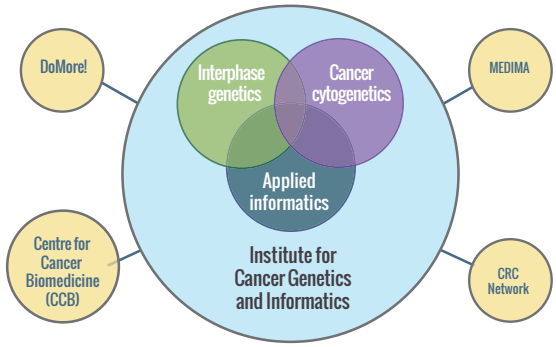
Institute for Cancer Genetics and Informatics

Annual Report 2017

The Institute for Cancer Genetics and Informatics, ICGI, is a department at Oslo University Hospital (OUS), located at the Norwegian Radium Hospital. The Institute is composed of three sections: Interphase Genetics (IFG), Cancer Cytogenetics (KCG) and Applied Informatics (AI). ICGI performs research within biomedicine and informatics to develop and establish new methods for diagnosis and prognostication of cancer. Our basic research strategy centers on nucleomics, our innovation strategy focuses on image analysis, and our overall goal is to enable better cancer treatment.

Organization

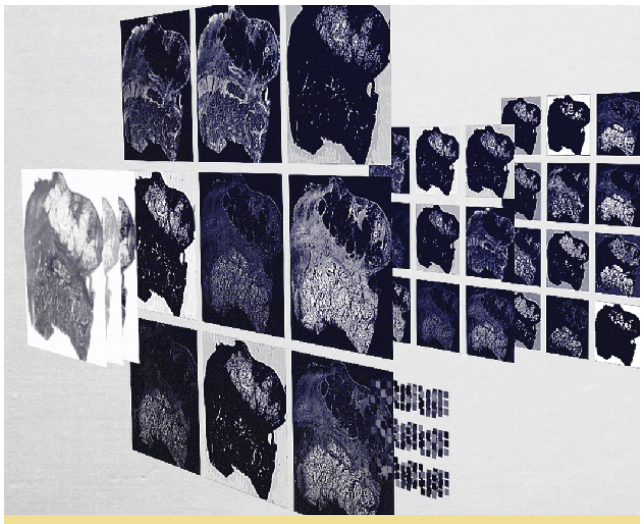
Since 2007, we have been a part of the Centre for Cancer Biomedicine (CCB), a centre of excellence in research. August marked the end of ten successful years of CCB (see the final CCB report). 2017 was also the first full year of the DoMore! Project, one of the prestigious Lighthouse projects awarded 60 million NOK by the Norwegian Research Council. With *in silico* pathology and an international consortium led by ICGI, the project aims to solve some of the large-scale societal challenges that cancer poses.



Staff

We are an 80-person staff at ICGI, of which 71 people are formally employed. This equates to 62 person years of work, 10 of which are financed by DoMore!, with an additional 6 years of work being financed at DoMore! partner organizations in 2017.

Of our 71 employees, 60% are permanent employees, and we can report a gender balance of 60%/40% women and men, respectively. Together, 13 different nationalities are represented at ICGI.



As an addition to the article in Lancet Oncology, 3D animations explaining deep learning and our nucleotyping method were developed by the section for Applied Informatics.

Funding

We had a budget of 67 million NOK in 2017, of which 52 million were from OUS. We used 83.5% of the budget on salaries. We used an approximate 30% on diagnostics, 15% on development and 55% of the total budget on research. We increased the external portion of research financing by 35% in 2017.

Research Goals

Our research is focused on (large-scale) genomic instability in cancer. Our aim is 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.

Publications in 2017

In total, we had 55 publications in 2017, which is an increase of 14.6 % from the previous year.

- The average impact factor was 5.9, which is an increase of about 5 %.
- The increase in impact points was approximately 20%.
- Additionally, three of our PhD candidates successfully defended their theses over the course of the year.

The DoMore! project was responsible for 9 of these publications, which gave an average impact factor of 12.3. The project has also already resulted in one patent application, titled: *Histological Image Analysis (filed in the UK, 29. November 2017).*

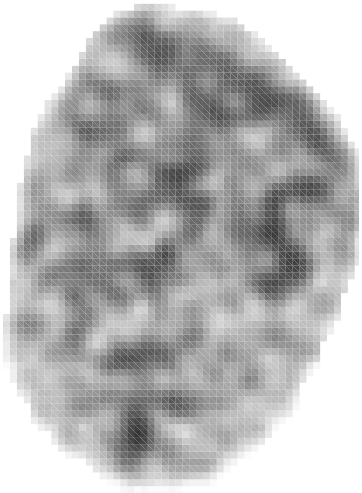
Main research projects

Prognostic markers

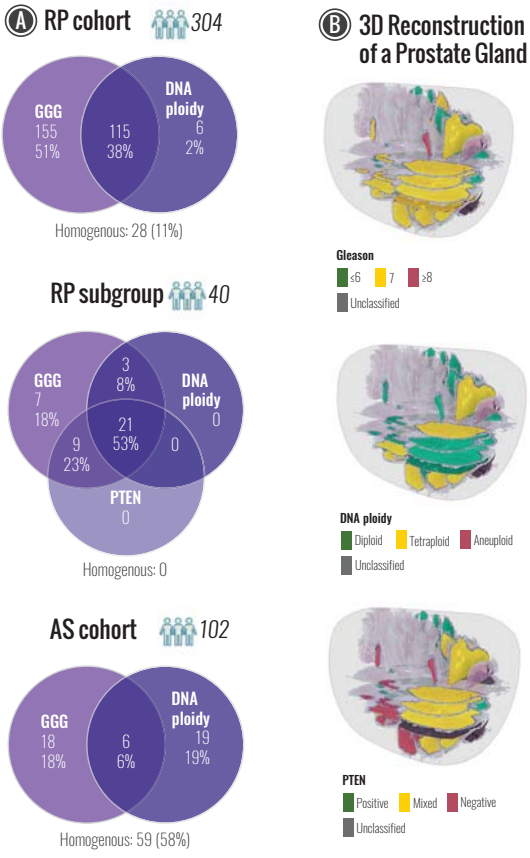
We had several projects focusing on prognostic markers, based on our own image-based methodology. We demonstrated that chromatin patterns with prognostic impact could be identified in a training set and then validated in a validation set from a cohort of endometrial cancer patients included in the Molecular Markers in Treatment in Endometrial Cancer (MoMaTEC) trial *(Hveem et al. Cancer Epidemiol Biomarkers Prev. 2017 Jan;26(1):61-67).*

We also succeeded in demonstrating that chromatin organization measured by our Nucleotyping method could serve as a generic prognostic marker *(Kleppe et al. Lancet Oncology, in press).*

We further showed that two relatively simple and established prognostic markers in colorectal cancer, 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 for cancer death *(Danielsen et al., Ann Oncol. 2017 Dec 27).*



Pattern and organization of chromatin has an impact on patient outcome.



Visualisation of tumour heterogeneity in prostate cancer using Gleason grading, PTEN expression and DNA ploidy analysis.

(A) *Venn diagrams showing the distribution of heterogeneity of the investigated biomarkers in patients from the radical prostatectomy (RP) cohort, RP subgroup and active surveillance (AS) cohort.* **(B)** *A 3D reconstruction of a prostate gland from the RP subgroup using H&E stained tissue sections. The results from all three biomarkers were applied to the sampled regions.*

Intratumor heterogeneity

Tumor heterogeneity poses a significant challenge in cancer biomarker research. We have assessed Gleason Score (GS), DNA ploidy status and PTEN expression in radical prostatectomy (RP) specimens from 304 prostate cancer patients operated at OUS and followed up for a median of 10 years. Extensive heterogeneity was observed for GS (89% of the patients) and DNA ploidy (40% of the patients) in the cohort. DNA ploidy was a significant prognostic marker when heterogeneity was taken into consideration. Our conclusion is that multi-sample analysis should be performed to undertake clinical treatment decisions. *(Cyll et al., Br J Cancer. 2017 Jul 25;117(3):367-375).* Currently we are investigating intratumor heterogeneity of a panel of target genes based on results from our gene expression analysis in prostate cancer.

We also investigated tumor heterogeneity in colorectal cancer through a pilot study including 105 patients from the Gloucester Cancer Study in England. For DNA ploidy, intratumor heterogeneity was observed in 24 % of the patients, and for the aneuploid tumors 43% showed DNA index heterogeneity. MSI was observed in 7% of the patients, but no heterogeneity in MSI status was observed between tissue blocks from the same patient.

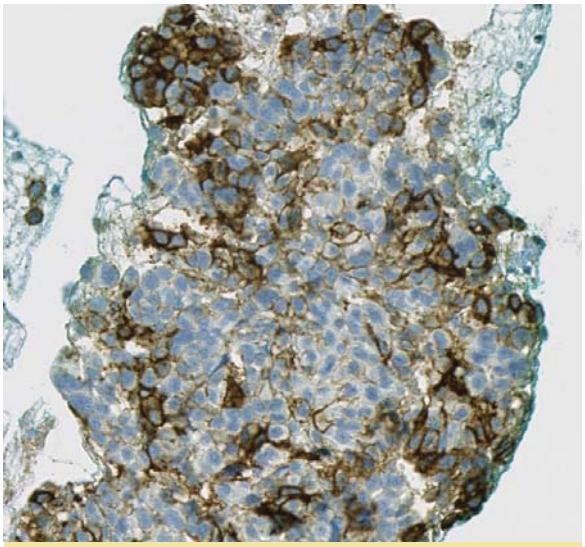
We are expanding the Gloucester cancer study to include all available tumor tissue blocks from 263 patients with stage II colon cancer. All 1375 blocks were sectioned in 2017. In 2018 we will be mapping intratumor heterogeneity in large-scale genomic instability using DNA ploidy, nucleotyping and microsatellite instability. Further, a panel of genes involved in genomic instability will be investigated by mRNA analysis using NanoString technology and protein expression will be analyzed by immunohistochemistry (IHC).

Gene expression analysis in prostate cancer

One of our main research interests is the role of large-scale genomic instability in cancer development. We are investigating the gene expression of 72 target genes involved in genomic instability in RP specimens from 304 patients at Oslo University Hospital (OUS) followed up for a median of 10 years, using NanoString mRNA analysis and IHC. Several promising genes are under investigation as new biomarkers in prostate cancer.

Fusion genes

The juxtaposition of two genes normally located apart from each other is a common mechanism behind the pathogenesis of many tumors. The most known fusion gene involves the ABL and BRC gene, through a 9;22-translocation, and leads to the development of chronic myeloid leukemia. This fusion as well as many other in both hematological malignancies and solid tumors are, at present, fundamental for the classification and the diagnosis of the tumors (according to the WHO guidelines). The research group at the section of Cancer Cytogenetics has identified and scientifically reported nine such fusion transcripts in 2017. *(Micci et al. Genes Chromosomes Cancer. 2017; 56(12):841-845.*
Brunetti et al. Genes Chromosomes Cancer. 2017 doi: 10.1002/gcc.22518.
Panagopoulos I et al., Oncol Rep, 2017; 37(6):3181-3188.)



Lung carcinoma with PD-L1 expression. Automatic scoring of PD-L1 established by ICGI could be of clinical use.

Immune response in cancer development

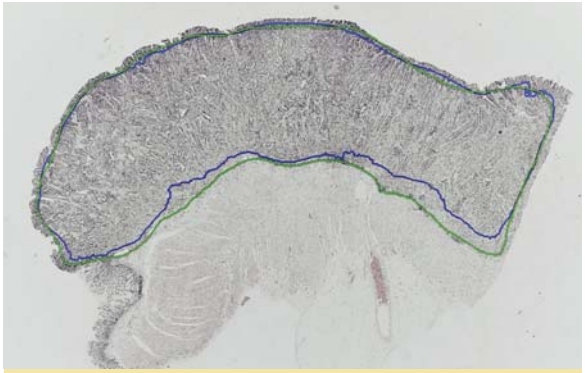
We have established automatic scoring of PD-L1 protein expression in lung tumors in patients from University College London and OUS. Objective scoring of PD-L1 should have a clinical use as the expression of this marker determines which lung cancer patients receive immunotherapy treatment.

We have also evaluated tumor-infiltrating CD8+ lymphocytes as a prognostic marker in colorectal cancer. Automatic scoring using our own developed Immunopath software has been used in a pooled analysis of the QUASAR2 (1.157 patients) and VICTOR (810 patients) trials in collaboration with Oxford University. (*Glaire MA et al., Tumour-infiltrating CD8+lymphocytes as a prognostic marker in colorectal cancer: a retrospective, pooled analysis of the QUASAR2 and VICTOR trials. Submitted)*

In silico Pathology

We trained deep neural networks to automatically identify tumor regions in scanned HE-stained sections. The pathologist's drawing was used as the ground truth. The result is relevant for diagnostic purposes and will be used as input for the automatic tumor prognostication method.

We further trained deep neural networks to estimate colorectal cancer patients' prognosis based on an HE-section from the surgical specimen and clinical follow-up information. Preliminary results are promising and represent a groundbreaking approach with great clinical potential if it generalizes to the validation set.



A pathologist marked the tumor area in green, and we used this as the ground truth. Using deep neural networks the area outlined in blue was automatically selected.

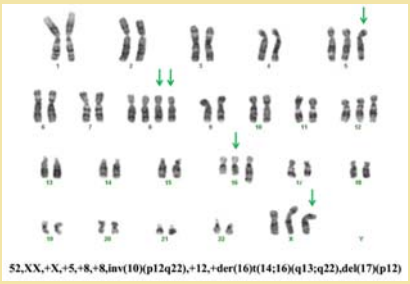
Diagnostics and lab production

Our goal is to enable better cancer treatment through new methods for improved diagnosis and prognosis of cancer. Our diagnostic discoveries contribute to personalized cancer medicine, and are included in several courses of treatment and care for cancer patients.

In 2017, more than 10.000 analyses (Karyotyping, FISH and Molecular analysis) were performed for diagnostic purposes, representing a 30% increase compared to 2016. These were primarily analyses of samples from hematological malignancies (leukemias and lymphoma), and solid tumors with sarcomas, gynecologic and brain tumors being the most frequently analyzed.

A further few hundred ploidy analyses were produced, primarily for prognostication of patients with early-stage ovarian cancer.

Additionally, our labs produced more than 8.500 units (Virtual slides, DNA sections, Monolayers) as part of the DoMore! Project, which was an increase of 48% compared to last year's production.



For patients with tumors in the central nervous system (CNS), our institution offers the best diagnostic service in Norway. Both for patients at Oslo University Hospital, as well as from other hospitals, we can give a correct classification of the tumor allowing adjustments of treatment plans.

Applied informatics

Apart from playing a key role in our main research projects, AI is focused on application development, Dissemination and Visualization, and Technology. We developed approximately 30 new or updated applications in 2017. Our unit for medical registries (Medinsight) moved to Oslo Hospital Services' office for Regional Research Support (OSS, Forskningsstøtte) in 2017, allowing us to focus even more on our research projects. Among the many activities in the Technology unit, the implementation of a platform for research and development utilizing deep learning, including GPU-servers for training neural networks and tile servers for image processing, has been crucial for the DoMore! Project. The expansion of our storage capacity was increased from 375TB to more than 700TB, and with a similar increase in backup capacity, we now have a total data capacity of about 1.5PB.

The unit for Dissemination and Visualization ensured that the ICGI received relatively broad media exposure in 2017 with around 40 pieces of coverage, with seven appearing in Norwegian national newspapers and eight in Norwegian professional publications. Our websites for cancer information had more than 1.3 million visits in total this year, with Kreftlex.no and its English version Oncolex.org continuing to demonstrate strong growth in particular. Our YouTube channel received 6.000 new members in 2017, and member numbers have now reached more than 26.000. We had just under 4.3 million views of our videos in 2017, which put us over 24 million views total.

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.

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