1651-9.

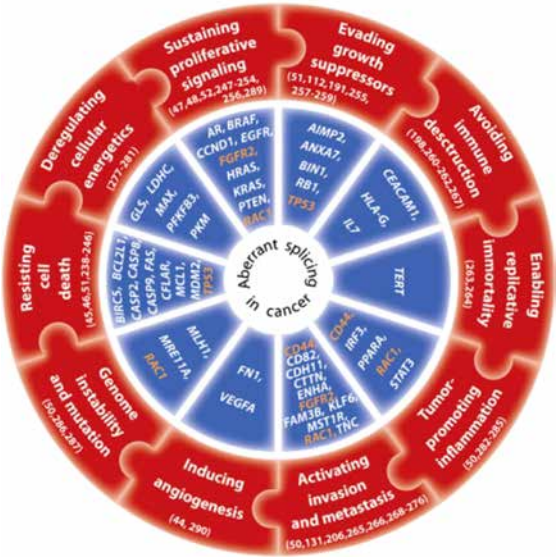


A biomarker assay with high sensitivity and specificity for cholangiocarcinoma, outperformes standard brush cytology. The biomarker panel, potentially in combination with cytological evaluation, may improve CCA detection. Receiver operating characteristic curves for the four-gene biomarker panel in all biliary brush samples. The area under the ROC curve is depicted for (A) the biomarkers CDO1, CNRIP1, SEPT9, and VIM and for (B) the combined biomarker panel, which is based on the sum of the four PMR values.

2016

Aberrant RNA splicing in cancer; expression changes and driver mutations of splicing factor genes

Sveen A, Kilpinen S, Ruusulehto A, Lothe RA, Skotheim RI.
Oncogene. 2016 May 12;35(19):2413-27. Review.



Alternative splicing and cancer hallmarks. Alternative splicing of important genes (blue background) have been implicated in regulation of each of the hallmarks of cancer (red background). Some genes (orange) are implicated in several of the hallmarks.

Rationale and design of the European Polyp Surveillance (EPoS) trials

Jover R, Bretthauer M, Dekker E, Holme Ø, Kaminski MF, Løberg M, Zauber AG, Hernán MA, Lansdorp-Vogelaar I, Sunde A, McFadden E, Castells A, Regula J, Quintero E, Pellisé M, Senore C, Kalager M, Dinis-Ribeiro M, Emilsson L, Ransohoff DF, Hoff G, Adami HO.
Endoscopy. 2016 Jun;48(6):571-8.

The present trials, EPoS I and II include close to 28,000 individuals, aim to develop evidence-based strategies for polyp surveillance, thereby maximizing effectiveness and minimizing resources. See page 46.

Population-based colonoscopy screening for colorectal cancer: a European randomized trial

Bretthauer M, Kaminski MF, Løberg M, Zauber AG, Regula J, Kuipers EJ, Hernán MA, McFadden E, Sunde A, Kalager M, Dekker E, Lansdorp-Vogelaar I, Garborg K, Rupinski M, Spaander MC, Bugajski M, Høie O, Stefansson T, Hoff G, Adami HO; Nordic-European Initiative on Colorectal Cancer (NordICC) Study Group.
JAMA Intern Med. 2016 Jul 1;176(7):894-902.

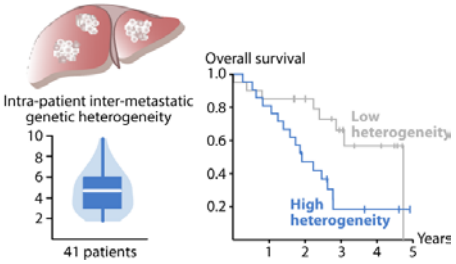
Colonoscopy screening entails high detection rates in the proximal and distal colon. Participation rates and endoscopist performance vary significantly. Postprocedure abdominal pain is common with standard air insufflation and can be significantly reduced by using CO_2.

Who is for CO_2? Slow adoption of carbon dioxide insufflation in colonoscopy

Bretthauer M, Kalager M, Adami HO, Hoff G.
Ann Intern Med. 2016 Jul 19;165(2):145-6. See page 57.

Intra-patient inter-metastatic genetic heterogeneity in colorectal cancer as a key determinant of survival after curative liver resection

Sveen A, Løes IM, **Alagaratnam S**, Nilsen G, **Høland M**, Lingjærde OC, Sorbye H, **Berg KC**, Horn A, Angelsen JH, Knappskog S, Lønning PE, **Lothe RA**.
PLoS Genet. 2016 Jul 29;12(7):e1006225.



This study shows that patients with a low level of heterogeneity among liver metastases, based on DNA copy number analyses of multiple metastatic deposits per patient, have a four times better overall survival rate than patients with a high level of heterogeneity.

Selected presentations

ASCO-GI 2016

American Society for Clinical Oncology – Gastrointestinal cancer.
San Francisco, CA, USA, January 2016.

Invited plenary session speaker: Michael Bretthauer "Colorectal polyp surveillance".

WEA San Diego 2016

Invited speaker: Bretthauer M
Effectiveness of colonoscopy screening in older adults.
Digestive Disease Week 2016, World Endoscopy Association meeting, San Diego, CA, May 2016.

AACR 2016

American Association for Cancer Research, New Orleans, Louisiana, USA, April 2016. Dr. Rodrigo Dienstmann, SAGE Bionetwork, presented first results from the American Joint Committee on Cancer - AJCC biomarker project. Prognosis prediction in colorectal cancer: from single markers to genomic signatures. A collaborative international partner study, including K. G. Jebsen Centre for Colorectal Cancer Research, Lothe RA and Nesbakken A.

ASCO Chicago 2016

At the Annual Meeting of American Society of Clinical Oncology Professor Josep Tabernero presented preliminary results from a multi centre study with international partners including K.G. Jebsen Centre for Colorectal Research (Guren TK). Tabernero J, van Geel R, Guren TK, et al. Phase 2 results: Encorafenib (ENCO) and cetuximab (CETUX) with or without alpelisib (ALP) in patients with advanced BRAF-mutant colorectal cancer (BRAFm CRC). J Clin Oncol 2016, 34: 3544a.

Biomarkers Helsinki 2015

Invited speaker: Lind GE
Epigenetic cancer biomarkers for early detection and monitoring – challenges in the path to innovation and commercialization.
Biomarkers in Clinical and Translational Research – the ABCs of Biomarkers, Helsinki, Finland, October 2015.

NERC Bergen 2015

Invited speaker: Guren MG
How have the guidelines for chemoradiotherapy affected treatment of rectal cancer in Norway?
Nordic Early Rectal Cancer meeting (NERC), Solstrand, Norway, May 2015.

JSGE Osaka 2015

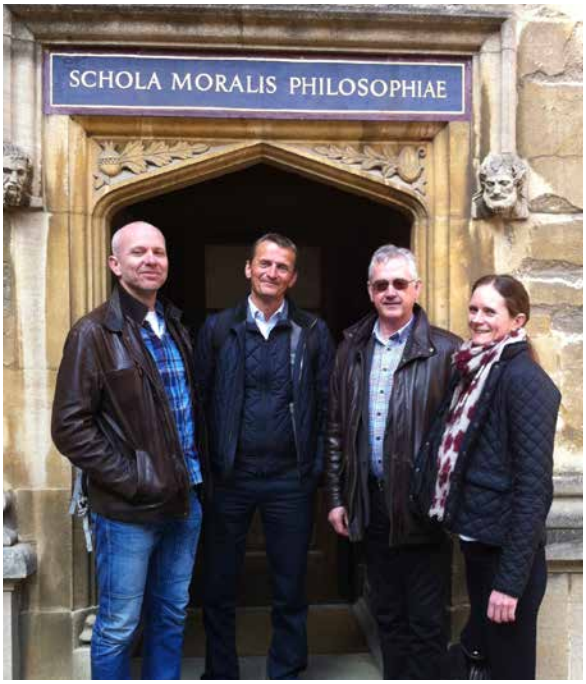
Invited speaker: Bretthauer M
State-of-the-art in Colorectal Cancer Screening.
Japanese Society of Gastrointestinal Endoscopy conference on colorectal polyps, Osaka, Japan, May 2015.

Colorectal cancer network seminar, The Queen's College, Oxford, March 2015

Invited speakers: Lothe RA
Biomarkers identified from temporal genomics of colorectal cancer. Challenges in clinical implementation.

Nesbakken A, Bjørnbeth BA
An interdisciplinary CRC research project: Focus on resectable liver metastases.

Sveen A
Prognostic potential of structural and quantitative transcriptome variation in CRC.



Bjørn Atle Bjørnbeth, Pål Dag Line, Arild Nesbakken and Anita Sveen, Oxford 2015

EATRIS Amsterdam 2014

Invited speaker: Lothe RA
Colorectal cancer biomarkers – an experience from discovery to innovation and clinical implementation.
EATRIS- Biomarkers. Amsterdam, Netherlands, November 2014.

GAP conference Seoul 2014

Oral presentations:
Skotheim RI*, Hoff AM, Bruun J, Nome T, Løvf M, Nesbakken A, Lothe RA. Novel fusion transcripts expressed at high frequency in colorectal cancer.

Sveen A*, Nesbakken A, Lothe RA.
One Size Fits Few ~ Molecular Subgrouping For Improved Prognostic Stratification and Optimized Treatment of Patients with Colorectal Cancer.

Global Academic Programs Conference, Seoul, South-Korea, 2014 *Presenting authors

University of Porto 2014

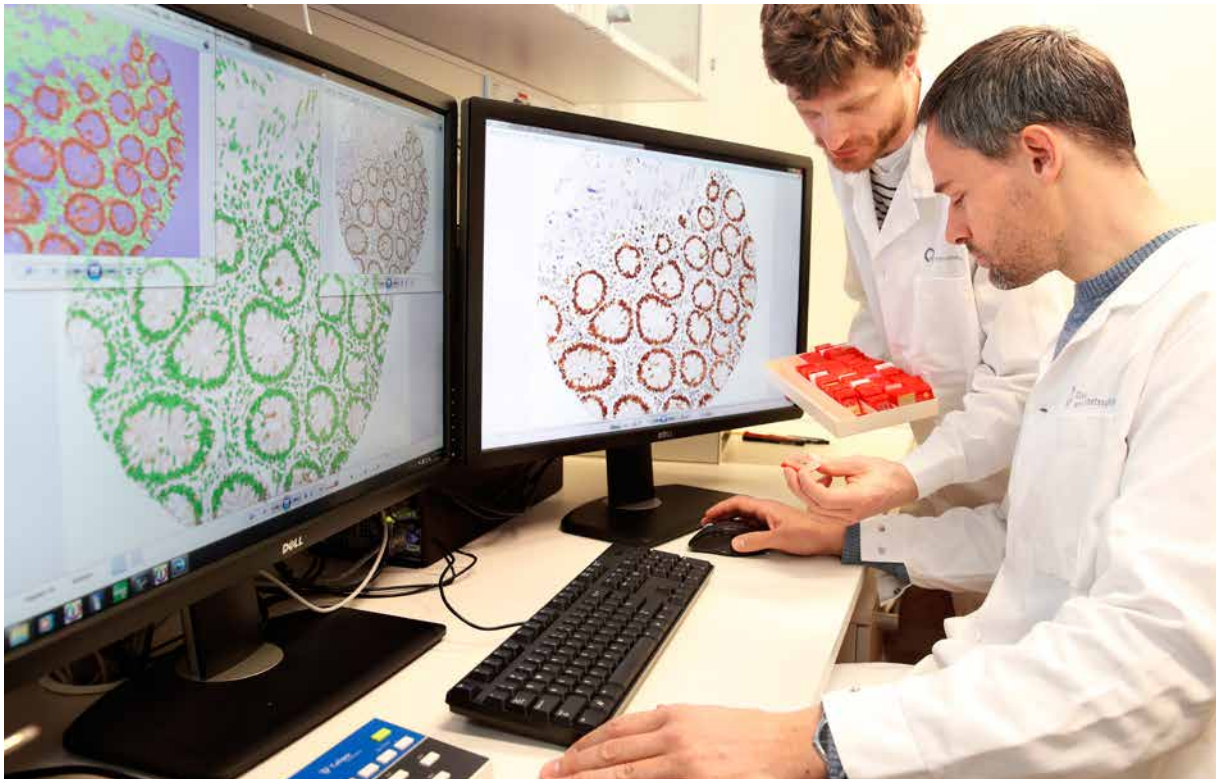
Invited speaker: Lothe RA
Translating basic research into clinically relevant information: the colorectal cancer model.
25 years anniversary, IPATIMUP, University of Porto, Portugal, September 2014.

Director of IPATIMUP, professor Manuel Sobrinho-Simoes and his team are a long term collaborator of the Norwegian Radium Hospital.
Recently, a formal collaboration agreement between the Portuguese Institution and Oslo University Hospital was signed.

RA Lothe and M Sobrinho-Simoes

Oncology Forum Oslo 2014

Invited speaker: Nesbakken A
Prognostic and predictive biomarkers in colorectal cancer
Oncology Forum, Oslo, Norway, 2014



Cutting Edge Technologies

Deep sequencing of DNA and RNA

The groups of Lothe and Skotheim have for the past seven years put emphasis on the establishment of deep sequencing technologies for cancer research, both for wet-lab protocols and computational infrastructure and analysis pipelines. For the discovery based sequencing such as exome, transcriptome, miR-ome we use the work horse platforms at the Genomics Core Facility, OUH, the Norwegian Radium hospital, receiving the raw data for storage and handling in-lab. Recently, and in full through the K.G. Jebsen Centre, we have installed a new Illumina sequencer in-lab, the so-called MiniSeq machine, which will enable full flexibility and access to deep sequencing technology on the day-to-day basis. This high-throughput sequencer enables mass sequencing of whole or selected parts of the DNA or RNA content within a sample.

High-performance computation

Medical research is one of the fastest growing fields of big data science, and with large progress being made on the technical laboratory side, there is now a challenge on how to transform all of the numbers and genome sequences into improved and more personalized cancer treatment. Tons of data are being generated from genome sequencing projects all over the world, and there are great opportunities for collecting relevant information and building a solid knowledge base. However, the computing power and storage capacity are constantly challenged by increasingly larger datasets. For genome-scale data from local patient cohorts, the Skotheim group has participated in the development of the Services for sensitive data, established at the Center for Information Technology (USIT) at the University of Oslo. These services not only pro-

vide storage space and computational resources for the Jebsen centre project, but they also comply with the national legislations concerning research on sensitive data. Members of the Lothe and Skotheim groups have established several data analysis pipelines within this computational infrastructure for transforming digital signals into meaningful biomedical information.

Digital PCR

Droplet digital PCR (ddPCR) takes advantage of oil/water emulsion, separating PCR reagents and DNA or RNA template into thousands of nanoliter -sized droplets. By digital counting of individual fluorescent droplets it is possible to perform absolute quantification of nucleic acid target sequences. The Bio-Rad QX200 system has been established in the Department of Molecular Oncology, and the Lind group has recently worked out a methodological protocol for quantitative detection of small amounts of DNA methylated molecules in liquid biopsies from cancer patients. Other applications of the technology within the Jebsen projects include measurement of linkage between two genetic loci to establish the presence of chromosomal rearrangements in cancer, absolute gene expression measurements, and detection of aberrant DNA copy numbers and rare mutations with low allele frequencies. The latter application is highly attractive in the prospect of detecting cancer mutations in liquid biopsies, where the mutated DNA has very low abundance compared to wild-type molecules.

Computational pathology for biomarker discovery

A complete cutting edge histopathology pipeline has been established in the Lothe group which enables large scale multidimensional biomarker studies in tissue sections. This pipeline is centered around the Vectra 3 quantitative pathology imaging platform from Perkin Elmer which integrates semi-automated high-throughput multispectral imaging (200 slide capacity) for both brightfield and fluorescence with advanced pattern recognition software to perform automated digital image analysis of biomarker expression according to tissue (stroma/epithelia) and cellular (nucleus, cytosol and membrane) compartments. This system can detect and measure weakly expressed and colocalized signals accurately for hematoxilin and eosin (HE)-, Immunohistochemical (IHC)- or immunofluorescence (IF)- stained sections from either whole formalin-fixed paraffin embedded (FFPE) blocks or from tissue micro arrays (TMA). Protocols for sequential multiplexed immunohistochemistry of up to seven (fluorescent), plus three (chromogenic) biomarkers are being established. Objective quantitation of multiplexed multispectral images of 4-10 biomarkers per tissue section allows assessment of biological and prognostic relationships in the tumor microenvironment that are not attainable by conventional immunohistochemistry/microscopy.

The use of CO2 versus air in colonoscopy

During colonoscopy, the colon needs to be distended to increase detection of cancer and polyps. Traditionally, 8-7 L of room air is used for insufflation (as compared to 1 L/day normally produced by the intestine). This leads to considerable abdominal pain and discomfort for many patients.

Through several groundbreaking studies over the past 15 years, the Bretthauer group has established that the replacement of room air by carbon dioxide as insufflation gas during colonoscopy significantly reduces patient pain and discomfort in colonoscopy.

CO2 insufflation is now standard gas at Norwegian hospitals, and is replacing air also at more and more leading centres worldwide.

Reference:

Who is for CO2? Slow Adoption of Carbon Dioxide Insufflation in Colonoscopy
Bretthauer M, Kalager M, Adami HO, Hoff G.
Ann Intern Med. 2016 Jul 19;165(2):145-6.

Events

28th August 2014: Formal opening of the K.G. Jebsen Colorectal Cancer Research Centre at Holmenkollen Park Hotel, Oslo

Hans Peter Jebsen (left) from the K.G. Jebsen Foundation, formally awarding the Centre to professor Ragnhild A. Lothe, Centre director, together with professor Sigbjørn Smeland, head of the Cancer Clinic at Oslo University Hospital, the host institution of the Centre.

The program included presentations by representatives from the K.G. Jebsen Foundation, the host institution, the University, the South-Eastern Norway Regional Health Authorities as well as the PIs and guest scientists.

Professor Ole Petter Ottersen, Rector of the University of Oslo

John Torgils Vaage, The director of Research and Innovation at the South-Eastern Norway Regional Health Authority

K.G. Jebsen Foundation board members Birger Magnus (left) and Borger A. Lenth (right) in discussions with associated investigator, professor Hans Olov Adami.

Postdoc Øyvind Holme (Bretthauer group), prof Ragnhild A. Lothe, prof Arild Nesbakken, associated investigator, Thomas de Lange, head of CRC screening program, the Cancer Registry of Norway

Associated investigator, prof Geir Hoff, the Cancer Registry of Norway, PhD Marianne Merok (Nesbakken group)

Steinar Funderud, the Radium Hospital Legacy Foundation, Stein Kvaløy, head of research, the Cancer Clinic, OUH, Ola Myklebost, Head of the Norwegian Cancer Genomics Consortium, Gunnar Sæter, head of Institute for Cancer Research, OUH

Professors Thoralf Christoffersen and Arild Nesbakken

Associated investigator, Tormod Guren, Trial Unit, OUH

Kåre Rommetveit, K.G. Jebsen Foundation

Associated investigators Dr Bjørn Atle Bjørnbeth (centre), head of liver surgery team and Andreas Abildgaard (right), head of the radiology team

Other events

21-22nd October 2014

The K.G. Jebsen Foundation's annual gathering of all their 14 Centres hosted by the K.G. Jebsen Inflammation Research Centre with the thematic area "Innovation" at Holmsbu.

10th February 2015

Centre member meeting at the Institute for Cancer Research, Oslo.

10th November 2015

Annual meeting with invited guests at the Grand Hotel, Oslo

From left, invited speaker professor of surgery Graeme Poston, University of Liverpool, Dr Bjørn Atle Bjørnbeth, head of liver surgery team, OUH, and professor Sigbjørn Smeland, head of the Cancer Clinic, OUH.

13-14th October 2015

The K.G. Jebsen Foundation's annual gathering of all their 14 Centres hosted by the K.G. Jebsen Thrombosis Research and Expertise Center with the thematic area "Research Dissemination" at Sommarøy, Tromsø.

Tormod Guren, Rodrigo Dienstmann, Anita Sveen, Jarle Bruun, Arild Nesbakken

25-27th November 2015, Centre members' visit to Barcelona

Post docs Anita Sveen and Jarle Bruun, together with AI Tormod Guren and PIs Ragnhild A. Lothe and Arild Nesbakken visited the Vall D'Hebron Institute of Oncology after invitation from Director, Professor Josep Tabernero. The two days were spent to see the trial unit and the research institute, to hear about their strategy on integrating the research projects with clinical trials and to discuss potential collaborative projects. Indeed, initiatives were taken both with our trial unit representative (Tormod Guren) and for joint projects with the translational and computer science team (Dr Rodrigo Dienstmann) and with the preclinical model unit (Dr Hector Palmer).

2016 Annual National Meeting on Clinical Genomics, Losby, Norway

The last three years, professors Ragnhild A. Lothe, Oslo Univeristy Hospital, and Per Eystein Lønning, Haukeland University Hospital, Bergen, have organized three national meetings on clinical genomics on behalf of the Norwegian Cancer priority area. At the 2016 meeting the key note speaker was Dr. Rodrigo Dienstmann who was invited through the K.G. Jebsen network. He held an inspiring lecture with the title "Paradigm shifts in Precision Medicine: Colorectal Cancer as a Model".

Collaboration

National and international collaboration

NORWAY:

- **MD PhD Bjørn Hofstad**, Dept. of Gastrointestinal Medicine, Oslo University Hospital, Oslo
- **Cand oecon, PhD Pål Joranger**, Oslo and Akershus University College of Applied Sciences, Norwegian University of Life Sciences, Oslo
- **MD PhD Christian Kersten**, Center for Cancer Treatment, Sørlandet Hospital, Kristiansand
- **MD PhD Lene Larsen**, Dept. of Gastrointestinal Medicine, Oslo University Hospital, Oslo
- **Prof. Per Eystein Lønning**, Haukeland Universitetssykehus, Bergen
- **Prof. Eirik Malinen**, Dept. of Medical Physics, Oslo University Hospital, Oslo
- **MD PhD Siri Rostoft**, Dept. of Geriatrics, Oslo University Hospital, Oslo
- **Prof. Eva Skovlund**, Norwegian University of Science and Technology, Trondheim
- **MD PhD Halfdan Sørbye**, Dept. of Oncology, University of Bergen, Bergen
- **MD Ellen Viktil**, Dept. of Radiology, Oslo University Hospital, Oslo

SWEDEN:

- **Prof. Bengt Glimelius**, Dept. of Immunology, Genetics and Pathology, Uppsala University, Uppsala
- **Prof. Bengt Gustavsson**, Dept. of Surgery, Sahlgrenska University Hospital, Gothenburg
- **MD PhD Anders Johnsson**, Dept. of Oncology, Skåne University Hospital, Lund

DENMARK:

- **Prof. Julia Johansen**, Dept. of Oncology and Medicine, Herlev Hospital, Copenhagen University Hospital, Copenhagen
- **Prof. Per Pfeiffer**, University of Southern Denmark, Odense
- **Ass. Prof. Karen-Lise Garm Spindler**, Dept. of Oncology, Århus University Hospital, Århus
- **Prof. Henrik Toft-Sørensen**, Dept. of Epidemiology, Aarhus University, Århus

FINLAND:

- **Professor Olli Kallioniemi**, Research director Finnish Institute for Molecular Medicine, Helsinki, and Director of Science for Life Laboratory, Sweden
- **Dr. Teijo Pellinen**, Finnish Institute for Molecular Medicine, Helsinki

USA:

- **Director Justin Guinney**, SAGE Bionetwork, Seattle
- **Prof. Matthew Meyerson**, Broad Institute of Harvard and MIT, Boston, MA
- **Prof. David Ransohoff**, Dept. of Epidemiology and Gastroenterology, University of Chapel Hill, SC
- **Prof. Robert Schoen**, Dept. of Gastroenterology, Pittsburgh University Medical center, Pittsburg, PA
- **Prof. Ann Zauber**, Sloan Kettering Memorial Cancer Center, New York, NY

NETHERLANDS:

- **Prof. Evelien Dekker**, Dept. of Gastroenterology, Academic Medical Center, Amsterdam
- **Prof. Ernst Kuipers**, Dept. of Gastroenterology, Erasmus Medical Centre, Rotterdam

ITALY:

- **Prof. Cesare Hassan**, Dep. of Gastroenterology, Catholic University Rome, Italy

SPAIN:

- **Prof. Antoni Castells**, Dept. of Gastroenterology, Barcelona University, Barcelona
- **Dr. Rodrigo Dienstmann**, Vall d'Hebron Institute of Oncology, Barcelona & SAGE Bionetwork, Seattle, US
- **Prof. Rodrigo Jover**, Dept. of Gastroenterology, University of Alicante, Alicante
- **Prof. Josep Tabernero**, Vall d'Hebron Institute of Oncology, Barcelona

GERMANY:

- **Prof. Thomas Rosch**, Dept. of Gastroenterology, Hamburg University Hospital Eppendorf, Hamburg

UK:

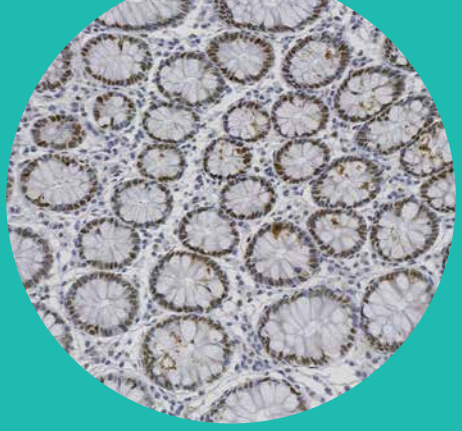
- **Prof. David Kerr**, Nuffield Dept. of Clinical Science, University of Oxford, Oxford
- **Eleanor McFadden**, Frontier Science Scotland, Kincraig
- **Prof. Ian Tomlinson**, Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford

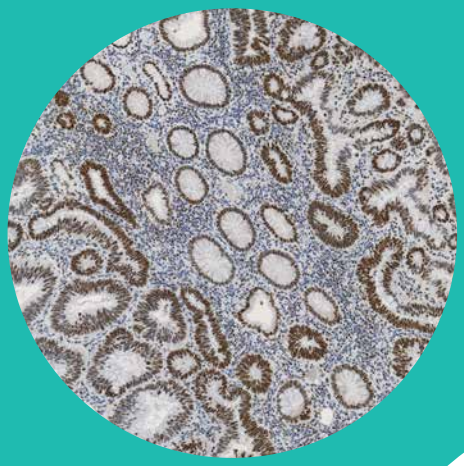
POLAND:

- **Dr. Michal Kaminski**, Maria Curie-Sklodowska Cancer Center, Warsaw
- **Prof. Jaroslaw Regula**, Maria Curie-Sklodowska Cancer Center, Warsaw

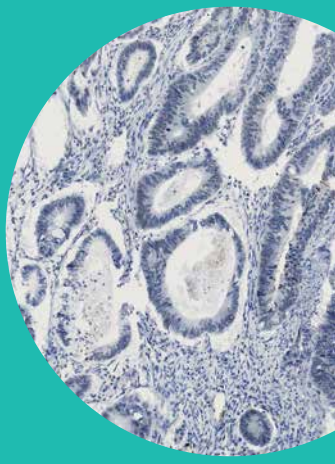
PORTUGAL:

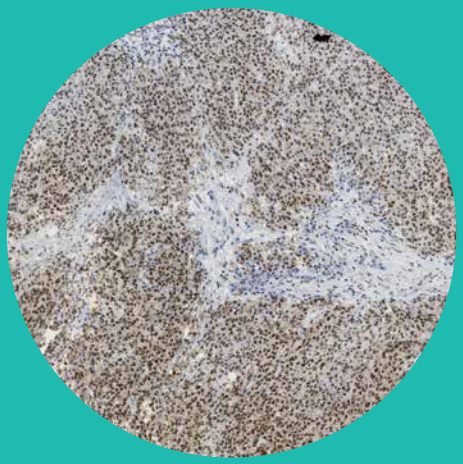
- **Dr. Raquel Almeida**, IPATIMUP, University of Porto, Porto
- **Prof. Leonor David**, IPATIMUP, University of Porto, Porto





We are indebted to Professor Aud Svindland and several other collaborators at the Department of Pathology, Oslo University Hospital, for their instrumental contributions to the Centre projects.





Publications June 2014 – August 2016

Publications are listed alphabetically according to the first author's last name. Centre member names in bold.

2014

Bruun J, Kolberg M, Nesland JM, Svindland A, Nesbakken A, Lothe RA.
Prognostic Significance of β-Catenin, E-Cadherin, and SOX9 in Colorectal Cancer: Results from a Large Population-Representative Series.
Front Oncol. 2014;4:118.

Guren MG, Undseth C, Rekstad BL, **Brændengen M**, Dueland S, Garm Spindler K-L, Glynne-Jones R, **Tveit KM.**
Reirradiation of locally recurrent rectal cancer: A systematic review.
Radiother Oncol. 2014 Nov; 113(2):151–157.

Holme Ø, Løberg M, Kalager M, Bretthauer M, Hernán MA, Aas E, Eide TJ, Skovlund E, Schneede J, **Tveit KM, Hoff G**.
Effect of flexible sigmoidoscopy screening on colorectal cancer incidence and mortality: a randomized clinical trial.
JAMA. 2014 Aug 13;312(6):606-15.

Leon O, **Guren M**, Hagberg O, Glimelius B, Dahl O, Havsteen H, Naucler G, Svensson C, **Tveit KM**, Jakobsen A, Pfeiffer P, Wanderås E, Ekman T, Lindh B, Balteskard L, Frykholm G, Johnsson A.
Anal carcinoma - Survival and recurrence in a large cohort of patients treated according to Nordic guidelines.
Radiother Oncol. 2014 Dec;113(3):352-8.

Løberg M, Kalager M, Holme Ø, Hoff G, Adami HO, Bretthauer M.
Long-term colorectal-cancer mortality after adenoma removal.
N Engl J Med. 2014 Aug 28;371(9):799-807.

Løvf M, Nome T, **Bruun J, Eknæs M, Bakken AC**, Mpindi JP, Kilpinen S, Rognum TO, **Nesbakken A**, Kallioniemi O, **Lothe RA, Skotheim RI.**
A novel transcript, VNN1-AB, as a biomarker for colorectal cancer.
Int J Cancer. 2014 Nov 1;135(9):2077-84.

Ommundsen N, Wyller TB, **Nesbakken A**, Jordhøy MS, Bakka A, Skovlund E, Rostoft S.
Frailty is an independent predictor of survival in older patients with colorectal cancer.
Oncologist. 2014 Dec;19(12):1268-75.

Sveen A, Johannessen B, Teixeira MR, **Lothe RA, Skotheim RI.**
Transcriptome instability as a molecular pan-cancer characteristic of carcinomas.
BMC Genomics. 2014 Aug 10;15:672.

2015

Andresen K, Boberg KM, **Vedeld HM, Honne H**, Jebsen P, **Hektoen M**, Wadsworth CA, Clausen OP, Lundin KE, Paulsen V, Foss A, Mathisen Ø, Aabakken L, Schrumpf E, **Lothe RA, Lind GE**.
Four DNA methylation biomarkers in biliary brush samples accurately identify the presence of cholangiocarcinoma.
Hepatology. 2015 May;61(5):1651-9.

Berstad P, **Løberg M**, Larsen IK, **Kalager M, Holme Ø**, Botteri E, **Bretthauer M, Hoff G**.
Long-term lifestyle changes after colorectal cancer screening: randomised controlled trial.
Gut. 2015 Aug;64(8):1268-76.

Bruun J, Kolberg M, Ahlquist TC, Røyrvik EC, Nome T, **Leithe E, Lind GE**, Merok MA, Rognum TO, Bjørkøy G, Johansen T, Lindblom A, Sun XF, **Svindland A,** Liestøl K, **Nesbakken A, Skotheim RI, Lothe RA.**
Regulator of Chromosome Condensation 2 Identifies High-Risk Patients within Both Major Phenotypes of Colorectal Cancer.
Clin Cancer Res. 2015 Aug 15;21(16):3759-70.

Danielsen SA, Eide PW, Nesbakken A, Guren T, Leithe E, Lothe RA.
Portrait of the PI3K/AKT pathway in colorectal cancer
Biochim Biophys Acta - Reviews on cancer. 2015 Jan; 1855(1):104-21.

Dueland S, **Guren TK**, Hagness M, Glimelius B, Line PD, Pfeiffer P, Foss A, **Tveit KM**.
Chemotherapy or liver transplantation for nonresectable liver metastases from colorectal cancer?
Ann Surg. 2015 May;261(5):956-60.

Dueland S, Hagness M, Line PD, **Guren TK, Tveit KM**, Foss A.
Is Liver Transplantation an Option in Colorectal Cancer Patients with Nonresectable Liver Metastases and Progression on All Lines of Standard Chemotherapy?
Ann Surg Oncol. 2015 Jul;22(7):2195-200.

Garborg K, Kaminski MF, Lindenburger W, Wiig H, Hasund A, Wronska E, Bie RB, Kleist B, Løvdal L, **Holme Ø, Kalager M, Hoff G, Bretthauer M**.
Water exchange versus carbon dioxide insufflation in unsedated colonoscopy: a multicenter randomized controlled trial.
Endoscopy. 2015 Mar;47(3):192-9.

Guren MG, Kørner H, Pfeffer F, Myklebust TÅ, Eriksen MT, Edna TH, Larsen SG, Knudsen KO, **Nesbakken A**, Wasmuth HH, Vonen B, Hofsli E, Færden AE, **Brændengen M**, Dahl O, Steigen SE, Johansen MJ, Lindsetmo RO, Drolsum A, Tollåli G, Dørum LM, Møller B, Wibe A.
Nationwide improvement of rectal cancer treatment outcomes in Norway, 1993-2010.
Acta Oncol. 2015 Nov;54(10):1714-22.

Gustavsson B, Carlsson G, Machover D, Petrelli N, Roth A, Schmoll HJ, **Tveit KM,** Gibson F.
A review of the evolution of systemic chemotherapy in the management of colorectal cancer.
Clin Colorectal Cancer. 2015 Mar;14(1):1-10.

Hoff AM, Johannessen B, Alagaratnam S, Zhao S, Nome T**, Løvf M, Bakken AC, Hektoen M, Sveen A, Lothe RA, Skotheim RI.**
Novel RNA variants in colorectal cancers.
Oncotarget. 2015 Nov 3;6(34):36587-602.

Holme Ø, Bretthauer M, Eide TJ, Løberg EM, Grzyb K, **Løberg M, Kalager M, Adami HO**, Kjellevold Ø, **Hoff G.**
Long-term risk of colorectal cancer in individuals with serrated polyps.
Gut. 2015 Jun;64(6):929-36.

Joranger P, **Nesbakken A, Hoff G**, Sorbye H, Oshaug A, Aas E.
Modeling and validating the cost and clinical pathway of colorectal cancer.
Med Decis Making. 2015 Feb;35(2):255-65.

Labori KJ, Schulz A, Drolsum A, **Guren MG**, Kløw NE, **Bjørnbeth BA.**
Radiofrequency ablation of unresectable colorectal liver metastases: trends in management and outcome during a decade at a single center.
Acta Radiol Open. 2015 Jul 6;4(7):1-9.

Leon O, **Guren MG**, Radu C, Gunnlaugsson A, Johnsson A.
Phase I study of cetuximab in combination with 5-fluorouracil, mitomycin C and radiotherapy in patients with locally advanced anal cancer.
Eur J Cancer. 2015 Dec;51(18):2740-6.

Robertson DJ, Kaminski MF, **Bretthauer M**.
Effectiveness, training and quality assurance of colonoscopy screening for colorectal cancer.
Gut. 2015 Jun;64(6):982-90.

Sclafani F, Kim TY, Cunningham D, Kim TW, Tabernero J, Schmoll HJ, Roh JK, Kim SY, Park YS, **Guren TK**, Hawkes E, Clarke SJ, Ferry D, Frödin JE, Ayers M, Nebozhyn M, Peckitt C, Loboda A, Mauro DJ, Watkins DJ.
A Randomized Phase II/III Study of Dalotuzumab in Combination with Cetuximab and Irinotecan in Chemorefractory, KRAS Wild-Type, Metastatic Colorectal Cancer.
J Natl Cancer Inst. 2015 Sep 23;107(12):djv258.

Spada C, Stoker J, Alarcon O, Barbaro F, Bellini D, **Bretthauer M**, De Haan MC, Dumonceau JM, Ferlitsch M, Halligan S, Helbren E, Hellstrom M, Kuipers EJ, Lefere P, Mang T, Neri E, Petruzziello L, Plumb A, Regge D, Taylor SA, Hassan C, Laghi A.
Clinical indications for computed tomographic colonography: European Society of Gastrointestinal Endoscopy (ESGE) and European Society of Gastrointestinal and Abdominal Radiology (ESGAR) Guideline.
Eur Radiol. 2015 Feb;25(2):331-45.

Tarpgaard LS, Christensen IJ, Høyer-Hansen G, Lund IK, **Guren TK**, Glimelius B, Sorbye H, **Tveit KM**, Nielsen HJ, Moreira JM, Pfeiffer P, Brünner N.
Intact and cleaved plasma soluble urokinase receptor in patients with metastatic colorectal cancer treated with oxaliplatin with or without cetuximab.
Int J Cancer. 2015 Nov 15;137(10):2470-7.

Vedeld HM, Andresen K, Eilertsen IA, Nesbakken A, Seruca R, Gladhaug IP, Thiis-Evensen E, Rognum TO, Boberg KM, **Lind GE.**
The novel colorectal cancer biomarkers CDO1, ZSCAN18 and ZNF331 are frequently methylated across gastrointestinal cancers.
Int J Cancer. 2015 Feb 15;136(4):844-53.

Walters S, Benitez-Majano S, Muller P, Coleman MP, Allemani C, Butler J, Peake M, **Guren MG**, Glimelius B, Bergström S, Påhlman L, Rachet B.
Is England closing the international gap in cancer survival?
Br J Cancer. 2015 Sep 1;113(5):848-60.

2016

Adami HO, Bretthauer M, Emilsson L, Hernán MA, Kalager M, Ludvigsson JF, Ekbom A.
The continuing uncertainty about cancer risk in inflammatory bowel disease.
Gut. 2016 Jun;65(6):889-93.

Bains SJ, Mahic M, Myklebust TÅ, Småstuen MC, Yaqub S, Dørum LM, **Bjørnbeth BA, Møller B, Brudvik KW**, Taskén K.
Aspirin As Secondary Prevention in Patients With Colorectal Cancer: An Unselected Population-Based Study.
J Clin Oncol. 2016 Jul 20;34(21):2501-8.

Berstad P, Botteri E, Larsen IK, **Løberg M, Kalager M, Holme Ø, Bretthauer M, Hoff G**.
Lifestyle changes at middle age and mortality: a population-based prospective cohort study.
J Epidemiol Community Health. 2016 Jun 16. [Epub ahead of print]

Boye K, Jacob H, Frikstad KM, Nesland JM, Maelandsmo GM, Dahl O, **Nesbakken A**, Flatmark K.
Prognostic significance of S100A4 expression in stage II and III colorectal cancer: results from a population-based series and a randomized phase III study on adjuvant chemotherapy.
Cancer Med. 2016 Jun 8. [Epub ahead of print]

Bretthauer M, Aabakken L, Dekker E, Kaminski MF, Rösch T, Hultcrantz R, Suchanek S, Jover R, Kuipers EJ, Bisschops R, Spada C, Valori R, Domagk D, Rees C, Rutter MD; ESGE Quality Improvement Committee.
Reporting systems in gastrointestinal endoscopy: Requirements and standards facilitating quality improvement: European Society of Gastrointestinal Endoscopy position statement.
United European Gastroenterol J. 2016 Apr;4(2):172-6.

Bretthauer M, Kalager M, Adami HO, Hoff G.
Who Is for CO2? Slow Adoption of Carbon Dioxide Insufflation in Colonoscopy.
Ann Intern Med. 2016 Jul 19;165(2):145-6.

Bretthauer M, Kaminski MF, **Løberg M,** Zauber AG, Regula J, Kuipers EJ, **Hernán MA**, McFadden E, Sunde A, **Kalager M**, Dekker E, Lansdorp-Vogelaar I, **Garborg K**, Rupinski M, Spaander MC, Bugajski M, Høie O, Stefansson T, **Hoff G, Adami HO**; Nordic-European Initiative on Colorectal Cancer (NordICC) Study Group.
Population-Based Colonoscopy Screening for Colorectal Cancer: A Randomized Clinical Trial.
JAMA Intern Med. 2016 Jul 1;176(7):894-902.

Cameron MG, Kersten C, Vistad I, van Helvoirt R, Weyde K, Undseth C, Mjaaland I, Skovlund E, Fosså SD, **Guren MG.**
Palliative pelvic radiotherapy for symptomatic rectal cancer - a prospective multicenter study.
Acta Oncol. 2016 Jun 22:1-8. [Epub ahead of print]

Cekaite L, Eide PW, Lind GE, Skotheim RI, Lothe RA.
MicroRNAs as growth regulators, their function and biomarker status in colorectal cancer.
Oncotarget. 2016 Feb 9;7(6):6476-505.

Domingo E, Freeman-Mills L, Rayner E, Glaire M, Briggs S, Vermeulen L, Fessler E, Medema JP, Boot A, Morreau H, van Wezel T, Leifers G-J, **Lothe RA, Danielsen SA, Sveen A, Nesbakken A**, Zlobec I, Lugli A, Koelzer VH, Berger MD, Castellvi-Bel S, Munoz J, The Epicolon consortium*, de Bruyn M, Nijman HW, Novelli M, Lawson K, Oukrif D, Frangou E, Dutton P, Tejpar S, Delorenzi M, Kerr R, Kerr D, Tomlinson I, Church DN.
Somatic POLE proofreading domain mutation, immune response, and prognosis in colorectal cancer: a retrospective, pooled biomarker study.
The Lancet Gastroenterology & Hepatology. Published online 2016 July 19.

Garborg K, Bretthauer M.
Cecal intubation failure: Refer or change technique?
Gastrointest Endosc. 2016 Jun;83(6):1245-7.

García-Albéniz X, Hsu J, Lipsitch M, **Bretthauer M,** Logan RW, Hernández-Díaz S, **Hernán MA**.
Colonoscopy and Risk of Infective Endocarditis in the Elderly.
J Am Coll Cardiol. 2016 Aug 2;68(5):570-1.

Gjøstein DK, Huitfeldt A, Løberg M, Adami HO, Garborg K, Kalager M, Bretthauer M.
Incentives and participation in a medical survey.
Tidsskr Nor Laegeforen. 2016 Jul 5;136(12-13):1082-1087.

Gleditsch D, Søreide OK, **Nesbakken A**.
Managing Malignant Colorectal Obstruction with Self-Expanding Stents. A Closer Look at Bowel Perforations and Failed Procedures.
J Gastrointest Surg. 2016 Jun 24. [Epub ahead of print]

Hassan C, Repici A, Sharma P, Correale L, Zullo A, **Bretthauer M**, Senore C, Spada C, Bellisario C, Bhandari P, Rex DK.
Efficacy and safety of endoscopic resection of large colorectal polyps: a systematic review and meta-analysis.
Gut. 2016 May;65(5):806-20.

Holme Ø, Bretthauer M.
Pain and sedation during colonoscopy - a never ending story.
Endosc Int Open. 2016 May;4(5):E538-9.

Holme Ø, de Lange T, Stallemo A, Wiig H, Hasund A, Dvergsnes K, **Garborg K**, Ystrøm CM, **Løberg M, Hoff G, Bretthauer M, Kalager M**.
Routine vs. on-demand analgesia in colonoscopy: a randomized clinical trial.
Endoscopy. 2016 Jun 15. [Epub ahead of print]

Jover R, **Bretthauer M**, Dekker E, **Holme Ø,** Kaminski MF, **Løberg M**, Zauber AG, **Hernán MA**, Lansdorp-Vogelaar I, Sunde A, McFadden E, Castells A, Regula J, Quintero E, Pellisé M, Senore C, **Kalager M**, Dinis-Ribeiro M, **Emilsson L**, Ransohoff DF, **Hoff G, Adami HO**.
Rationale and design of the European Polyp Surveillance (EPoS) trials.
Endoscopy. 2016 Jun;48(6):571-8.

Kalager M, Adami HO, Bretthauer M.
Recognizing Data Generation.
N Engl J Med. 2016 May 12;374(19):1898.

Kaminski MF, Anderson J, Valori R, Kraszewska E, Rupinski M, Pachlewski J, Wronska E, **Bretthauer M**, Thomas-Gibson S, Kuipers EJ, Regula J.
Leadership training to improve adenoma detection rate in screening colonoscopy: a randomised trial.
Gut. 2016 Apr;65(4):616-24.

Kjersem JB, Thomsen M, **Guren T**, Hamfjord J, Carlsson G, Gustavsson B, Ikdahl T, Indrebø G, Pfeiffer P, Lingjærde O, **Tveit KM**, Wettergren Y, Kure EH.
AGXT and ERCC2 polymorphisms are associated with clinical outcome in metastatic colorectal cancer patients treated with 5-FU/oxaliplatin.
Pharmacogenomics J. 2016 Jun;16(3):272-9.

Mezheyeuski A, Lindh MB, **Guren TK,** Dragomir A, Pfeiffer P, Kure EH, Ikdahl T, Skovlund E, Corvigno S, Strell C, Pietras K, Ponten F, Mulder J, Qvortrup C, Portyanko A, **Tveit KM,** Glimelius B, Sorbye H, Östman A.
Survival-associated heterogeneity of marker-defined perivascular cells in colorectal cancer.
Oncotarget. 2016 May 26. [Epub ahead of print]

Rees CJ, Ngu WS, Regula J, Bisschops R, Saftoiu A, Dekker E, Gralnek I, Ciocirlan M, Dinis-Ribeiro M, Jover R, Meisner S, Spada C, Hassan C, Valori R, Hucl T, Le Moine O, Domagk D, Kaminski MF, **Bretthauer M**, Rutter MD, Aabakken L, Ponchon T, Fockens P, Siersema PD.
European Society of Gastrointestinal Endoscopy - Establishing the key unanswered research questions within gastrointestinal endoscopy.
Endoscopy. 2016 Aug 2. [Epub ahead of print]

Røhrl K, **Guren MG**, Miaskowski C, Cooper BA, Diep LM, Rustøen T.
No Differences in Symptom Burden Between Colorectal Cancer Patients Receiving Curative versus Palliative Chemotherapy.
J Pain Symptom Manage. 2016 Jul 25. [Epub ahead of print]

Rønning B, Wyller TB, **Nesbakken A**, Skovlund E, Jordhøy MS, Bakka A, Rostoft S.
Quality of life in older and frail patients after surgery for colorectal cancer - A follow-up study.
J Geriatr Oncol. 2016 May;7(3):195-200.

Stornes T, Wibe A, **Nesbakken A**, Myklebust TÅ, Endreseth BH.
National Early Rectal Cancer Treatment Revisited.
Dis Colon Rectum. 2016 Jul;59(7):623-9.

Sveen A, Kilpinen S, Ruusulehto A, **Lothe RA, Skotheim RI.**
Aberrant RNA splicing in cancer; expression changes and driver mutations of splicing factor genes.
Oncogene. 2016 May 12;35(19):2413-27.

Sveen A, Løes IM, **Alagaratnam S**, **Nilsen G, Høland M**, Lingjærde OC, Sorbye H, **Berg KC**, Horn A, Angelsen JH, Knappskog S, Lønning PE, **Lothe RA**.
Intra-patient Inter-metastatic Genetic Heterogeneity in Colorectal Cancer as a Key Determinant of Survival after Curative Liver Resection.
PLoS Genet. 2016 Jul 29;12(7):e1006225.

Dissertations

2016

Hege Marie Vedeld:
Epigenetic biomarkers for early detection and prognosis of colorectal cancer
Faculty of Medicine, University of Oslo, submitted June
Supervisor: Guro E. Lind/Ragnhild A. Lothe

Bjarne Johannessen:
Identification of novel DNA and RNA changes in solid tumors by high-throughput methodologies
Faculty of Medicine, University of Oslo, public defence August
Supervisor: Rolf I. Skotheim

2015

Pål Joranger:
Health economic evaluations of shoulder pain, colorectal cancer and scoliosis
Faculty of Health Sciences, Oslo and Akershus University College of Applied Sciences
Supervisor: Arild Nesbakken

Andreas M. Hoff:
Identification of novel fusion genes and transcript variants in cancer
Faculty of Medicine, University of Oslo
Supervisor: Rolf I. Skotheim/Ragnhild A. Lothe

Øyvind Holme:
Flexible sigmoidoscopy screening for colorectal cancer
Faculty of Medicine, University of Oslo
Supervisor: Michael Bretthauer

Janne Beathe Kjersem:
Metastatic colorectal cancer – implications of single nucleotide polymorphisms and circulating microRNAs on treatment outcome
Faculty of Medicine, University of Oslo
Supervisor: Elin Kure/Kjell Magne Tveit

Magnus Løberg:
Prevention and early detection of colorectal cancer - A study of epidemiological methods to evaluate cancer screening and surveillance
Faculty of Medicine, University of Oslo
Supervisor: Mette Kalager

2014

Marianne Aarstad Merok:
Genetic and clinical prognostic markers for colorectal cancer
Faculty of Medicine, University of Oslo
Supervisor: Arild Nesbakken/Ragnhild A. Lothe

Jarle Bruun:
Biomarkers with functional and clinical impact on colorectal cancer
Faculty of Medicine, University of Oslo
Supervisor: Ragnhild A. Lothe

Marthe Løvf:
Detection of fusion genes and novel RNA variants in cancer
Faculty of Mathematics and Natural Sciences, University of Oslo
Supervisor: Rolf I. Skotheim/Ragnhild A. Lothe

Our thanks to the K.G. Jebsen Foundation and other funding sources

We are grateful for the opportunity given us by the K.G. Jebsen Foundation when the K.G. Jebsen Colorectal Cancer Research Centre was granted after international evaluations of competitive proposals.

The Centre funding from the Foundation amounts to 16 MNOK for the period from June 2014 to June 2018. We are pleased that the grant led to financial support of 6 MNOK from the South-Eastern Norway Regional Health Authority during the same period.

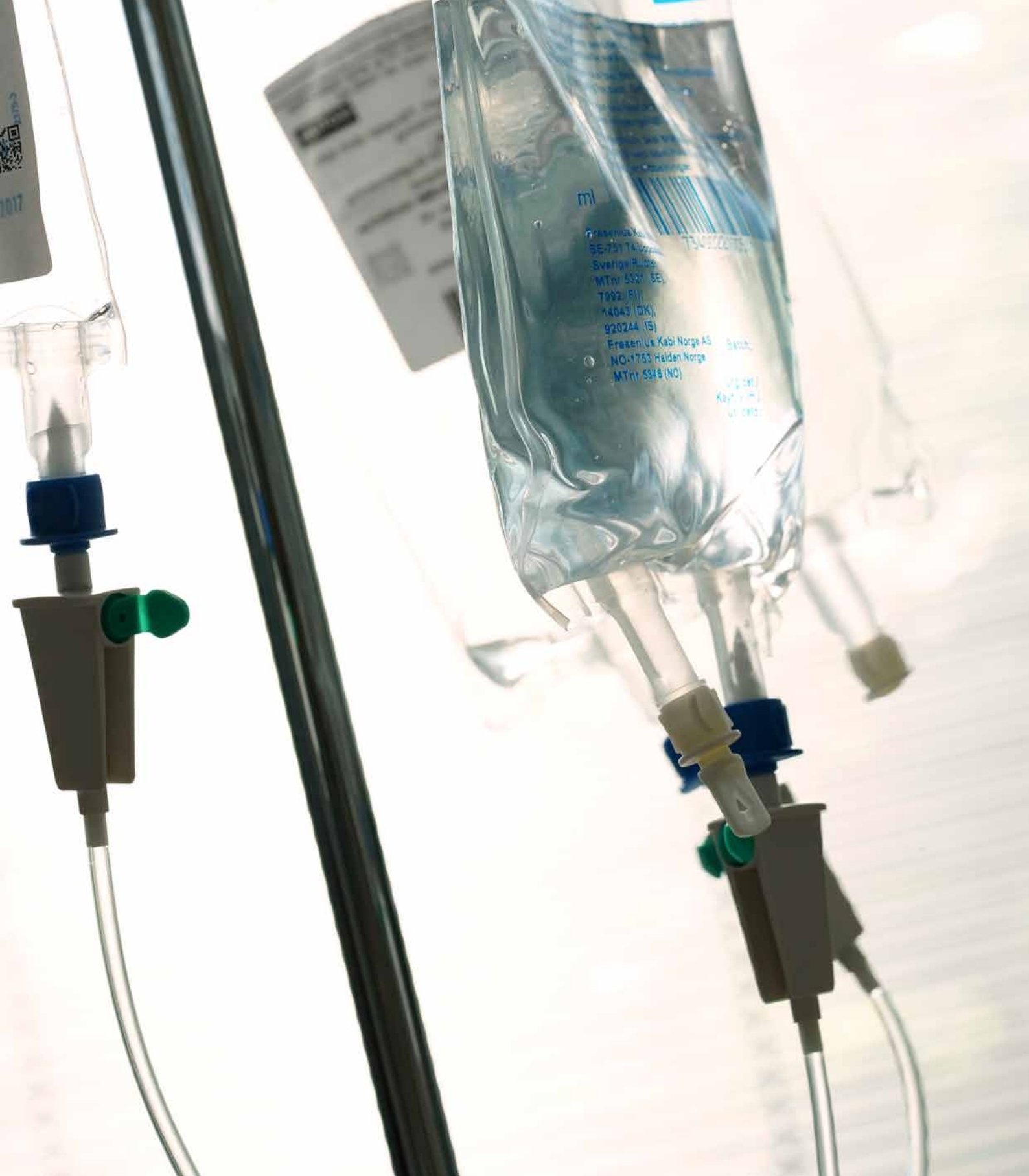
The Oslo University Hospital's current five selected focused research areas includes the SMART (Screening, management, research and translation) - Colorectal Cancer project, which overlaps with several K.G. Jebsen Centre projects and has the same leadership. SMART-CRC is supported with 5 MNOK and in June this year the OUH Scientific Advisory Board conducted a mid-term evaluation and recommended continuance of the project with the following conclusion: "Overall, SMART has an impressive activity in an important translational research field."

Furthermore, we are grateful for the substantial internal funding from Oslo University Hospital and the University of Oslo as well as other external support that the Centre scientists receive from the Norwegian Cancer Society, The Health Region and the Research Council of Norway.

Staff

Name	Position	Academic title	Group	Institution	Centre affiliation
Abildgaard, Andreas	Radiologist	MD PhD	Radiology	Division of Radiology and Nuclear Medicine, OUH	Associated investigator
Adami, Hans-Olov	Professor MD PhD	MD PhD	Bretthauer group	Harvard School of Public Health	Member
Alagaratnam, Sharmini	Senior scientist	PhD	Lothe group	Department of Molecular Oncology, OUH	Member
Andresen, Kim	Postdoc	PhD	Lind group	Department of Molecular Oncology, OUH	Member
Bakken, Anne Cathrine	Research associate	MSc	Skotheim group	Department of Molecular Oncology, OUH	Member
Batool, Irshi	Study nurse		Nesbakken group	Department of Gastrointestinal and Paediatric Surgery, OUH	Member
Bergsland, Christian	Research assistant	MSc	Lothe group	Department of Molecular Oncology, OUH	Member
Bjørnbeth, Bjørn Atle	Surgeon, Head of Dep	MD PhD	Bjørnbeth group	Department of Gastrointestinal and Paediatric Surgery, OUH	Associated investigator
Bjørnslett, Merete	Senior technician	PhD	Lothe group	Department of Molecular Oncology, OUH	Member
Bretthauer, Michael	Professor, PI	MD PhD	Bretthauer group	Department of Health Management and Health Economics, UoO	PI
Bruun, Jarle	Postdoc	PhD	Lothe group	Department of Molecular Oncology, OUH	Member
Brændengen, Morten	Consultant oncologist	MD PhD	Tveit/Guren group	Department of Oncology, OUH	Member
Carm, Kristina	Master student		Skotheim group	Department of Molecular Oncology, OUH	Member
Cengija, Vanja	Radiologist	MD	Radiology	Division of Radiology and Nuclear Medicine, OUH	Member
Dajani, Olav	Consultant oncologist	MD PhD	Tveit/Guren group	Department of Oncology, OUH	Member
Danielsen, Stine Aske	Postdoc	PhD	Lothe group	Department of Molecular Oncology, OUH	Member
de Lange, Thomas	Researcher	MD PhD	Bowel Cancer Screening	Cancer Registry of Norway	Member
Eide, Peter A. Wold	PhD student	MSc	Lothe group	Department of Molecular Oncology, OUH	Member
Eilertsen, Ina Andrassy	Research associate	MSc	Lothe group	Department of Molecular Oncology, OUH	Member
Eknæs, Mette	Medical technologist		Lothe group	Department of Molecular Oncology, OUH	Member
Emilsson, Louise	Postdoc	PhD	Bretthauer group	Department of Health Management and Health Economics, UoO	Member
Flaaten Backe, Ingeborg	Study nurse		Nesbakken group	Department of Gastrointestinal and Paediatric Surgery, OUH	Member
Furholm, Siv	Research coordinator		Bretthauer group	Department of Health Management and Health Economics, UoO	Member
Garborg, Kjetil Kjeldstad	PhD student	MD	Bretthauer group	The Medical Faculty, UoO	Member
Gjøstein, Dagrun Kyte	PhD student	MSc	Bretthauer group	Department of Health Management and Health Economics, UoO	Member
Graue Berg, Kaja Christine	PhD student	MSc	Lothe group	Department of Molecular Oncology, OUH	Member
Guren, Marianne	Co-PI, Cons. oncologist	MD PhD	Tveit/Guren group	Department of Oncology, OUH	Co-PI
Guren, Tormod	Consultant oncologist	MD PhD	Tveit/Guren group	Department of Oncology, OUH	Associated investigator
Gustafsson Olsen, Sofia	Research coordinator	Master of Nursing	Bretthauer group	Department of Health Management and Health Economics, UoO	Member
Güere, Mariella Evelyn	Master student		Lind group	Department of Molecular Oncology, OUH	Member
Hektoen, Merete	Medical technologist	MSc	Lothe group	Department of Molecular Oncology, OUH	Member
Hernán, Miguel	Professor	MD PhD	Bretthauer group	Harvard School of Public Health	Member
Hoff, Andreas Midbøe	Postdoc	PhD	Skotheim group	Department of Molecular Oncology, OUH	Member
Hoff, Geir	Professor	MD PhD	Bowel Cancer Screening	Cancer Registry of Norway	Associated investigator
Holme, Øyvind	Researcher	MD PhD	Bretthauer group	Sørlandet Hospital Trust	Member
Honne, Hilde	Research associate	MSc	Lind group	Department of Molecular Oncology, OUH	Member
Huitfeldt, Anders	Researcher	MD PhD	Bretthauer group	Harvard School of Public Health	Member
Høst Brunsell, Tuva	PhD student	MD	Nesbakken group	Department of Gastrointestinal and Paediatric Surgery, OUH	Member

Name	Position	Academic title	Group	Institution	Centre affiliation
Jeanmougin, Marine	Postdoc	PhD	Lind group	Department of Molecular Oncology, OUH	Member
Jodal, Henriette	PhD student	MD	Bretthauer group	Department of Health Management and Health Economics, UoO	Member
Johannessen, Bjarne	PhD student	MSc	Skotheim group	Department of Molecular Oncology, OUH	Member
Kalager, Mette	Associate Professor	MD PhD	Bretthauer group	Department of Health Management and Health Economics, UoO	Member
Kolberg, Matthias	Senior scientist	Dr. rer. nat.	Lothe group	Department of Molecular Oncology, OUH	Member
Kowalewska, Magdalena	Study nurse		Bjørnbeth group	Department of Gastrointestinal and Paediatric Surgery, OUH	Member
Leithe, Edward	Senior scientist	PhD	Lothe group	Department of Molecular Oncology, OUH	Member
Lind, Guro Elisabeth	Professor, Group leader	Dr.philos	Lind group	Department of Molecular Oncology, OUH	Associated investigator
Lind, Nina	Adm. coordinator	Cand. philol.	Bretthauer group	Department of Health Management and Health Economics, UoO	Member
Lothe, Ragnhild A.	Professor, PI	PhD	Lothe group	Department of Molecular Oncology, OUH	Centre leader, PI
Løberg, Magnus	Postdoc	MD PhD	Bretthauer group	Department of Health Management and Health Economics, UoO	Member
Løvf, Marthe	Postdoc	PhD	Skotheim group	Department of Molecular Oncology, OUH	Member
Lågstad, Stian	Master student		Skotheim group	Department of Molecular Oncology, OUH	Member
Meier Strømme, Jonas	Master student		Skotheim group	Department of Molecular Oncology, OUH	Member
Møller, Bjørn	Researcher	Dr.philos	Bowel Cancer Screening	Cancer Registry of Norway	Member
Mørland Knudsen, Lars	PhD student	MSc	Lothe group	Department of Molecular Oncology, OUH	Member
Nesbakken, Arild	Professor, PI	MD PhD	Nesbakken group	Department of Gastrointestinal and Paediatric Surgery, OUH	PI
Pedersen, Ina B.	PhD student	MSc	Bretthauer group	Department of Health Management and Health Economics, UoO	Member
Pharo, Heidi	PhD student	MSc	Lind group	Department of Molecular Oncology, OUH	Member
Røsok, Bård	HPB surgeon	MD PhD	Bjørnbeth group	Department of Gastrointestinal and Paediatric Surgery, OUH	Associated investigator
Salvador, Silje R.	Research coordinator		Bretthauer group	Department of Health Management and Health Economics, UoO	Member
Sjo, Ole	Consultant surgeon	MD PhD	Nesbakken group	Department of Gastrointestinal and Paediatric Surgery, OUH	Member
Skotheim, Rolf Inge	Associate Professor, PI	Dr.philos	Skotheim group	Department of Molecular Oncology, OUH	PI
Smeby, Jørgen	PhD student	MD	Tveit/Guren group	Department of Oncology, OUH	Member
Sveen, Anita	Scientist	PhD	Lothe group	Department of Molecular Oncology, OUH	Member
Svindland, Aud	Professor	MD PhD	Pathology	Department of Pathology, OUH	Associated investigator
Sørensen, Anette	Senior advisor		Lothe group	Department of Molecular Oncology, OUH	Adm. coordinator
Thomsen, Maria	Consultant oncologist	MD	Tveit/Guren group	Department of Oncology, OUH	Member
Tveit, Kjell Magne	Professor, PI	MD PhD	Tveit/Guren group	Department of Oncology, OUH	PI
Vedeld, Hege Marie	PhD student	MSc	Lind group	Department of Molecular Oncology, OUH	Member
Watten Brudvik, K.	Surgical fellow	MD PhD	Nesbakken group	Section for Transplantation Surgery, OUH	Member
Yohannes, Zeremariam	Head technician	MSc	Lothe group	Department of Molecular Oncology, OUH	Member
Zachrisson Totland, Max	Research assistant	MSc	Lothe group	Department of Molecular Oncology, OUH	Member
Zhao, Sen	Postdoc	PhD	Skotheim group	Department of Molecular Oncology, OUH	Member
Øines, Mari Nanna	Researcher	MD	Bretthauer group	Department of Health Management and Health Economics, UoO	Member
Aalby, Anita	Research coordinator		Bretthauer group	Department of Health Management and Health Economics, UoO	Member


ml
Fresenius Kabi Norge AS
NO-1753 Halden Norge
MTnr 5845 (NO)

VISITING ADDRESS
Oslo University Hospital
Norwegian Radium Hospital
Ullernchausseen 70
0379 Oslo, Norway

POSTAL ADDRESS
Oslo University Hospital
Norwegian Radium Hospital
P. O. Box 4953 Nydalen
0424 Oslo, Norway

APPOINTED BY
STIFTELSEN KGJ

HOST INSTITUTION
Oslo University Hospital

IN COOPERATION WITH
UiO : University of Oslo