Institute for
Cancer Genetics and Informatics

Annual Report 2018

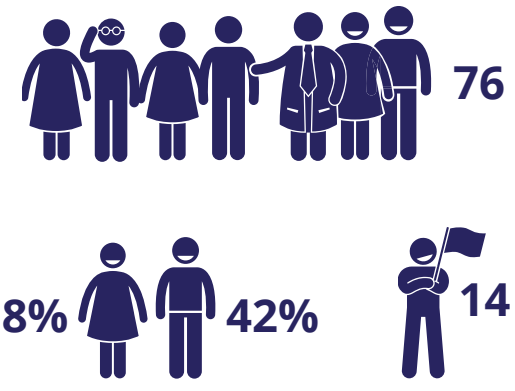
The Institute for Cancer Genetics and Informatics (ICGI) is a department within the Division of Cancer Medicine at Oslo University Hospital (OUS), located at the Norwegian Radium Hospital in Oslo, Norway. The ICGI has a strong focus on the diagnosis and prognostication of cancer, working in the fields of medical informatics, cancer genetics and pathology. We are using informatics as a method to study genetic alterations in cancer, and our overall goal is to enable better cancer treatment through improved diagnostics.

Organization

The ICGI consists of three sections: Section for Cancer Cytogenetics, Section for Interphase Genetics and Section for Applied Informatics. We have a multifunctional team structure - a matrix organization. Among our employees are surgeons, pathologists, computer scientists, professors, PhD-students, technicians, system developers, health personnel, bio-engineers, and communicators.

Staff

Our staff consists of 76 persons, 10 of which are financed by means from the Lighthouse project DoMore!, and with an additional six years of work being financed at DoMore! partner organizations in 2018. 64% are permanent employees, and we can report a gender balance of 58% women and 42% men, respectively. Together, 14 different nationalities are represented at ICGI.



Funding

The institute had a total budget of 94 million NOK in 2018. Of this budget, 76 million was available funds. We used approximately 30% on diagnostics, 19% on development, 51% of the budget on research, and 77% of the available funds on salaries. The external research funding was near 18 million NOK.

The Domore! project aims to utilize new technology to improve prognostication of cancers using artificial intelligence for pathology.

Research

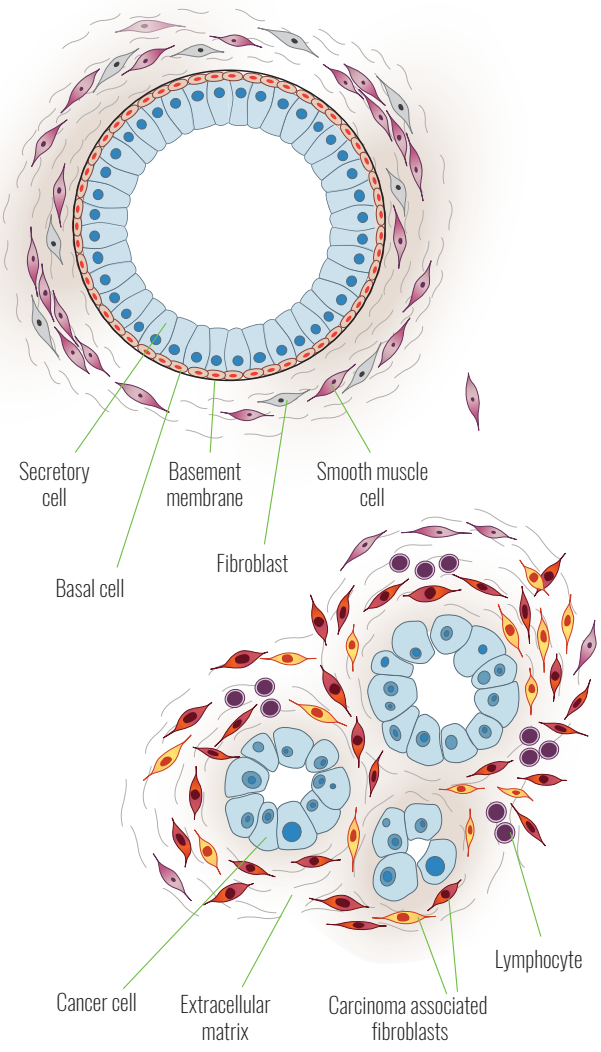
We concentrate our research on large-scale genomic instability, assessed with nucleomics such as Nucleotyping and DNA ploidy and big data imaging. We aim to understand the process of changes in DNA- and chromatin structure during cancer development and to use this knowledge to predict treatment response and prognosis for cancer patients. Several projects were ongoing in 2018, focusing on prognostic markers, based on our image-based AI methodology.

Our largest project is the DoMore! project - one of three prestigious Lighthouse projects awarded 60 million NOK by the Norwegian Research Council, running from 2016-2021. With in silico pathology and an international consortium led by ICGI, the project aims to solve some of the societal challenges that cancer poses. With deep learning (convolutional neural networks), we have both developed methods that automate existing assessments in pathology, such as the counting of mitotic cells, and developed tools that automatically identify the tumor region and patterns in histological images relevant for patient prognosis. We are working to utilize new technology to improve prognostication of cancers using artificial intelligence for pathology. The goal has been to increase the number of diagnostic and prognostic tests for cancer patients to provide a more accurate prognosis for the patient.

Our results so far show that it is, in fact, possible for a computer to train itself, not only to do the same but through Deep Learning and Big Data, to establish more robust grading systems in cancer types where pathology is less successful, while at the same time eliminating the subjective component.

During 2018 we have achieved results that have brought us far closer to developing a complete transferal of complex human decision-making from its current basis in visual observation to a computer basis by the use and development of methods based on artificial intelligence (AI).

In 2018 we published three studies on novel prognostic tests in cancer: chromatin analysis as a pan-cancer marker was published in March (*Kleppe et al., Lancet Oncology*). A related approach was used to identify the prognostically most relevant cell nuclei as a new prognostic marker that was validated in gynecological cancer types. This result was published in December (*Nielsen et al., J Natl Cancer Inst.*). A novel marker combining DNA ploidy and stroma content for improved prognostication of colorectal cancer patients was published in March (*Danielsen et al., Ann Oncol.*). Furthermore, we have used deep learning to develop new methods for the prognostication of colorectal cancer patients based on routine HE-sections, we have developed a method for the detection and counting of cells undergoing mitosis as well as improved methods for the quantification of protein expression in immunohistochemistry.

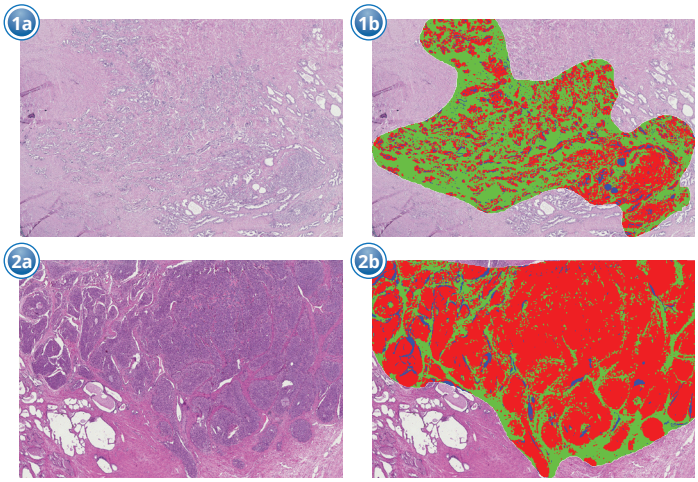


Components of the tissue microenvironment and the tumor microenvironment in the prostate:
Benign prostatic secretory glands (left) are surrounded by fibromuscular stroma or tissue microenvironment. (Right) Cancer cells interact with the surrounding tumor microenvironment.

To better understand our results and how they correlate, we have further developed MicroTracker, a tool for visualization of tissue sections with aligned results from multiple result sources, such as chromatin analysis, genomic instability, and immunohistochemistry. This novel tool lets us inspect cell features in tissue context and allows an improved understanding of existing results, the generation of new results combining cell features and their tissue context, as well as generation of new hypotheses.

The Nucleotyping method was initially developed in Matlab but has been implemented into a standalone application for use in clinical routine. To allow the inspection of scanned tissue sections and automatically extracted image features we have developed the web-based tool InterPath. Our publications on chromatin analysis in 2018 were based on specifically-prepared samples, called monolayers. In parallel, we have been working on transferring the methodology to routine sections stained with DNA-specific stain. This work is still in progress.

We have developed software which automatically detects stroma in scanned tissue sections (here shown in red).

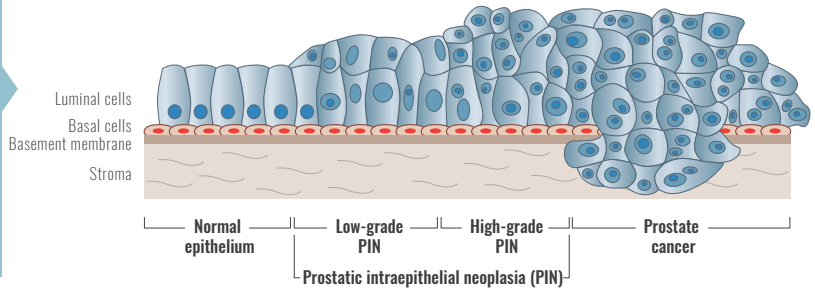


Prognostic markers in prostate cancer and colorectal cancer

In 2018 we completed one of our projects on prognostic markers in prostate cancer, where we have shown that DNA ploidy by image cytometry and automatically assessed stroma fraction in HE-sections, could be used together to identify patients at low-, intermediate- and high risk of clinical recurrence (*Ersvær et al., manuscript submitted*).

Also, we have several ongoing studies related to gene expression analysis in prostate cancer and colorectal cancer. We are investigating the gene expression of selected candidate genes involved in genomic instability in 304 patients with prostate cancer at Oslo University Hospital (OUS) and 263 patients with colorectal cancer from the Gloucester Colorectal Cancer Study, using NanoString mRNA analysis and immunohistochemistry (IHC). Several promising genes are under investigation as new biomarkers in prostate cancer.

Prostate cancer development:
Normal prostate epithelium is composed of basal epithelial cells and columnar secretory epithelial cells, which are separated from the supportive stroma by the basement membrane. Prostate cancer state is initiated by disruption of the basal cell layer nad the invasion of malignant cells into the the stroma.

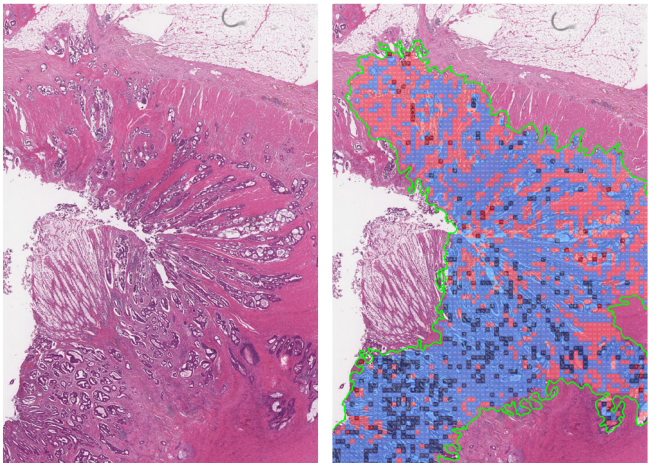


Intratumor heterogeneity

We have previously shown that intratumor heterogeneity poses a significant challenge in cancer biomarker research in prostate cancer. In radical prostatectomy (RP) specimens from 304 patients at OUS followed up for a median of 10 years, extensive heterogeneity was observed for Gleason score (89% of the patients) and DNA ploidy (40% of the patients) in the cohort. In 2018 we continued our studies on intratumor heterogeneity in prostate cancer. Currently, we are investigating a panel of candidate genes based on results from our gene expression analysis in prostate cancer, and to what extent intratumor heterogeneity affects the expression of these genes.

Further, we have also started investigating tumor heterogeneity in colorectal cancer. We have mRNA data from all available tissue blocks from 263 patients with stage II colon cancer from the Gloucester Cancer Study in England. So far we have mapped intratumor heterogeneity in large-scale genomic instability using DNA ploidy and microsatellite instability (MSI) and will continue our investigations into nucelotyping, mRNA analysis using the NanoString technology.

We aim to develop methods that can be easily implemented in clinical routine. Adapting methods that were developed for images from light microscopy to the more available and high-throughput-friendly scanner platform is one step in this direction. Correspondingly, we have developed a system for DNA ploidy analysis based on scanner images that have similar performance to the microscope system as well as a scanner version of the published pan-cancer marker Nucleotyping with identical results as the original system.



Histotyping:
A colorectal cancer tissue section stained with haematoxylin and eosin is analysed automatically to predict patient prognosis. The computer utilises a deep learning model that identifies the tumour region (the green line) before the region is split into smaller images, called tiles, that are analysed individually in another deep learning model. Each tile is assigned a poor prognosis probability reflecting its similarity with tiles from patients with a poor prognosis, and the probabilities are visualised in the figure using a blue to red colour scale to represent the low to high poor prognosis probabilities. A red-coloured tile therefore represents an image containing patterns that are indicative for poor prognosis for the patient. Eventually, the computer assigns a probability for poor prognosis for the patient, based on the tile probabilities.

Cancer cytogenetics

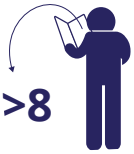
The main projects at the Section for Cancer cytogenetics are molecular analysis of female genital tract tumors, investigations of tumors of the brain and molecular genetic studies of connective tissue tumors and leukemias.

Among the results we found we can mention a specific microRNA family, miR-192/215, upregulated in mucinous ovarian carcinomas and not in the other histological subtypes (*Agostini et al., 2018*). The identification of fusion transcripts involving cyclin genes in endometrioid ovarian carcinomas (*Agostini et al., 2018*) and the specific EPC2-PHF1 and GREB1-NCOA2 fusion genes for endometrial stromal sarcoma (*Brunetti et al., 2018*) and undifferentiated uterine sarcoma, respectively (*Brunetti et al., 2018*). The latter fusion has been recently demonstrated to identify a specific group of uterine tumor resembling ovarian sex-cord tumor (UTROSCT) which is a rare mesenchymal neoplasm of unclear histogenesis and, according to the WHO classification, it is a subgroup of endometrial stromal tumors (WHO 2014). Furthermore, we have reported the assessment of methylation status using five two different approaches (*Johannessen et al., 2018*), all of them applicable in the diagnostic routine. At last, a PAN-PSMA2 fusion transcript was discovered from a 7;13-translocation in a myelodysplastic syndrome that evolved into acute myeloid leukemia (*Panagopoulos et al., 2018*) and a RUNX1-PDCD6 from a 5;21-translocation in myelodysplastic syndrome secondary to chronic lymphocytic leukemia (*Panagopoulos et al., 2018*).

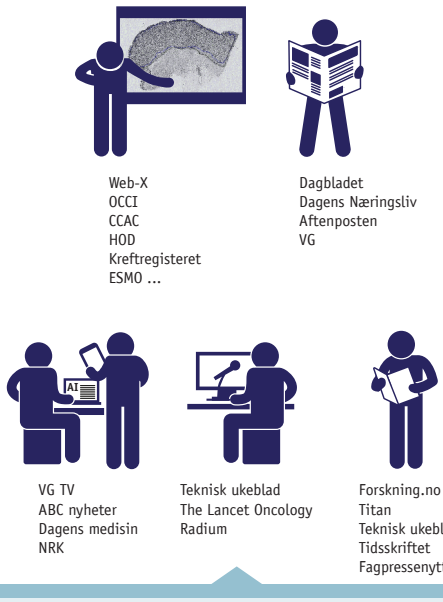
ICGI perform diagnostics for Oslo University Hospital and other Norwegian hospitals, and the number of diagnostic patients recorded at the Section for Cancer cytogenetics in 2018 was 3269. This gives an increase of 6% in the number of patients compared to the year before and corresponds to the number of G-banding analyses performed. The section also performed fluorescent in situ hybridization (FISH) investigations and molecular analysis in the form of mutation and/or methylation tests. The FISH laboratory has registered 8460 investigations, which correspond to an increase of 54%. The molecular tests were 1147 for the entire 2018.

Publication and dissemination

Our publication strategy has been to focus more on quality and less on quantity, and this is reflected in the overall publication results for 2018, which ended with 41 publications with a mean impact factor of 8.2 and a median impact factor of 5.5.



An essential element of the Lighthouse projects is to work in cooperation with users, public and commercial players to convert knowledge into clinical applications. The institute's investment in research dissemination ensured broad media exposure with around 30 pieces of coverage, with eight appearing in Norwegian daily publications. Our websites for cancer information had close to 1,1 million visits in total. The public cancer encyclopedia kreftlex.no demonstrated 18 percent growth. Our YouTube channel received 20 000 new subscribers in 2018 – 12 000 more than the year before. The total number of members of the channel are now 48 000. Our informative and scientific videos together got over 7 million views in 2018, which put us over 32 million views total.



The DoMore! project has been presented, mentioned and referred to on many occasions during 2018.

Institute for
Cancer Genetics and Informatics

Oslo universitetssykehus

The Institute for Cancer Genetics and Informatics performs research within genetics, biomedicine and informatics to develop prognostic and diagnostic tools for cancer treatment.

Visiting address: Ullernchausséen 64, Oslo
Postal address: Oslo University Hospital
P:O. Box 4953 Nydalen, 0424 Oslo

icgi.no | @icgiNO | info@icgi.no

2019-IKI-Aarsrapport2018-C | August 1, 2019