ANNUAL REPORT 2017 Oslo University Hospital Comprehensive Cancer Centre (OUH CCC)





Comprehensive Cancer Centre

Content





- **01** Oslo University Hospital Comprehensive Cancer Centre
- 02 OUH CCC Audit Process
- **03** Major Events for OUH Cancer Centre 2017
- 04 OUH CCC Management Structure
- **06** Campuses
- 07 OUH Cancer Strategy 2017-2021
- **08** OUH CCC: Core activity data for 2017
- 09 Relative Survival
- **10** Patient Satisfaction
- **12** Patient Involvement
- 13 Clinical Pathway Management and Governance
- **13** Regional MDT-Meetings by Video Conference
- 14 Standardised Patient Pathways
- **15** Opening of the Cancer Rehabilitation Centre
- **16** OUH CCC Research Activity 2017
- 17 2017 CCC Research Highlights
- **18** Key Indicators
- **19** The Early Clinical Trial Unit
- **20** Oslo Myeloma Centre
- **21** Centre of Excellence: Centre for Cancer Biomedicine (CCB)
- 22 The Lumiblast Project
- **23** Photodynamic Detection and Therapy
- 24 In Silico Digital Pathology: The DoMore! Project
- **25** REirradiation and PD-1 Blockade in Recurrent Squamous Cell Head and Neck Tumours – The REPORT-Study CA209-669;
- 26 Can One Aspirin a Day Impede Recurrence of Colorectal Cancer Metastases? The ASAC trial
- 27 Gene-Transduced Autologous T-cells (CAR-T cells) in the Treatment of Leukaemia and Lymphoma
- 28 The HPV Vaccine Project
- 29 Colorectal Cancer Screening Heading for a National Programme in 2019
- **30** Precision Medicine 1: The MetAction Study: Actionable Targets in Cancer Metastasis
- **31** Precision Medicine 2: The EMIT Study
- **32** Precision Medicine 3: The BigMed Project
- 33 Clinical Nutrition: Effect of Diet Intervention on Colorectal Cancer; Comorbidities and Late Effects



Oslo University Hospital Comprehensive Cancer Centre

In April 2017 Oslo University Hospital (OUH) Cancer Centre was designated by the Organisation of European Cancer Institutes (OECI) as an European Comprehensive Cancer Centre (CCC).

The accreditation is based on documented high volume and high quality clinical cancer care, with integration of high level cancer research and innovation. This accomplishment followed a rigorous review and audit of cancer care, the cancer care organization and cancer research at OUH. The accreditation means that the OUH CCC meets the highest quality standard in line with currently 18 other premier cancer institutions across Europe. During the accreditation process OUH made substantial adjustments on both clinical and research sides and with the aim of integrating all cancer-related activities in a joint cancer centre structure. The process included the elaboration of an institutional cancer strategy with an incorporated research strategy.

The OUH CCC Board is responsible for the institutional governance in cancer and encompasses all Heads of divisions and departments strongly involved in cancer care and/or research, and also include patient representation. The OUH CCC Board is set up to reinforce the Divisional Directors and Department Heads' executive power across the organisation to forge coordination and collaboration on both a daily and long-term strategic basis.

The OECI-CCC designation is the starting point for further evolution, and we are devoted to continuously develop the OUH CCC to become one of the top cancer centres in Europe, not at least to benefit our patients.



Prof. Sigbjørn Smeland MD Head, Division of Cancer Medicine Chair, OUH CCC Board



Prof. Gunnar Sæter MD Research Director, Division of Cancer Medicine Head, OUH CCC Research Council

OUH CCC Audit Process



• Work started fall (Visit to Helsinki University Hospital, November

2015

- June: Preliminary self-assessment submitted
- October: Pre-visit report from the audit team: Main critiques: No institutional governance for the Cancer Centre: i.e. no Cancer board, and no Cancer strategy
- November: Institutional cancer strategy project initiated

2016

- June: Institutional Cancer Strategy approved
- July: Submission of revised self-assessment: «Go» decision from the OECI accreditation and designation board
 - September 22.-23.: Audit visit
 - October: Preliminary report
 - November: First meeting of the OUH CCC Board appointed by the CEO

2017

- January: Improvement plan decided by the OUH CCC Board
- March: First meeting of the OUH CCC Research Council
- April 10th: CCC Accreditation approved by OECI
- April: OUH CCC Scientific Advisory Board appointed

Major Events for OUH Cancer Centre 2017



- Monthly meetings in the OUH CCC Board started
- Regular meetings in the OUH CCC Research Council started
- Cancer Centre improvement plan approved
- Centre for Cancer Cell Reprogramming granted as Norwegian Centre of Excellence (SFF centre) by the Research Council of Norway. Head: Prof Harald Stenmark



- OUH designated as a Comprehensive Cancer Centre by OECI
- A CCC Scientific Advisory Board of internationally highly recognized scientists was appointed
- Cancer rehabilitation centre opened by the Ministry of Health at Aker hospital



• Plan for development of standardised patient pathways for all cancers approved



- Governmental decision on building a new clinical building and a centre for proton therapy at the Radium Hospital at a total cost of approx. 5 000 MNOK.
- Regular follow-up meetings between the OUH CCC Board and Pathway Management team
- Major grant (20 MNOK) from the national interventional clinic research program "KLINBEFORSK": Establishment of Molecular Profiling for Individual Clinical Routine Treatment Decisions in Early Breast Cancer (EMIT study). Primary Investigator: Prof Bjørn Naume

OUH CCC Management Structure







CCC Board

Prof. Sigbjørn Smeland MD, Head, Division of Cancer Medicine (Chair) Assoc. Prof. Morten Tanberg Eriksen MD, Head, Division of Surgery, Inflammatory diseases and Transplantation Assoc. Prof. Lars Eikvar MD, Head, Division of Laboratory Medicine Prof. Hans Jørgen Smith MD, Head, Division of Radiology and Nuclear Medicine Lisbeth Sommervoll MD, Vice President, Oslo University Hospital Executive committee Per Magnus Mæhle, Secretary, Division of Cancer Medicine Elin Henriksen, Head, Department of Gasto- and Paediatric Surgery Torill Krøvel, Senior advisor, Staff Division of Surgery, Inflammatory diseases and Transplantation Prof. Harald Stenmark, Head, Department of Molecular Cell Biology Prof. Giske Ursin, Director, The Cancer Registry of Norway Prof. Geir Tjønnfjord MD, Head, Department of Haematology Prof. Gunnar Sæter MD, Head of Research, Division of Cancer Medicine Tove Nakken, Chair, The OUH Patient Council Erik Rokkones MD, Head, Department of Gyneacological Cancer Prof. Stein Kaasa MD, Head, Department of Oncology

CCC Research Council

Prof. Gunnar Sæter MD, Head of Research, Division of Cancer Medicine (Chair)
Prof. Tom Hemming Karlsen MD, Head of Research, Division of Surgery, Inflammatory diseases and Transplantation
Prof. Kristin Bjordal MD, Head, Department of Research Support, Oslo Hospital Services
Prof. Kjetil Taskén MD, Head, Institute for Cancer Research, Division of Cancer Medicine
Tove Nakken, Chair, The OUH Patient Council
Prof. Ben Davidson MD, Department of Pathology, Division of Laboratory Medicine
Prof. Stein Kaasa MD, Head, Department of Oncology
Prof. Elisabete Weidepass, Head, Research Department, The Cancer Registry
Per Magnus Mæhle, Secretary, Division of Cancer Medicine

CCC Scientific Advisory Board

Prof. Carl-Henrik Heldin, University of Uppsala and Chairman of the Board, The Nobel Institute (Chair)

Prof. Fabien Calvo, Chief Scientific Officer, Cancer Core Europe and Institut Gustave Roussy

Prof. Jenny Chang-Claude, Division of Cancer Epidemiology, DKFZ Heidelberg

Prof. Mef Nilbert, Director of Research, Danish Cancer Society, Copenhagen

Prof. Inger Sandlie, Institute of Biosciences, University of Oslo

Prof. Kjeld Schmiegelow, Professor of Pediatrics and Pediatric Oncology, University Hospital Rigshospitalet, Copenhagen



OUH Cancer Strategy 2017-2021

Vision and mission for OUH Cancer Centre

Vision: OUH will be a leading cancer centre in Europe Mission: We are a complete cancer centre and the hub of Norwegian cancer care. We are developing the hospital for the future in cooperation with our patients

Unique properties and and advantages at OUH as a cancer centre

- Offers all diagnostics and treatments available in Norway for cancer patients. Responsible for cancer care for the population of Oslo, specialized care for the population in South-East Norway and highly specialized care for some patient categories for all Norway – performed by highly competent professionals
- Cancer registry with national quality register, epidemiological research and screening programme
- Large cancer-research environment as part of dedicated institute and own organisational units for clinical research, innovation and commercialisation
- 10. Increased commitment to primary and secondary prevention of cancer in collaboration with the Cancer Registry
- 11. Establish institutional governance for the CCC
- 12. Set the agenda for public discussion of cancer in Norway

OUH: All components "in house"



The OUH Cancer Centre's most important strategic measures from 2017-2021

- 1. Strengthen the information, education and involvement of patients at all stages in illness
- 2. Develop standardised pathways for all patient groups
- 3. Gather the same type of patient treatment in one location in OUH and improve infrastructure, including new buildings and a proton centre
- 4. Increase the use of personalised diagnostics as the basis for correct treatment and to avoid over- and under-treatment
- 5. Further-develop work-sharing with other hospitals in the region and the primary health service
- 6. Develop existing and establish new prioritized areas of research with particular international impact fraction or potential
- 7. Increase the number of clinical studies and patient accrual to trials
- 8. Establish national and enterprise-based quality registers for all cancer groups
- 9. Establish IT solutions which facilitate quality improvement and improve patient security, support patient pathways, and support research



Close cooperation with a broad spectrum of professional

• Close cooperation with the primary health service

Close cooperation with innovative environments

User-participation, and cooperation with user

environments at the University of Oslo

in Oslo

organisations

All located within one hospital



OUH CCC: Core Activity Data for 2017





Relative Survival

The data for relative survival is from the Cancer Registry. (See Cancer in Norway for definition of relative survival).

Table 1. Five-year relative survival for 2002-06 and 2012-16 – a selection of cancer diagnoses for patients treated at OUH (surgery and/or radiotherapy).

Gender	ICD-10	Location	2002-06	2012-16
Female	C-18	Colon	60.2 (55.5–64.8)	60.1 (55.6–64.3)
	C19-20	Rectum	60.7 (55.7–65.5)	67.3 (62.8–71.5)
	C33-34	Lung	19.4 (16.9–22.0)	33.0 (30.7–35.4)
	C-50	Breast	90.3 (89.2–91.3)	93.4 (92.4–94.3)
	C56-57	Ovarii	47.5 (43.7–51.4)	62.8 (58.8–66.7)
	C70-72	CNS	71.2 (67.6–74.4)	72.4 (69.0–75.5)
Male	C-18	Colon	53.7 (48.4–58.8)	53.7 (49.2–58.2)
	C19-20	Rectum	60.5 (55.6–65.1)	65.6 (61.9–69.2)
	C33-34	Lung	15.1 (13.2–17.1)	25.9 (23.7–28.1)
	C61	Prostata	93.0 (91.6–94.3)	98.0 (97.0–98.9)
	C70-72	CNS	54.1 (50.1–57.9)	53.8 (50.3–57.2)





Patient Satisfaction

OUH has developed web-based patient satisfaction survey open for all patients treated at OUH and approx. 1/3 of the patients participate in the survey. The survey provides us with unique quantitative data (percentages) and qualitative data (comments) to create a holistic picture of the patient satisfaction during their stay at OUH.

Purpose and scope

A main purpose of the survey is to identify areas for improvement. This is anchored in the Oslo University Hospital's strategy plan for 2013 – 2018 and in the vision: *Future treatment will be developed in cooperation with the patients*. The data is updated monthly. In addition to the standard report by organisational unit, we have developed a report for cancer patients across units sorted by tumour group – that is all breast cancer patients or lung cancer patients or any other cancer diagnosis are gathered in one report.

There is open access to the standard report at the internal OUH website. The reports for cancer patients across are distributed three times annually.

The twelve questions asked to all participating patients are:

Where have you stayed? Please enter the department code from the invitation

- 1. Did the doctor speak to you in such a way that you understood them?
- 2. Do you have confidence in the skills of the doctor?
- 3. Do you have confidence in the skills of the other staff?
- 4. Did you receive sufficient information about your diagnosis/your ailments?
- 5. Did you feel that the treatment was adapted to your situation?
- 6. Were you involved in decisions concerning your treatment?
- 7. Did you feel that the institution's work was well organized?
- 8. Did you have the impression that the equipment in the institution was in good condition?
- 9. All in all, was the assistance/treatment you received in the institution satisfactory?
- 10. Do you believe that you were given the wrong medical treatment (as far as you can judge)?
- **11.** Did you have to wait to receive help from the institution?
- 12. All in all, what benefits have you had from the treatment in the institution?





The overall results for cancer patients are very good. Cancer patients score higher or much higher than the OUH reference at all questions except on shared decision making.

In addition to the twelve questions, the survey is open for comments. In the report the comments are sorted according to unit treated and thematic area. The comments are in general positive and examples are:

"I'm very pleased with the way I was met. I was met with compassion, was seen and listened to, very good information and last but not least great professional skills by the attending physician. A doctor I experienced as highly interested in their work. For me, as a patient, it felt reassuring. A pleased patient." - Breast cancer patient

"Experienced the treatment, which I had dreaded, as excellent. Good and compassionate professionals, who made me feel well cared for."

- Skin cancer patient

However, some also comments for improvement:

"Fantastic! The only think I'll comment is that I think the waiting time for test results is too long".

- Patient with malignant tumor in thyroid or other endocrine glands

"Was taken care of in a fantastic way. Was very anxious upon arrival, but was quickly reassured. Everyone I was in contact with were just great. And I was finally taken seriously and got a definite diagnosis. THANK YOU!!"

- Head and neck cancer patient

"The professionals' skills and compassion is great, but the logistics and administrative routines are inefficient." - Patient with head and neck tumour





Patient Involvement

Chair of OUH Patient Council, Tove Nakken

The OUH Patient Council is an advisory structure for the CEO and division heads. 'The chair of the council meets at the OUH board meetings.

Both the OUH CCC board and the CCC Research Council include a patient representative. In 2017, users participated in 43 councils and projects in OUH, demonstrating the increasing commitment to engage patients and patient relatives and use their competence and experience to develop the hospital.

Standardised patient pathways for cancer and monitoring time to delivery of care give patients great expectations on the continuity and logistics.

Past and present patients are strong advocates for research. The research groups have to include how they envision user involvement in their research. Without the user perspective, the project will have limited possibilities to achieve external financial support! Thus, the users' perspectives are embedded in the research process, from designing the project to publishing results. OUH is the largest cancer research institution in Norway, reflecting the need of user contribution.

The Norwegian cancer Society is a major financial contributor to cancer research. They encourage their members to contribute in research projects.

Tove Nakken is a cancer survivor and chair of OUH Patient Council. She is a member of the OUH CCC Board and CCC Research Council.



Example of patient-centred research: The Pallion project; integrated palliative care and shared decision making

PALLION is a national, multi-centre, cluster-randomized trial. Six hospitals form the 'active cluster'. Six matching hospitals constitute the 'control cluster'. Six hundred patients who are receiving chemotherapy and have a life expectancy of one year are eligible to the study.

The overall aim of the trial is to integrate palliative care with standard oncological treatment at earlier timepoint than in current practice.

The intervention consists of three parts: Implementation of an integrated care pathway, systematic assessment of symptoms and an educational program for oncologists and palliative care physicians.



The integrated care pathway gives an outline of the patient "journey" integrating oncologic treatment, palliative care and end-of-life care as well as community care. The pathway promotes early introduction of a patientcentred focus.

The educational program, developed for the study, aims to increase participating physicians' skills in patientcentered communication, prognostication and symptom management.

Combined, the three elements of the intervention are expected to improve symptom management, improve quality of life for the patients and their families, and

empower them to play an active part in decision-making. We also hypothesize that the intervention will lead to reduced hospital stays in the final months of life. The main outcome will be the proportion of patients treated with chemotherapy in the last three months of life.



Prof. Jon Håvard Loge MD. Project leader.



Clinical Pathway Management and Governance

High quality patient pathways have high priority both for the ministry of health and from the OUH CCC Board. Capacity at all sites, good coordination of logistics and cooperation on clinical and diagnostic decisions are crucial to accomplish this. To support this target OUH has established structures and roles:

- Pathway managers
- Pathway management group
- Multidisciplinary team meetings
- Patient pathway coordinator / case coordinator

The pathway manager for each pathway is appointed by the chief medical officer after recommendation from the OUH CCC board. *The pathway management group* consists of representatives from all involved departments, professions and units, as well as pathway coordinators.

The pathway coordinator is the patients' and relatives' primary contact. The main responsibility is ensuring flow in patient logistics within and between departments.

The pathway manager, together with the pathway management group, is responsible for documenting a standardised patient pathway, and organizing improvement of the patient pathways.

During 2017 the Executive Committee of the OUH CCC Board started systematically follow-up dialogues with the pathway management teams. The meetings are prepared with key information based on the pathways managements' own input. Additionally, standardised information dashboards are employed to create an overview of the pathway These dashboards include relative survival, patient satisfaction, and goal achievement in regards to normative times for referral processing, evaluation, diagnosis and treatment.

Regional MDT-Meetings by Video Conference

In 2017 OUH made the decision to start up multidisciplinary team (MDT)-meetings for regional patients referred to OUH, including specialists from other hospitals. These meetings were facilitated with new three-channel video technology. The new video technology was installed at all hospitals in south-east health region during 2017. Each tumour group makes criteria for inclusion of patients to the regional video meetings. Regional video meetings were pioneered in lung cancer utilizing two channel technology. The first tumour group to start up meetings at a regular basis with the three channel system was gynaecological oncology.

Regional Multi disciplinary team (MDT) meetings for Thorax at, OUH

OUH hosts three weekly thorax meetings for the south-east region.

Management: A managing doctor, specialised in respiratory medicine, organise and lead the thorax meetings.

Preparation: The patient pathway coordinators within the lung department have a key role in organising. The patients' referral to a given time at a meeting and standardised information are sent ahead of the meeting.

The meeting: A radiologist, nuclear medicine specialist, thorax surgeon(s), oncologist(s) and lung doctors are attending the meetings, as well as coordinators from the respective specialities. Additionally, other hospitals within the region are connected via video transmission. OUH's video transmission equipment is facilitated for three-stream technology. The other hospitals provide information about patients they themselves have assessed. To ensure the best evaluation possible for the patient, we strive for that the doctor who have the most insight in the patient's case, are the one who present the case at the meeting. The patient should be ferdig utredet ahead of the meeting.

If treatment of metastases is relevant, the patient case should be presented by the responsible doctor in the other department.

Minutes: A responsible OUH doctor writes minutes from the thorax meeting, so there is written information within OUH on everyone involved in discussing the patient case independent on where the patient has been assessed.

Follow up: A OUH doctor refer internally in our system to further examinations and/or treatment in OUH, including patients from other hospitals. This is done to avoid excess assessment time or time before treatment.

Frøydis Stornes

Pathway manager and head of MDT Thorax meetings.

Standardised Patient Pathways (SPPs)

To develop and implement standardised cancer patient pathways (SPPs) is a prioritized task for OUH-CCC. The goal is that all pathways should be documented in the OUH internal quality handbook by the end of 2019 and with the methodology shown in figure 1.

Documentation of the respective SPPs are organized as projects. The OUH CCC Board give the pathway manager a

mandate to lead the documentation process (see page 13). Experienced facilitators assist the pathway management team, and representatives from all the involved professional groups contribute. Platforms for the SPPs are the national guidelines, but SPPs are more in depth and more comprehensive and cover the whole journey from admission to hand-over to the primary health care system.



Experience from developing SPPs

Dr. Anna Winge-Main, consultant melanoma oncologist

We reviewed the entire patient management process with the aim to improving the effectiveness and efficiency of melanoma patient care. Our project delivered a new simplified and standardised patient referral template and then went on to strengthen our multidisciplinary team meetings broadening specialists' participation and embracing digital technologies. Consultants currently spend less time on administrative tasks and are able to refer some patient check-ups to our nurse clinic, enabling more physician-patient interaction time. Our patients also benefit from up-to-date comprehensive written information about their treatment, procedures and key contact information.

This project has been important to me because we were empowered to make improvements which will have a lasting impact for patient management.





Opening of the Cancer Rehabilitation Centre

The Division of Cancer Medicine has an outpatient "return to work" rehabilitation unit that offers multidisciplinary rehabilitation programs and psychological support after cancer treatment for patients within working age. Focus is on improving daily function and work ability, and patients are referred to the unit from hospital doctors or general practitioners.

Group-based programs are by cancer diagnosis (breast-, gynaecological-, haematological-, gastrointestinal cancer or lymphoma) and are primarily for patients treated with curative intent. Programs involve a daily session/ over 7 weeks consisting of patient education (physical activity, nutrition, return to work, psychological coping, late effects, sexuality), group talk, and physical exercise (fitness, strength and relaxation).

Individual tailored rehabilitation programs are offered to patients regardless of cancer diagnosis, and for patients with chronic cancer or with long-term side effects. Based on needs, the program consist of guided physical exercise and/or counselling about coping, physical activity, nutrition or work-related matters. Two psychologists offer *short-term psychological treatment* for patients and close relatives with substantial cancer-related psychological distress.

We encourage patients to pursue their rehabilitation in their home environment, and reports for follow-up are sent to their general practitioners. Patients evaluate the rehabilitation service given as relevant, and in a quality study from the group programs 4 out of 5 are back at work (full or part-time) 6 months after end of the program.



Minister of Health Bent Høie, Tove Nakken, Torhild Birkeland, Cathrine Lofthus, Sigbjørn Smeland, Håvard Aagesen, Werner Frimanslund.

OUH CCC Research Activity 2017

Since the designation of OUH by OECI as a Comprehensive Cancer Centre (CCC) in 2016, efforts have been made to gain oversight and better coordinate the high quality cancer research which is performed throughout OUH. An institutional cancer research strategy has been developed, and as an overarching strategic and coordinating body the CCC Research Council has been appointed, with senior members (Heads of Research) from all relevant OUH divisions, the Cancer Registry of Norway, and the Chair of the Patient Council. In 2017 an international CCC Scientific Advisory Board was appointed, chaired by Prof. Carl-Henrik Heldin of Uppsala University and the Nobel Foundation (see p. 5).

Cancer research is performed at all four hospital sites, and includes high quality basic, translational, epidemiological and clinical research. In total approx. 550 FTEs are dedicated to cancer research, including approx. 260 researchers, 135 Ph.D. students, 260 technical or administrative staff and approx. 20 clinicians with formalised and protected research time. The largest research unit is the Institute for Cancer Research at the Radium Hospital site, which has a principal focus on basic and translational research with 320 employees, 24 research groups and 202 peer-reviewed publications in 2017. The largest clinical cancer research activity is within the Division of Cancer Medicines' departments of Oncology, Haematology and Gynaecologic Oncology. The division has a dedicated Phase I unit, and in 2017 a total of 182 clinical trials were in operation.

Most CCC Research Council members and senior researchers have part time positions at the University of Oslo (UiO), securing alignment between OUH and UiO cancer research efforts. The total cancer research budget is in the order of €50 million, of which approx. 60% is from external, competitive funding. This does not include the Cancer Registry of Norway which has a separate research budget of €9,25 million, whereof approx. 41% is from external competitive funding. The number of cancer research groups within the divisions and departments is outlined on page 18.







Prof. Gunnar Sæter MD Research Director, Division of Cancer Medicine Head, OUH CCC Research Council



2017 CCC Research Highlights:

- The volume of full publications was stable compared to previous years (617) and 68 (11%) had an Impact Factor >10. 42 Ph.D. degrees were completed within the cancer field.
- OUH CCC coordinates four EU projects and participates as a partner in another 16.
- Four high-ranking external research centres were in operation in 2017, with strong collaborations both within and outside the OUH CCC.
- Two new research centres won competitive national funding and are being established from 2018:
 - Centre for Cancer Cell Reprogramming (Centre of Excellence), Director Prof. Harald Stenmark, Institute for Cancer Research, OUH and Institute for Clinical Medicine, UiO.
 - KG Jebsen Centre for B Cell Malignancies, Director: Prof. Ludvig Munthe, Division of Laboratory Medicine, OUH and Institute for Clinical Medicine, UiO.

In addition, the KG Jebsen Centre for Colorectal Cancer Research (Director Prof. Ragnhild Lothe) gained a prolongation for two years after an excellent external review.

- Major grant from the interventional clinical research program "KLINBEFORSK": Establishment of Molecular Profiling for Individual Clinical Routine Treatment Decisions in Early Breast Cancer (EMIT study). Principal Investigator: Prof. Bjørn Naume, Division of Cancer Medicine, OUH (see p.31).
- Individual awards and grants for top OUH CCC researchers:
 - *ERC Advanced Grant* for Prof. Harald Stenmark, Institute for Cancer Research, OUH and Institute for Clinical Medicine, UiO. (his second ERC Advanced Grant running): Coincidence detection of proteins and lipids in regulation of cellular membrane dynamics
 - Norwegian Research Council funding program for Research of Excellence ("TOPPFORSK"), with funding initiation in 2018:
 - Prof. Karl-Johan Malmberg, Institute for Clinical Medicine, UiO and ICR OUH: "Programming natural killer cell function through organelle function".
 - Prof. Tor Erik Rusten, Institute for Clinical Medicine, UiO, and ICR OUH: Deciphering Tumour-Host Biology".
 - The award of *Commander of the Royal Order of St. Olav* was given to Prof. Emerita Anne-Lise Børresen-Dale, ICR and UiO, for her extraordinary and life-long achievements in international cancer research.
 - *King Olav V Award for Cancer Research* (Life achievement award by the Norwegian Cancer Society in June 2017) to Prof. Per Ottar Seglen, Institute for Cancer Research, OUH and Centre for Molecular Medicine, UiO. Topic: Fundamental biological mechanisms and regulation of autophagy.
 - Election to the Norwegian Academy of Science and Letters: Magnar Bjørås and Eivind Hovig in 2017

2017 CCC Innovation Highlights:

- On the basis of CCC research, 17 Disclosures of Invention (DOFIs) and 4 patent applications were filed. Examples of major innovations:
- Formal agreement between Prof. Johanna Olweus' research group and the US company KITE Pharma on the development of novel TCR-based immunotherapy.
- Formal agreement between Prof. Karl-Johan Malmberg's research group and the US company Fate Therapeutics on the development of NK cell based immunotherapy.



Key indicators

617 (338) Total number of peer-reviewed publications (with OUH CCC first or last author) **68 (11%)** Number of publications with impact factor >10

23 (4%) Number of publications with IF>20

182 (767) Number of active clinical studies (patients included in 2017):

71

Number of research groups within the cancer area across the divisions

549 Approx. total number of FTEs in cancer research

€50 million

Budget: estimate of research budget (by parameters)

20 Active projects funded by EU (H2020)

42 Completed Ph.D. degrees **17** Disclosures of Invention (DOFIs)



In the following a few selected units and projects ongoing in 2017, illustrating the strength and diversity of cancer research in OUH CCC:

The Early Clinical Trial Unit

The Early Clinical Trial Unit was established was established in 1995 as one of the first of its kind in the Nordic region. It serves as a facility in the Department of Oncology at Oslo University Hospital (OUH) to focus on early phase trials and experimental medicine for patients with different cancer types.

Early phase (I/II) clinical trials are the first step in testing of a new drug, and might be the first time a new drug is given to patients. The studies are primarily designed to determine the dose a new drug can safely be given to a patient, either as monotherapy or in combination with other drugs, to obtain knowledge about the side effects, but also to explore the mechanism of antineoplastic effect in the tumour.

The team consists of site project managers, study nurses, and physicians who are trained in conducting clinical trials according to the ICH-GCP guidelines ("Good Clinical Practice") and who are experienced in the management of patients with different cancer types. Involvement in several trials with targeted therapies and advanced immunotherapy has acquired knowledge in managing potential serious side effects of new cancer therapeutics, including immunotherapy. The Early Clinical Trial Unit aims to be a preferred partner for early drug development and for the testing of complex trials with human cellular products, in academic projects and industry-sponsored clinical trials.

There is a well-established and long-standing collaboration between The Early Clinical Trial Unit and pharmaceutical industry, both big pharma and smaller Scandinavian bio-tech companies. Investigatorinitiated studies are ongoing, primarily in collaboration with the Institute for Cancer Research at OUH, including immunotherapy and vaccine studies and ancillary translational projects.

A total number of 50 – 70 patients are recruited onto early phase trials per year. In 2017 14 trials were ongoing, and per Q2 seven additional early phase trials are planned to open for inclusion in 2018.





Oslo Myeloma Centre

Oslo Myeloma Centre (OMC) is now the largest clinical research centre for multiple myeloma in the Nordic region. The centre was started in late 2014, with the aim of providing clinical trial opportunities for Norwegian myeloma patients. Today, myeloma is the cancer in Norway enrolling the highest number of patients in clinical trials; 84 patients in 2017, belonging to 16 different hospital regions, including Bergen and Bodø. 53 of the patients were enrolled in academic trials and 31 in to industry sponsored trials. The large majority of patients also donated material for basic and translational research to the Institute of Immunology and the Norwegian Centre for Molecular Medicine.

Our centre has 10 study nurses, 6 doctors, 3 secretaries and 1 research coordinator. It is a part of the department of haematology and located at Rikshospitalet.

The centre is based on the idea that patient participation in clinical studies benefits the patients with better treatment, the doctors with more competence and experience, the hospital with academic credit and lower costs, and with all this, the society as a whole. We believe and have showed that this can be achieved at a lower cost than standard treatment.



Back row from left: Liv Sigrun Eide, Kristin Låstad, Sylvia Rognli, Ann Døli, Anna Lysén, Anita Husøy, Marrydith Tran. Front row from left: Nina Gulbrandsen, Magnus Moksnes, Anne Carlsen, Puneet Kaur, Esther Morilla, Ulla Madsen, Fredrik Schjesvold, Larisa Myrseth



Fredrik Schjesvold MD, Ph. D., project leader





Myeloma patients enrolled in clinical studies



Centre of Excellence: Centre for Cancer Biomedicine (CCB)

CCB was a Norwegian Centre of Excellence that was funded by the Research Council of Norway from 01.09.2007 to 31.08.2017. The centre's vision was to join cell biological research aimed at discovering new mechanisms in carcinogenesis and tumour suppression with translational cancer research focusing on discovery of novel molecular and phenotypic hallmarks of cancers that can be exploited in diagnostics, prognostics and therapy. Through collaboration with CCB's experts in biostatistics, this has indeed proven to be a fruitful strategy, and CCB scientists have made several discoveries and innovations that promise to be useful for future patients with lymphoma, colorectal cancer or prostate cancer.

A paper that received considerable attention in 2017 came from PhD student Nadja Katheder in Tor Erik Rusten's CCB project group. Katheder, Rusten and their co-workers published in Nature that tumours instruct cells in their microenvironment to turn on autophagy, a cellular process that entails degradation of some of the cell's own proteins into amino acids. These amino acids are then transported back to the tumour as constituents of new cancer cell proteins. If this mechanism is inhibited, the tumour shrinks, which provides us with a new target for future cancer therapy. These findings were dedicated commentary articles in *Cell Metabolism*, *Developmental Cell and Scientific Reports* and were covered by the news on national TV.

Another project leader in CCB, June Myklebust, has, in collaboration with colleagues at Stanford, revealed individual differences in B-cell receptor signalling in patients with non-Hodgkin's lymphomas that correlate with differences in therapy responses. Postdoc Hege Marie Vedeld and her co-workers in Guro E. Lind's CCB group have identified a specific DNA methylation phenotype that identifies high- risk patients among microsatellite stable BRAF mutated colorectal cancers.

Researcher Anita Sveen and colleagues in Ragnhild A. Lothe's CCB group have analysed a large number of microsatellite-instable colorectal cancers and revealed molecular heterogeneity with clinical relevance, including mutations that predict favourable prognosis.

Even though CCB will not continue as a centre, key elements of CCB's research will be sustained in the form of other centres and projects. These include a new Centre of Excellence, Centre for Cancer Cell Reprogramming, KG Jebsen Colorectal Cancer Research Centre, KG Jebsen Centre for B-Cell Malignancies, Lighthouse project "DoMore", Toppforsk project "Modeling tumor heterogeneity in colorectal cancer", Toppforsk project "Deciphering tumor-host biology", and NANO2021 project "Biodegradable nanoparticles in cancer diagnosis and therapy".







The Lumiblast Project

A paradigm shift in cancer therapy – using mitochondria-powered chemiluminescence for non-invasive treatment of inaccessible tumours.

Background

Brain tumours like Glioblastoma Multiforme (GBM) are difficult to treat because of their location and aggressive characteristics. Approximately 28,000 new cases of malignant glioma such as GBM are diagnosed every year in the EU and the US and 240,000 patients globally every year. The current standard therapy consists of surgery, followed by radiotherapy and chemotherapy. However, these therapies offer limited overall patient survival: The combination of surgery with radiotherapy increases the median survival from 4.5 months (untreated) to 12.1 months. Additional chemotherapy with temozolomide extends survival to 14.6 months. The relative survival for adults diagnosed with GBM is less than 30% within one year of diagnosis, and only 3% of patients live longer than five years after initial diagnosis, showing unmet medical need.



Prof. Kristian Berg



Theodossis A. Theodossiou Ph. D.

tumor-localized photosensitizers, such as in photodynamic therapy (PDT) has been clinically evaluated, but with limited success. This is mainly due to the limited penetration of light into tissue and the efficient spread of tumor cells typically up to at least 2 cm from the resection margin. Moreover, the existing photon based treatments (photodynamic therapy) are highly invasive and usually require open-cranium surgery, due to the need for external light sources.

The use of light-based treatments of GBM by activating

In the Lumiblast project the photons are produced inside the tumour cells in the form of chemiluminescence avoiding the major limitation of using external light to treat solid, deep-sited and inaccessible tumours. This may also be relevant for cancers of other origins. Due to its nature Lumiblast is expected to act on individual cells, and may thus completely eliminate the hitherto incurable GBM. Each GBM cell is expected to become a small "lamp" providing the light required for the photosensitive agents to become activated, killing the tumour cells from the inside. So far, this principle has been firmly documented.

The idea of Lumiblast is to develop a non-invasive and highly specific treatment of GBM with a potential for a curative end-point. If Lumiblast becomes successful this will be a paradigm-shift in the treatment of GBM.

Simplified description of Lumiblast:

Drug A and B are delivered individually and when they meet in the GBM one will produce light in the individual cells, which will then convert the other to exert cytotoxicity.

Qian Peng Ph. D.





Photodynamic Detection and Therapy

Research activities of this group focus on the combination of radiation (X-ray, UV-A, visible light, ultrasound) with radio-/photo-/sono-sensitisers and/or nanoparticles to develop diagnostic and therapeutic (nano)technologies. For example, photodynamic therapy (PDT) of cancer is a two-step therapeutic technology in which the topical or systemic delivery of a tumour-localising photosensitiser is followed by irradiation with visible light. The light-absorbed photosensitiser then transfers the light energy to molecular oxygen, generating reactive oxygen species that kill tumour cells. The absorbed energy of the photosensitiser can also be released via fluorescence, which can be utilised for the photodetection (PD) of tumour.

Three major ongoing research projects

1. 5-Aminolevulinic Acid-based Photopheresis (2015-2020, HSØ & DNK)

This project uses the PDT principle to develop a technology to photodeplete highly proliferative/activated T cells that are involved in malignant and non-malignant diseases. There are two ongoing clinical trials in patients with graft versus host disease, cutaneous T cell lymphoma or Crohn's disease.

2. Sonoactivable Nanotheragnostics for Cancer Treatment (2014-2018, EuroNanoMed)

This EU project aimed at developing liquid-cored stable nanoemulsions (NEs) of perfluorocarbon suitable for tumour imaging and controlled therapy. These NEs were optimized with a fluorinated surfactant ensuring their water solubility and stability. Thanks to their fluorinated core the NEs can be detected by 19F MRI or by echography after vaporization. The core/shell of the NEs can also be loaded with a sono/photo-sensitizer (eg. PpIX) to induce ultrasound- or light-mediated tumour damage.

3. Nanoscintillator-Porphyrin Complexes for Bimodal RadioPhotoDynamic Therapy (2016-2019, EuroNanoMed)

This EU project develops a bimodal cancer treatment modality by combining two clinically used radiotherapy and photodynamic therapy, mediated by theranostic nanoparticles (composed of nanoscintillators and photosensitisers). Upon exposure to ionizing radiation the nanoscintillators (polysiloxane core/terbium oxide) transfers the X-ray energy to the tethered photosensitiser that produces cytotoxic singlet oxygen. With this novel therapeutic approach the problem of limited visible light penetration into solid tumour tissue in PDT can be solved. In addition, this new modality will allow treatment of deep tumours with lower radiation doses than those in conventional radiotherapy.

Major strengths of this group:

- Multidisciplinary expertise in photophysics, photochemistry and photobiology
- Translational research in vitro and in vivo and clinical trials with PDT and photopheresis
- Scientific collaborations with other groups in Norway, EU, USA and China
- Collaborations with industries in Norway, Germany, USA and Japan



Qian Peng Ph. D.





In Silico Digital Pathology: The DoMore! Project

The DoMore! Project activates the Institute for Cancer Genetics and Informatics' entire interdisciplinary structure with an emphasis on both academic and structural change. Pathology, as it is practiced today, has remained largely unchanged for the last 200 years. New developments have occurred only in the last two decades, with immunohistochemistry and molecular biology having found their natural place in pathology. With this project, we have proposed a complete transferal of complex human decision-making from its current basis in visual observation to a computer basis - in silico. Our ambition is to replace some of this very complex thinking and decision-making with objective, reproducible algorithms. The concepts involved are based on image analysis and more specifically on deep learning, texture analysis, and quantification of DNA, with the specific aim of implementing in silico pathology in the clinical routine.

Development of new methods for faster and more secure prognosis is the key to a more precise treatment. We are using new tools and developing methods in cancer types where pathology has met its limits. Recent years' advances in computing and processing have made it possible to explore far greater amounts of data than before, which we are utilizing to establish more robust grading systems. Our computers will be able to retrieve and treat far more information about a tumour than pathologists can do with today's methods. The work in DoMore! has already resulted in the development of a method for automated tumour delineation based on deep learning as well as a novel method called Nucleotyping, which is an automated process used to determine chromatin heterogeneity in a tumour. Our efforts resulted in the submission of a UK patent application for Histological Image Analysis (on deep learning and tumour grading), and additional progresses include the publication of nine original

research papers, with a mean impact factor of 12.3 (3.025 – 33,90) as well as two editorials, and one review paper. We have also made strides in the dissemination of our results, with 20 articles, two videos, 20 oral presentations, and one podcast.



Prof. Håvard E. Danielsen





REirradiation and PD-1 Blockade in Recurrent Squamous Cell Head and Neck Tumours – The REPORT-Study CA209-669;

Head and neck cancer is a rare disease in Norway with 800 new cases every year. Based on the low incidence of this cancer and the multimodal and advanced treatment, the treatment is centralized to the four university hospitals. In total more than 60% of the head and neck cancers are treated at Oslo university hospital. Recurrent head and neck squamous cell carcinomas (HNSCC) after aggressive multimodal treatment with chemoradiotherapy, hypoxic-modulators and surgery are a common clinical challenge.Treatment options are often limited. Head and neck squamous cell carcinomas are often radiosensitive tumours. Re-irradiation to doses of 60 Gy or more can give long-term response for selected patients.

Immunotherapy with antibodies against PD-1 in monotherapy has been shown to be effective in metastatic head and neck squamous cell carcinomas. Moreover, there is compelling evidence that radiotherapy is capable of inducing immunogenic cell death, which serves as a trigger for the immune system ("in situ vaccine"). Intriguingly, though radiotherapy induces direct tumour regression by killing of cancer cells, more recent evidence suggests that the long term protection against relapse often depends on mobilizing the host immune system. In the REPORT study, the strategy is to induce a personalized immune response by radiotherapy, and to release the break of the immune response by use of nivolumab, an inhibitory antibody against PD-1. The aim is to gain long-term tumor control locally and systemic.

REPORT is a phase I study and the primary objective is to determine the safety and tolerability of nivolumab when administered together with radiotherapy, and determine a safe dose of nivolumab in this combination. The patients are followed to evaluate toxicity, but also objective responses by PET-CT scan. Biopsies are done regularly during treatment to investigate biological and immunological response, including biomarkers for response.

The study opened for patients in August 2017. In total, 6 patients have been included in REPORT so far. Our experience is that the combination of immunotherapy and radiotherapy treatment is well tolerated, and objective responses have been observed.





Can one Aspirin a day Impede Recurrence of Colorectal Cancer Metastases? The ASAC trial

The ASAC trial is a Scandinavian, multi-centre, double-blinded, randomized, placebo-controlled study to determine whether treatment with low-dose acetylsalicylic acid (ASA/Aspirin) can improve disease free survival in patients treated with resection of colorectal cancer liver metastases (CRCLM). Several studies have shown beneficial effect of ASA on primarv prevention of CRC. ASA is known to irreversibly inhibit the enzyme cyclooxygenase and thereby stopping production of prostaglandin E2 (PGE2). PGE2 has several pro-oncogenic effects by increasing the blood flow to the tumour (angiogenesis), stimulating tumour growth, and inducing regulatory T cells which results in tumour immune tolerance in both primary and metastatic colorectal cancer (our findings). We next did a registry based study linking all patients in Norway diagnosed with CRC from 2004 to 2011 with aspirin use and found that aspirin use after the diagnosis on CRC was associated with improved cancer-related survival and overall survival (Bains SJ, et al. J Clin Oncol 2016). In order to assess whether the survival benefit is caused by aspirin, we are conducting the ASAC trial with a design where 800 patients operated for CRCLM will be randomized to Arm#1 ASA 160 mg once daily or Arm#2 Placebo for a period of 3 years or till disease recurrence. The patients will be treated and followed up according to standard-of-care and national guidelines. The first patient was recruited in November 2017 at Oslo University Hospital, and from 2018 there are 5 sites in Norway, 6 sites in Sweden and 3 sites in Denmark that will recruit patients to the trial.

The ASAC trial will be the first clinical interventional trial to assess the beneficial role of ASA in recurrence of CRC liver metastases and survival. ASA is an inexpensive, well tolerated, and easily accessible drug that could be a potent adjuvant drug in secondary prevention of CRC liver metastases if the study shows a beneficial effect. We will also determine the effect of ASA as adjuvant treatment on Health-related Quality of Life and the cost-effectiveness.

The trial is initiated by Oslo University Hospital and University of Oslo, Norway and is funded by The Norwegian Research Council, The Norwegian Cancer Society, and KLINBEFORSK with head of the HPB Surgical Section Bjørn Atle Bjørnbeth as PI, Senior Consultant Sheraz Yaqub and Head of Institute of Cancer Research, Kjetil Taskén at Oslo University Hospital as co-PIs. See also www.asac.no for further information.



MD



MD, Ph.D.

Sheraz Yaqub MD, Ph.D.



The ASAC study will try to answer this





Gene-Transduced Autologous T-cells (CAR-T cells) in the Treatment of Leukaemia and Lymphoma

Different types of immunotherapy have changed cancer treatment considerably during recent years like monoclonal antibodies, check point inhibitors (releasing the break on tumour-infiltrating normal cytotoxic T-cells) and immunomodulators (especially for the treatment of multiple myeloma).

Recently, another breakthrough in immunotherapy was achieved. By reinfusing autologous (own) T-cells containing an artificial gene product, leukaemia and lymphoma cells are killed efficiently, curing patients, otherwise having no further treatment options. The treatment consists of only one intravenous infusion of the autologous T-cells with an inserted gene coding for a receptor which directly recognizes a surface structure on the malignant leukemia or lymphoma cells. In advance, the autologous T-cells have been harvested by leukapheresis, frozen down, shipped thawned and stimulated and transduced in a central laboratory with a gene coding for the receptor, subsequently expressed uniformly on the T- cell surface.

Due to a renowned reputation of the cancer research quality and organization, as well as the Stem Cell Laboratory harvesting and isolating the cells, Oslo University Hospital (OUS) was selected as one of very few European centres to take part in two industry sponsored studies (Novartis®). Patients were recruited during 2016 and 2017 on a study for children or adolescents with therapy resistant acute lymphoblastic B-cell leukaemia or on a study for adult patients with a second relapse of aggressive B-cell lymphomas. Altogether five leukaemia patients and six lymphoma patients were reinfused at OUS. Totally, 75 leukaemia patients and 100 lymphoma patients were treated. Responses were seen in 80% of the leukaemia and 50% of the lymphoma patients. Long term survival is expected in 50% of the leukaemia and 30-40% of the lymphoma patients having no other curative treatment options. Side effects can, however, be severe with need for intensive care unit treatment for a relatively short period in 20-35% of the patients.

Several industry companies are now competing with synonymous cell products for leukaemia and lymphomas, and two of the products are now approved by FDA in the US and expected to be approved in Europe in a short period of time. We will take part in several new studies, also on multiple myeloma in the near future. One scenario is that this therapy may be given first line or second line to selected patients groups, substituting autologous and allogeneic hematopoietic stem cell transplantation and the most intensive chemotherapy regimen.

So far, there is no breakthrough for this therapy modality for solid cancers.

Several OUS - researcher initiated protocols with gene manipulated autologous T-cells or NK cells for different cancer types are planned to start in 2020.



Duration of remission and survival acute lymphoblastic leukemia The figures only concern the patients who got infusion with tisagenlecleucel (75 percent).



Duration of remission for patients with lymphoma. The figure shows the patients with effective treatment (52 percent).

The HPV Vaccine Project

The Cancer Registry of Norway uses real-world data to follow-up the long-term effectiveness of the HPV vaccine, which has the potential to prevent thousands of cancers worldwide.

Knowledge of the role of human papillomavirus (HPV) in the development of cancer is leading to a paradigm shift in cancer prevention. Worldwide, about 5% of the cancer burden is associated with oncogenic HPV infection. Clinical trials have documented close to a 100% HPV vaccine efficacy on surrogate cancer endpoints, and a favourable vaccine safety profile over a 3-5 year trial period. However, HPV-related cancer typically takes more than a decade to develop. An extended follow-up that exceeds the duration of clinical trials is thus required to assess whether the protection lasts and ultimately prevents cancer. We combine real-world data from nationwide health registries to meet rigorous scientific and regulatory standards to estimate the vaccine effect with minimal loss to follow-up.

The project is a collaboration between the pharmaceutical company Merck Inc., which developed the first HPV vaccine, and scientific teams associated with the cervical cancer screening programs and nationwide cancer registries in Denmark, Iceland, Norway and Sweden. The long-term effect of the vaccine is monitored through extensive registry linkages. By identification through registries, we collect biological material that has been used to diagnose HPV-related disease, to establish whether the disease is associated to the HPV types of the vaccine. We also monitor the long-term side effects and vaccine-induced immune responses.

Close to 10,000 women who originally participated in clinical vaccine trials are under surveillance. Less than 5% have been lost to the long-term follow-up, mostly due to emigration. To date, our long-term follow-up of the HPV vaccine shows a continued protection in women through at least 10 years, with a trend for continued protection through 12 years of follow-up.

This collaboration shows that the Nordic registry infrastructure and competence can yield "health gold" that is beneficial to public health, and that the medical industry can take part in this process.





Colorectal Cancer Screening – Heading for a National Programme in 2019

Colorectal cancer is the second most common cancer in Norway. The number of cases has increased almost three-fold during the last 50 years, which is far more than in the other Scandinavian countries. Screening for colorectal cancer reduces the risk of dying from the disease, and a national programme will be implemented in 2019. To prepare for national roll-out, a pilot programme was initiated in 2012 in two hospitals in South-Eastern Norway, organized by the Cancer Registry of Norway. The pilot study is a randomized trial comparing sigmoidoscopy (endoscopic examination of the rectum and the lower part of the colon) with biennial testing for faecal blood. Inclusion of 140.000 individuals will be completed in early 2019. In 2017, two PhD students completed their thesis in the screening pilot, investigating psychological effects of screening and the impact of screening on future lifestyle. Two additional PhD students are currently involved in other projects in the screening pilot.

Following positive experience with the pilot, the government granted around NOK 20 million in the national budget for 2018 for planning of a national colorectal cancer screening programme starting in 2019. The ongoing preparations for the national programme include recruitment and education of personnel, investments in equipment and planning of the logistics and IT software. The capacity at the future screening centres is to be developed and increased, with the aim of having a nationwide screening programme for men and women at the age of 55 years within five years after start-up in 2019.

There are multiple tests available for colorectal cancer screening. As there is uncertainty regarding which screening test is most effective and cost-effective, the national screening programme will include a randomized trial comparing two screening tests: Colonoscopy and testing for faecal blood. The trial will be the world's largest colonoscopy screening trial conducted so far, aiming at including 120.000 individuals from all Norwegian health regions.



Precision Medicine 1: The MetAction Study: Actionable Targets in Cancer Metastasis

The MetAction project (Research Council of Norway, 2013-2017) had as primary objective to design and conduct the first clinical precision cancer medicine (PCM) trial in Norway. Treatment decisions were based on targeted Next Generation Sequencing (NGS) data generated from metastatic tumours (NCT02142036). Patients with end-stage metastatic cancer from any solid primary site (n=50). progressing on at least one line of standard treatment were eligible for the study. An important goal for the project was to establish an efficient diagnostic pipeline allowing treatment decisions based on comprehensive NGS-data (see Figure). The pipeline includes imageguided biopsy sampling, routine pathology examinations, NGS analyses, and bioinformatics workup. Furthermore; the project established Molecular Tumour Boards (MTB) for interpretation of possible sequence-drug combinations and Clinical Tumour Boards (CTB) where treatment decisions were concluded during video conferences between the two study centres, Oslo University Hospital (OUH) and Akershus University Hospital (AHUS). The mean time between sampling and treatment decision was 18 days. Actionable targets were identified in 13/50 patients. (26%). Six patients met the primary endpoint (30% extension of progression free survival (PFS) compared to the previous line of therapy). In four cases the disease course was reversed, and two patients are still on treatment (currently >12 months PFS). The conclusion is that the MetAction study has established a diagnostic pipeline that allows treatment decisions based on NGS-analysis within an acceptable time frame. The sampling procedures were safe and the treatment reversed end-stage cancer in a reasonable percentage of the cases (4/26 patients in the second half of the study, 15%).

Currently, targeted NGS-analyses are being implemented in routine diagnostics in Norway, but only for identification of selected mutations known to have impact on standard of care for a given diagnosis. The MetAction study has demonstrated feasibility of a broader examination of molecular aberrations as foundation for personalized treatment decisions. We have applied for funding for a second clinical trial where we aim to utilize the established diagnostic pipeline to demonstrate *clinical utility*, and to evaluate cost-effectiveness and societal impact of PCM. We plan to enrol patients with metastatic cancer progressing on earlier lines of therapy, and offer treatment based on biological target identification in the progressing tumour. We also aim to prepare for clinical translation and implementation of the established multidisciplinary diagnostic pipeline.



Prof. Gunhild Mælandsmo, project leader



Schematic overview of the diagnostic pipeline established in the MetAction precision cancer medicine clinical trial



Precision Medicine 2: The EMIT Study

This project aims to reduce both over- and undertreatment with adjuvant chemotherapy in early breast cancer. By the evaluation of a multigene-test in a large number of patients in Norway, the study seeks to identify those patients who are likely to benefit from chemotherapy whilst sparing those who are unlikely to do so.

Chemotherapy and hormonal therapy are currently offered to many as part of their breast cancer treatment to reduce the recurrence risk. The decision to offer chemotherapy, or not, is currently made using histopathological measurements such as the size of the tumour, histological grade, Ki67-proliferation index and the number of lymph nodes affected. Despite the use of these prognostic factors, treatment recommendations for a large group of patients with oestrogen receptor-positive/ HER2-negative disease remains uncertain and many patients may be given chemotherapy unnecessarily. Future progress in treatment of breast cancer therefore depends on improved riskand subtype-classification of the disease. One strategy is to use detailed molecular characterization (multigene-tests) of the individual breast cancer tumour. The EMIT project will evaluate the consequences of including a multigene-test (Prosigna) on treatment selection as well as on late effects and health-economic issues. Results from the first retrospective phase of the EMIT-study was completed in 2017 and showed that the test improved classification of patients with early breast cancer into prognostic groups, allowing for a more precise identification of future recurrence risk. The test outperformed the histopathological measurements. The current prospective phase of the project (EMIT1 and EMIT2) will include approximately 3000 patients from 15 hospitals across Norway, partly in collaboration with the OPTIMA research group in UK.

This will be a substantial contribution to the establishment of molecular based diagnostics for breast cancer in Norway and may refine early breast cancer classification to better select patients for treatment, sparing patients and society unnecessary costs.



Bjørn Naume MD, Ph. D., project leader

EMIT2/OPTIMA



EMIT1



Precision Medicine 3: The **BigMed Project**

The aim of BigMed is to lay the foundation for an ICT platform that addresses the analytic bottlenecks for the implementation of precision medicine to improve patient outcomes. BigMed develops novel solutions for (i) bioinformatics genome analysis; (ii) integrated analysis of electronic health record information with genomic data and structured and unstructured background information; and (iii) big data analytics that can extract and analyse relevant information; BigMed aims in this way to provide physicians currently facing data overload with much needed assistance in their decision-making.

Today, existing clinical systems are not enabled to harvest information from genomic technologies in a structured way. Similarly, data from other patients previously treated are not readily available for pattern discovery to subsequently guide precise treatment choices. BigMed will develop the necessary technologies to fill these gaps.

The workflow upon successful BigMed implementation will change: Biological specimens are collected through harvesting of molecular biology information through various high-throughput technology platforms, including DNA sequencing. Following a fully automated pipeline enriched and annotated genomic data then enters BigMed in standardised and integrated forms. These data are complemented with available electronic health record data, structured and combined with rich background knowledge. With the analytical intelligence and combined data of BigMed, the clinicians, e.g., a multidisciplinary tumor board (see graphic) treating a cancer case will be given a completely new level of treatment support.





Thomas Smedsrud MD, project leader

BIG M



Clinical Nutrition: Effect of Diet Intervention on Colorectal Cancer; Comorbidities and Late Effects

Using a translational research strategy including extensive chemical- and cell-based screening, novel preclinical transgenic reporter mice models, and epidemiological and clinical studies, we have identified several anti-inflammatory and anti-oxidative foods and drinks. We are now testing whether such foods and drinks are beneficial in a long-term randomized controlled trial (RCTs) with colorectal cancer (CRC) patients. The RCT (called the CRC-NORDIET study) focus on effects of anti-inflammatory and anti-oxidative foods and drinks under the umbrella of the Norwegian Food-Based Dietary Guidelines. Newly diagnosed stage I-III post-surgery CRC patients (50-80 years of age, n=500) with expected mean 5-year overall-survival of 68 % are recruited. The intervention arm receives an intensive dietary follow-up during the first 12 months. Patient are monitored extensively after 1, 3, 5, 7, 10 and 15 years (blood, urine and faeces samples, body composition, numerous questionnaires, physical tests, stress tests, tumour biomarkers, data from patient records, health registries etc). The aim is to test whether intensive one-year anti-inflammatory and anti-oxidative diet intervention improve survival and reduce comorbidity and late effects, and dampen inflammation and oxidative stress in CRC patients.

Clinical nutrition -Nutrition screening in the Divison of Cancer Medicine.

Cancer patient are at high risk of developing malnutrition due to a variation of factors such as:

- Varying degrees of inflammation
- Symptoms and nutritional issues due to the cancer itself or the cancer treatment
- Reduced physical function (e.g. mobility and fatigue) that hinders the purchase and preparation of food
- Psychological factors (e.g. depression and anxiety)
- Social factors (e.g. family, poor network, poverty)

The prevalence of malnutrition varies between the different cancer types, ranging from 30-70 % of cancer patients suffering from disease-related malnutrition.

Malnutrition has a negative impact on the patient's state of health. Malnourished people often have a poorer immune status, delayed wound healing, a greater risk of developing decubitus, a lower quality of life and increased mortality. These factors contribute to a longer hospitalization, a poorer response to the medical treatment (chemotherapy and radiotherapy) and a greater use of medicines, which is associated with increased health costs.

A summary of the implementation project

The aim of implementation Nutrition screening was to introduce a timely, optimal and uniform recognition and treatment of cancer related malnutrition.

300 of The Cancer Division's 500 nurses participated in a one hour course in how to recognize malnutrition with the use of NRS2002, a Nutritional screening tool.

300 out of 500 nurses also completed a full day course in how to prevent and treat malnutrition.



Prof. Rune Blomhoff, project leader In the full day course the nurses learned how to

- 1. Perform nutritional assessment (estimate nutritional requirement, nutritional intake, being aware of risks and symptoms of the refeeding syndrome and identify which patient to refer to a dietitian.
- 2. How to secure adequate nutritional intake through creating a nutritional plan and learning the importance of monitoring and changing the nutritional plan if the patient does not meet estimated nutritional requirements.
- Document nutrition diagnosis, nutrition status and nutrition treatment and send it to the next health care facility/ primary health care.



Comprehensive Cancer Centre

Oslo University Hospital

P.O Box 4950 Nydalen

N-0424 Oslo Norway

www.oslo-universitetssykehus.no/oslo-university-hospital

Oslo University Hospital is a local hospital for parts of Oslo's population, region hospital for residents in the South-East Region and has a variety of national functions.

Swichboard: inside Norway: 02770, outside Norway: +47 915 02770