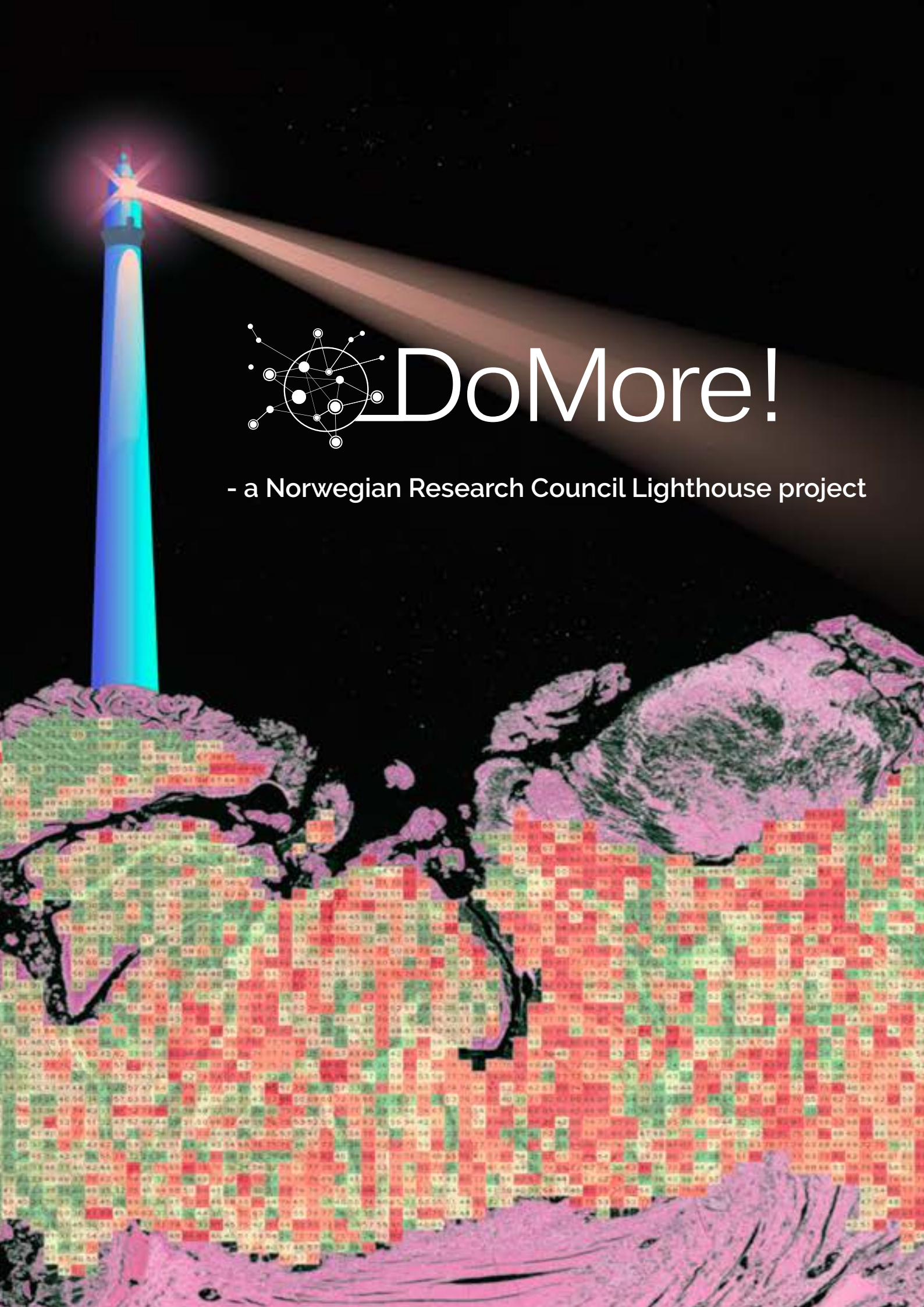
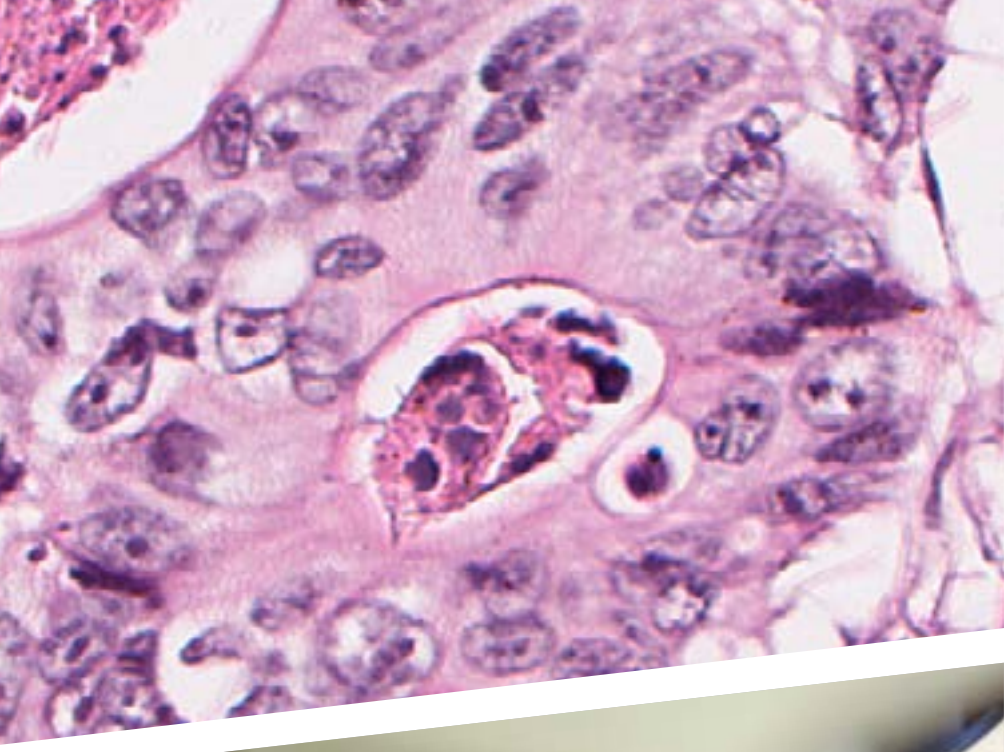

DoMore!
- a Norwegian Research Council Lighthouse project



CONTENTS

The DoMore! project
was initiated by The Institute for Cancer Genetics and Informatics (ICGI) at Oslo University Hospital, and funded by the Norwegian Research Council

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Oslo, August 2022

Developing methods using artificial intelligence (AI) to give cancer patients a more precise prognosis and counteract overtreatment

In 2016, following a comprehensive multistep-evaluation by national and international experts in ICT and E-Health, the Research Council of Norway selected DoMore! as one of three projects to receive funding as part of its ambitious Lighthouse Project scheme. As the name suggests, Lighthouse Projects were intended to be beacons, guiding and inspiring future projects to address large societal challenges using cutting-edge technology.

Norwegian Research Council's definition of Lighthouse projects

"Lighthouse projects are ambitious and visionary projects where research institutions, in cooperation with commercial, public and user actors, solve social challenges of importance. The target of this call was to develop health-, care-, and welfare-ICT solutions for the future."

Projects were funded by IKTPLUSS as part of an initiative with BIA and HELSEVEL, which called for the development of new innovative ICT-based products and solutions in response to key societal challenges to be deployed in Norway's public and private sectors. Assessed on the basis of Excellence, Impact, and Implementation, projects were expected to have long-term goals and challenge-driven aims to create value in health, healthcare, and welfare. The DoMore! project was awarded 60 million Norwegian Kroner on the basis of its fulfilment of these criteria.

MANUAL PATHOLOGY

Clinically staged and graded

Time-consuming and subjective

DIGITAL PATHOLOGY

Equal health care with digital sharing

Automatic analysis

More standardized practice

Increased productivity and quality

Background and challenges to address

Cancer poses enormous personal, clinical and societal challenges, and the number of global annual cancer cases keeps increasing at a high rate. Successful cancer treatment relies on a correct diagnosis, preferably at an early stage of the disease. However, cancers are heterogeneous and can follow multiple paths, not all of which progress to metastases and death; some cancers are indolent, causing little or no harm during the patient's lifetime. The ability to assess the disease's likely outcome is equally important, and the importance of prognostic methods and markers cannot be overstated.

Before starting primary treatment, a patient's disease is clinically staged, a process to determine the extent to which the cancer has progressed, and graded, assessing the aggressiveness of the disease and the patient's likely outcome. The prognostic value of histological grading varies both by cancer type and between pathologists, as this is a subjective process.

Grading depends heavily on the pathologist's expertise, and inter-observer and intra-observer agreements are moderate only. The grading performed by specialist pathologists working at a tertiary centre is prognostically better than grading by general pathologists. The inter-observer agreement among specialist pathologists is better than that of general pathologists, so a patient's care can also be impacted by their location and ability to access higher--tier hospitals. Ultimately, patients pay the price through under- or overtreatment.

The variability of grading systems' abilities to prognosticate, and the subjectivity in using these systems, pose significant challenges for accurate diagnosis and prognosis. Furthermore, pathologists are scarce, and the resources in the health service are limited, necessitating efficiency, productivity, and quality improvements without using more resources. To adequately address the heterogeneity issue, one needs to analyse more samples, DoMore!, with the same number of resources.

As pathology has demonstrated, critical prognostic information may be deduced from a tumour's growth pattern through subjective comparisons of such patterns and patients outcome. By applying tools using AI and Deep Learning on Big Data, DoMore! sought to establish more robust grading systems, developing generic and objective digital prognostic markers for prostate, colon, rectum, and lung cancers.

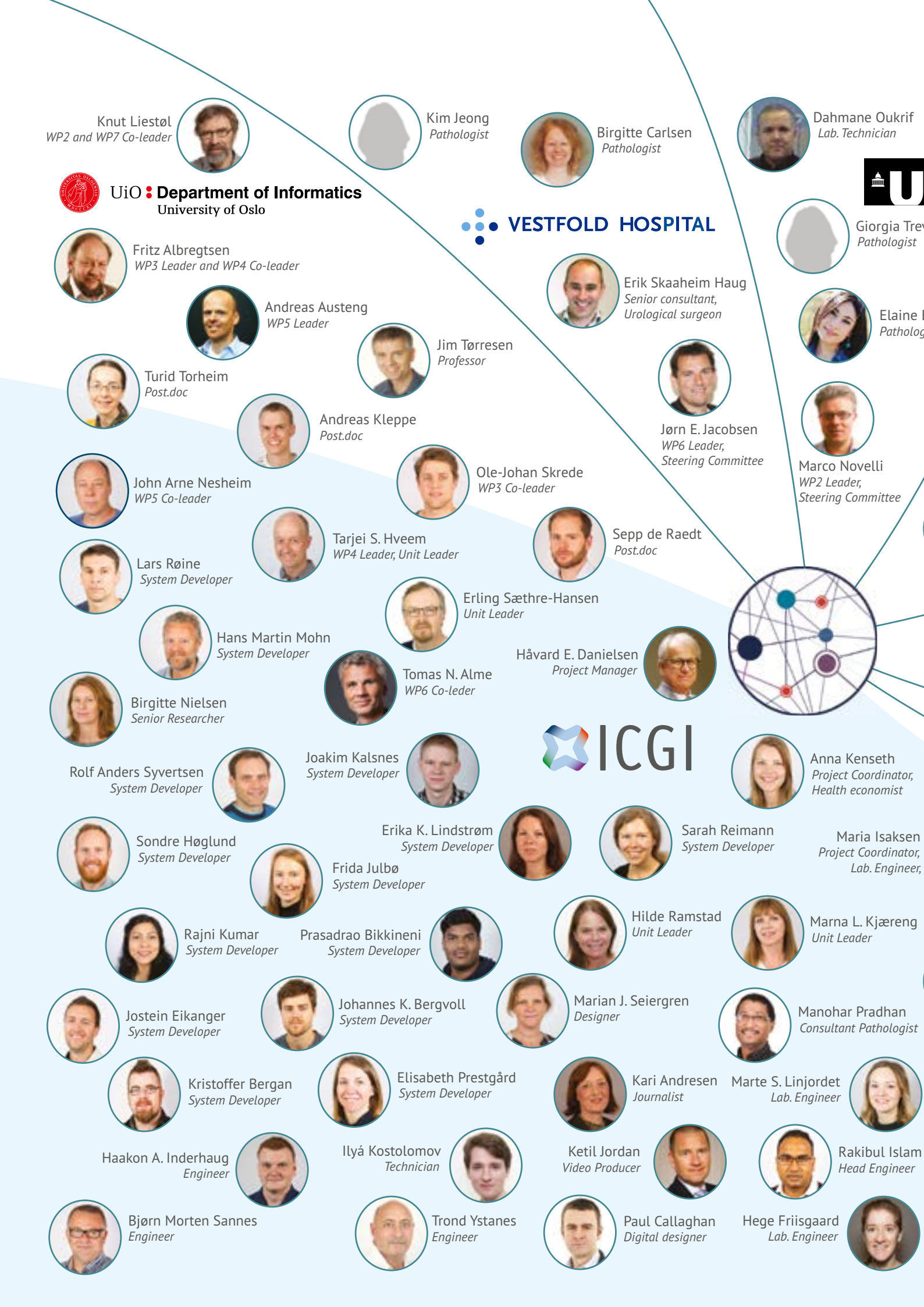
Materials

All the materials used in DoMore! were collected from surgically resected tumours from the prostate (Pca), colorectal (CRC), and lung cancer patients provided by our collaborators (see figure). These three cancer types were selected for the degree to which they represent the wide-ranging spectrum of cancer in heterogeneity, aggressiveness, and incidence. The use of machine learning and deep learning demands "big data", and as digital pathology is in an early phase, most of the "big data" used in DoMore! needed to be produced within the project. Initially, we planned to include 18 162 tumour blocks from a total of 7055 patients divided between the three cancer types. Devoting roughly 1/3 of the total budget to data production along with the increased interest from new collaborators during the project, we were able to do more than initially planned, with a total inclusion of 12 370 patients and digitalisation of 81 173 hematoxylin and eosin (H&E) stained sections (virtual slides).

	Originally planned		Included in DoMore!			Origin of materials
PROSTATE 	1.706	6.028	1.925	6.247	15.395 / 15.491	Oslo University Hospital; VESTFOLD HOSPITAL; UNIVERSITETSSYKEHUSET NORD-NORGE UNIVERSITY HOSPITAL OF NORTH NORWAY
COLORECTAL 	4.521	8.822	8.355	19.482	28.779 / 46.899	Oslo University Hospital; UNIVERSITY OF OXFORD; UCL; AKERSHUS UNIVERSITY HOSPITAL; UNIVERSITY OF LIVERPOOL; NHS Gloucestershire Hospitals
LUNG 	828	3.312	2.090	3.693	13.152 / 18.783	Oslo University Hospital; UNIVERSITETSSYKEHUSET NORD-NORGE UNIVERSITY HOSPITAL OF NORTH NORWAY

Patients · Tissue Blocks · Samples · Slides

Photo: K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Tarjei S. Hveem
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Sepp de Raedt
Post.doc
Lars Røine
System Developer
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Trond Ystanes
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CL

visan

Borg
gist

Team

Under the guidance of its Director, Professor Håvard E. G. Danielsen, ICGI initiated the DoMore! Project in 2016 with an interdisciplinary consortium of international experts in digital image analysis, tumour pathology, cancer surgery, and oncology. We built a strong leadership structure with a steering committee and executive board that oversaw DoMore! progress, managing both risks and innovation over its five years of activity.

We carefully selected partners based on their unique competence and perspectives to ensure that we had the best possible chance to achieve our goals. Two-thirds of the partners work directly and daily with the issues we addressed in this project. The other third are companies working with and investing in health services. By partnering with key opinion leaders within their fields, we strove to ensure the knowledge was converted into clinical application.

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Sigbjørn Smeland
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Ketil Widerberg
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OSLO CANCER CLUSTER

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Kristian Wittek
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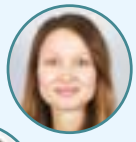

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Naomi Målbakken
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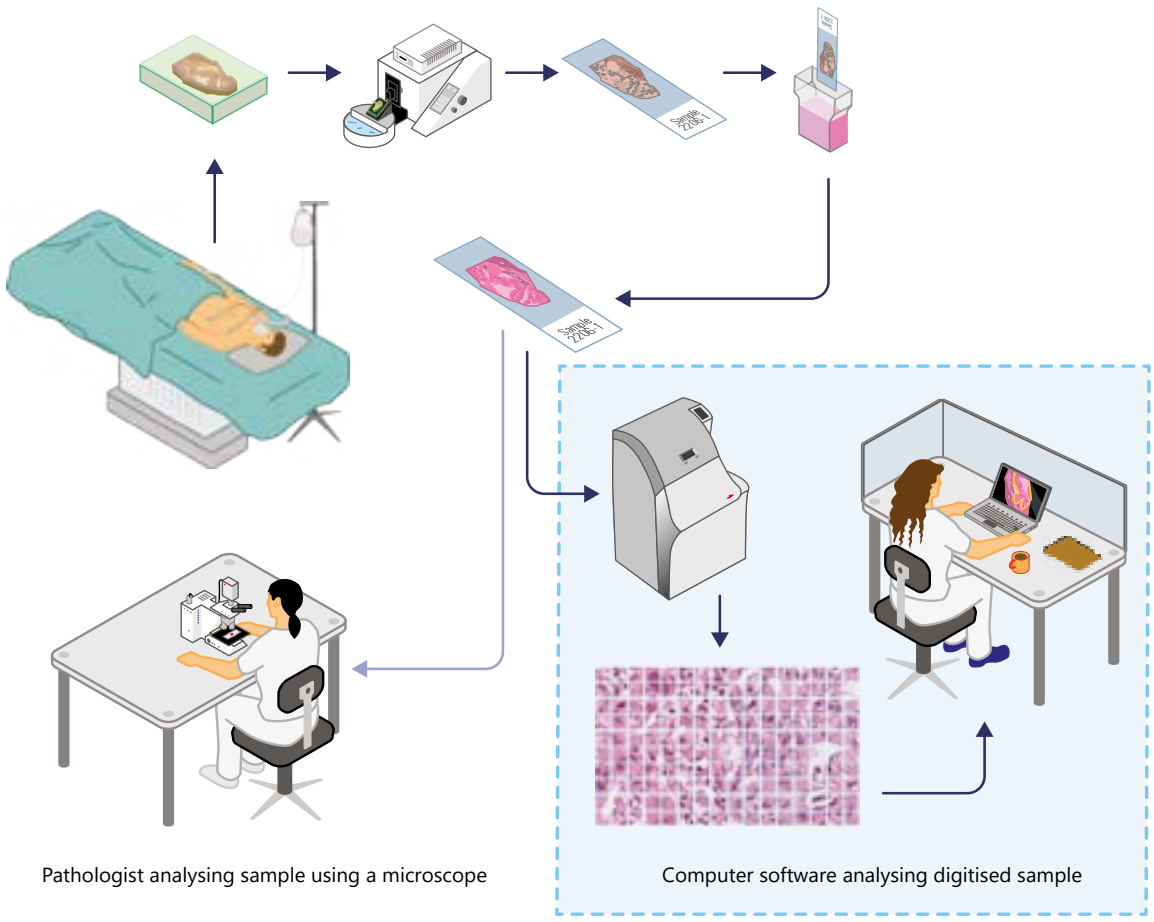
Scientist



Pathologist analysing sample using a microscope

Computer software analysing digitised sample

In silico pathology

The digitalisation of pathology is currently being established in most pathology departments nationally and internationally, and the digitalisation of routine sections poses many advantages in both diagnosis and prognosis. Not only will it allow for equal health care regardless of geography, but it has the potential to address many of the challenges faced in the pathology field. This can be achieved mainly by implementing methods for *in silico* pathology, i.e. automated analyses of pathological samples such as tissue sections stained with haematoxylin and eosin (H&E) scanned with high-resolution scanners. Deep learning combined with ground truth based on the pathology assessment and patient outcome forms the basis for methods developed in the DoMore! project.

The current procedures needed to render a prognosis are time-consuming and subjective. During the project, we have utilized Deep Learning and Big Data to develop robust systems and ICT solutions to supplement or replace methods in pathology to increase productivity, quality, and hence treatment. All experiments described in this report have been designed to examine multiple samples from each tumour and patient. With this approach, we have addressed the heterogeneity issue by analysing more of the tissue samples with fewer resources.

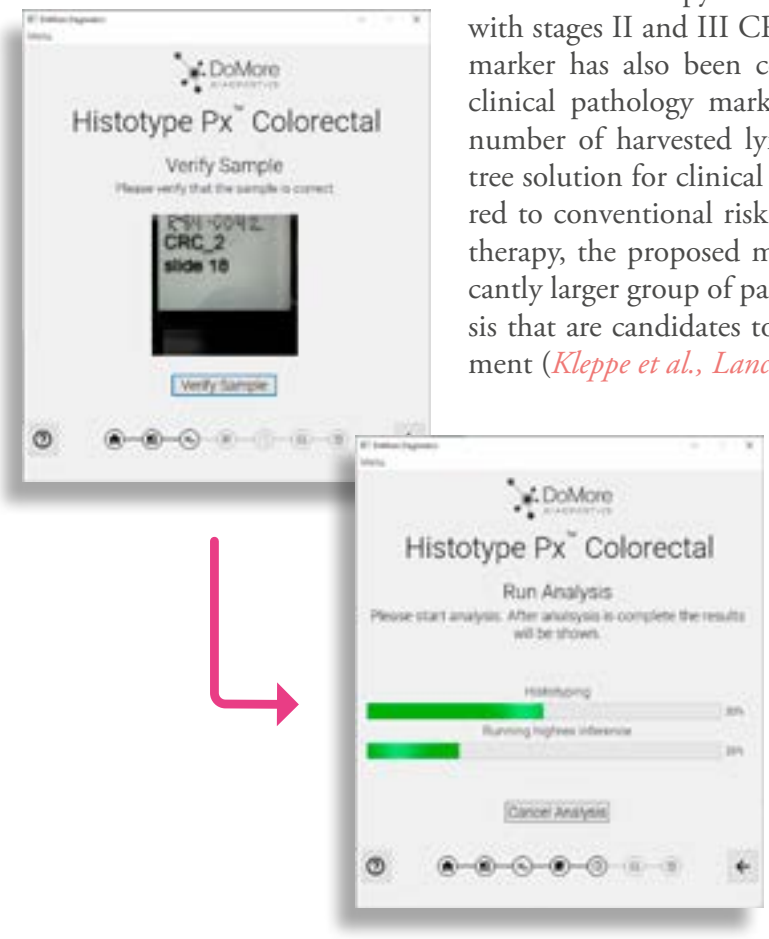
With more digital tools on the market, we can increase efficiency in pathology and provide a more accurate prognosis to cancer patients. Many of the current tasks are performed manually under a microscope. One obvious advantage of digitalisation is that it would allow the pathologist to work from anywhere using only a computer. It would also be easier for clinicians to receive both second and expert opinions when one has the opportunity to make an assessment remotely.


Histotype Px™ Colorectal

Photo: Montebello foto

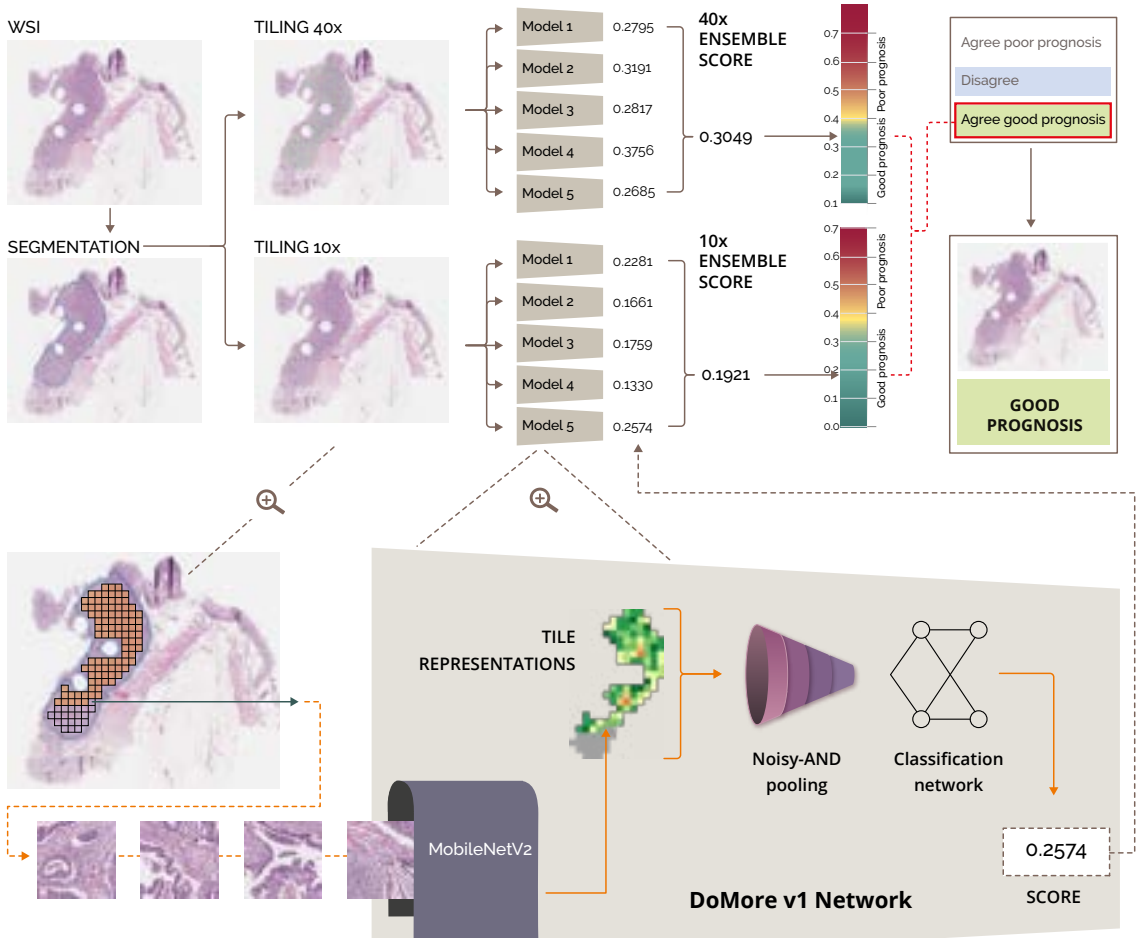
Histotyping

One of the products emerging from the project is called "Histotyping", which uses the marker DoMore-v1-CRC, and culminated in 2020 in a landmark artificial intelligence (AI) publication in the Lancet (*Skrede et al., The Lancet 2020*). Histotyping involves an automated analysis of high-resolution scans of cancerous tissue stained with routine hematoxylin and eosin (H&E). ICGI developed convolutional neural networks for this method and trained on extensive retrospective clinical trial data with known patient outcomes. Deep learning models were trained to identify and analyse the morphology of a tumour in a surgically resected tissue section. Histotyping estimates the probability of a good or poor outcome, i.e., the likelihood of a recurrence. It could be employed as a supplementary diagnostic service to support clinicians and patients in their adjuvant chemotherapy decision-making for patients with stages II and III CRC. The DoMore-v1-CRC marker has also been combined with established clinical pathology markers (T and N stage, and number of harvested lymph nodes) in a decision tree solution for clinical decision support. Compared to conventional risk stratification for adjuvant therapy, the proposed method identified a significantly larger group of patients with a good prognosis that are candidates to be spared adjuvant treatment (*Kleppe et al., Lancet Oncology 2022*).



Screenshots from the Histotyping application

Giving cancer patients a more precise prognosis



Pipeline of DoMore-v1-CRC classification
A whole-slide image is segmented, and the segmented regions tiled at 40× resolution and 10× resolution. For each resolution, the five trained models each produce one score reflecting the probability of poor outcome. The average of those scores is the ensemble score, one for 10× and another for 40×. If the ensemble score is above a certain threshold, the whole-slide image is classified as poor prognosis. The DoMore-v1-CRC class is determined by the agreement between the two ensemble classifications. The DoMore v1 network is comprised of a representation network (MobileNetV2),21 a pooling function (Noisy-AND),22 and a simple fully connected classification network. All components of the DoMore v1 network involve trainable parameters, and the entire network is trained end-to-end. All tiles from a whole-slide image are processed by the representation network one by one, resulting in a collection of tile representations. The pooling function reduces the representations into two numbers, which are then processed by the classification network to produce the score outputted by the model. CRC=colorectal cancer. *(From: Skrede et al., The Lancet 2020)*

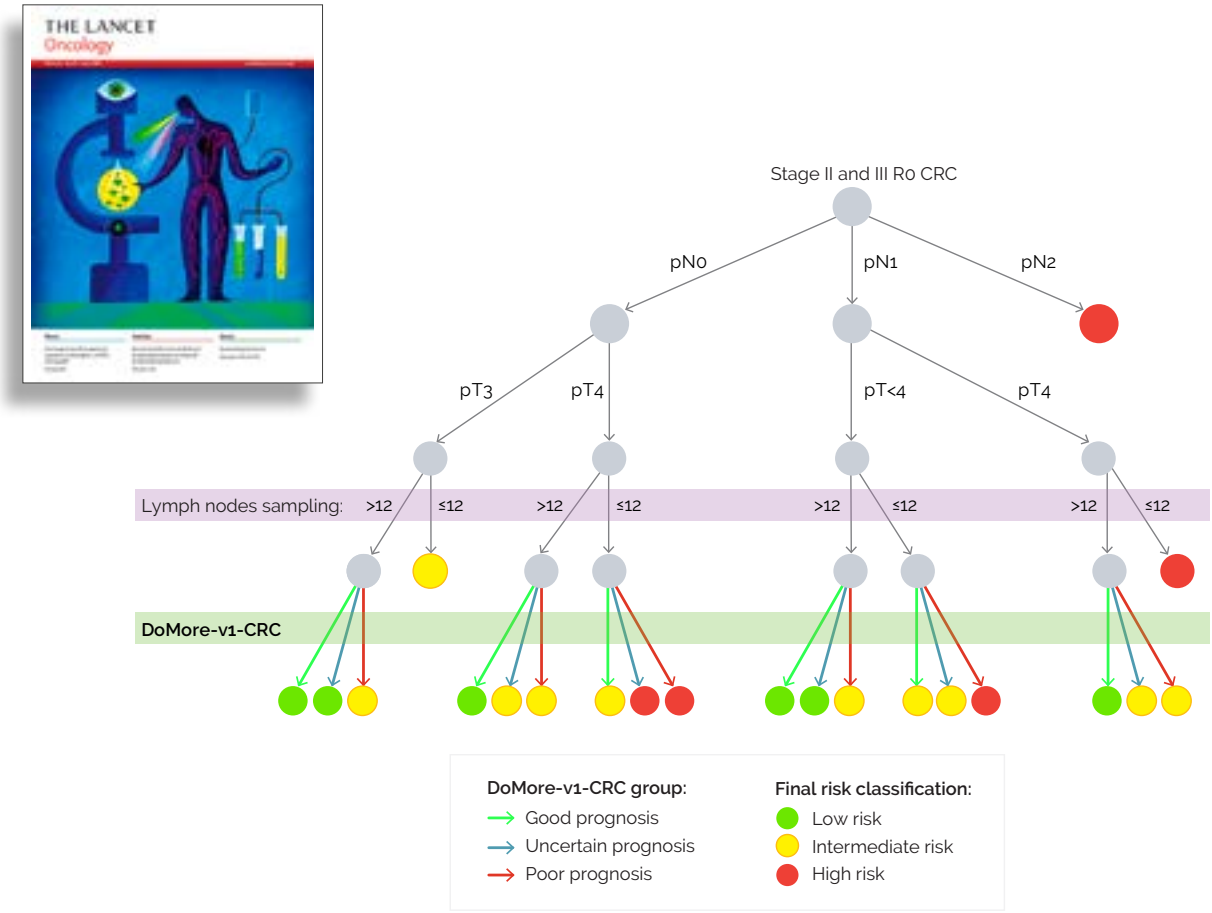


Figure above (from the Lancet Oncology paper "*A clinical decision support system optimising adjuvant chemotherapy for colorectal cancers by integrating deep learning and pathological staging markers: a development and validation study*".): Decision tree combining DoMore-v1-CRC marker with T and N stage, and number of lymph nodes.

Using the DoMore-v1 network, a similar approach has been performed on prostate cancer patients. The adaption of this method from CRC to PCa included using sections from multiple tissue blocks as input images, as prostate tumours are far more heterogeneous than colorectal tumours. The product, the DoMore-v1-PCa marker, predicts the risk of recurrence after radical prostatectomy, and the marker shows strong prognostic results (HR=7.6) when tested in a publicly available cohort (TCGA-PRAD). Final validation and publication will be submitted during 2022.

Initial results in non-small cell lung cancers also show comparable results, and the project is expected to be completed by 2023.

With the increasing number of publications on deep learning and systems claiming to perform comparable with or better than clinicians, few have yet to demonstrate real-world medical utility. We published a Perspective in Nature review Cancer in 2021 to discuss the reasons for the moderate progress and to present our suggestions for recommended protocol items for the field to facilitate the transition to the clinic (*Kleppe et al., Nat Rev Cancer 2021*).

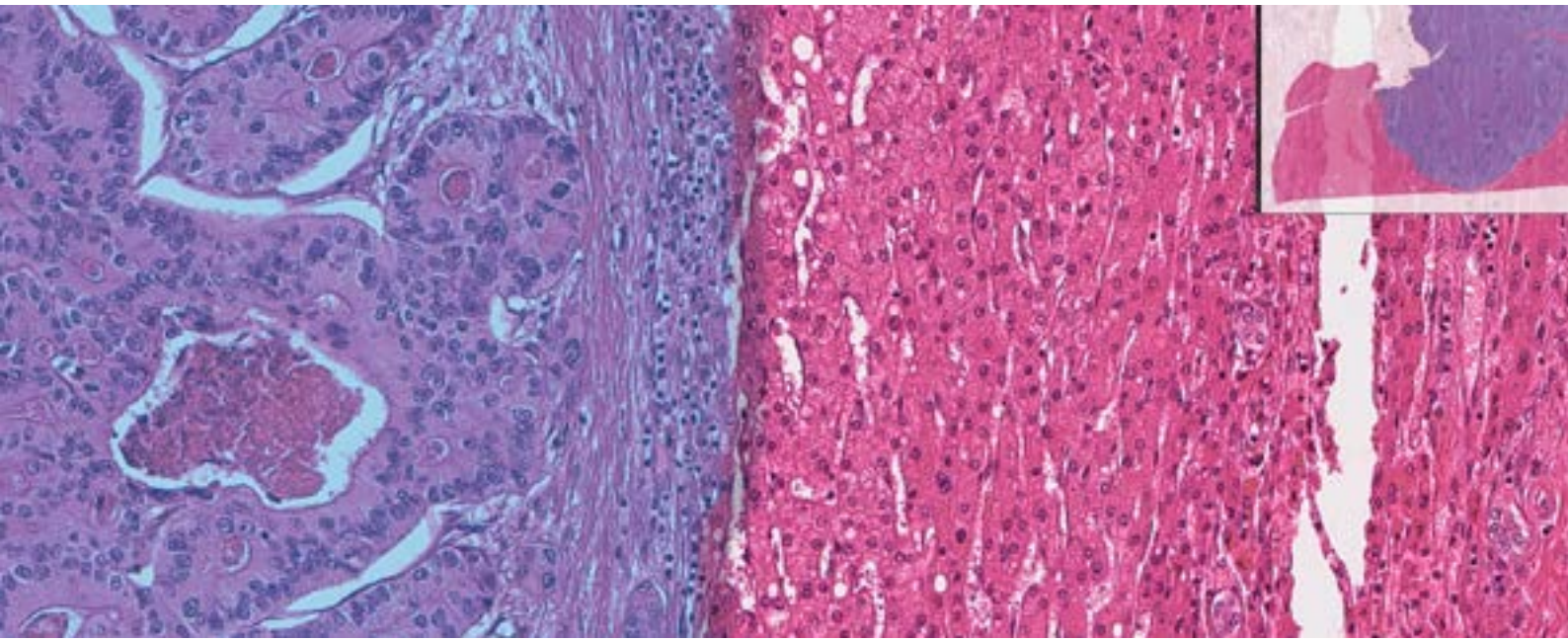
ICT solutions

To allow full automation independent of pathologists, the area of interest (e.g. the tumour area) should be identified by the AI system.

A network for delineation of the tumour area was first successfully developed for CRC and published in the Lancet 2020 publication. However, as pathology goes digital, a significant amount of time and resources can be saved if the tumour is already delineated in the specimens presented to the pathologist in routine diagnostics. We have developed a generic method, trained on several different cancer types, intended to work on all solid tumours. The result is a pan-cancer network for tumour delineation validated in 14 different patient cohorts with seven cancer types, making it the most extensive study of its kind. The result will be published in 2022.

Another requirement for full automation is good image quality to run any analysis. This is also true for manual assessment, but the human eye and brain are notoriously robust to variations in stain intensity and image quality. Standardised quality, both internally in a lab and cross-laboratory, is of importance and has been of high priority throughout the project. By using deep learning to quantify the level of focus in a scan, we can today offer users a product that calculates a score reflecting the focus level in subregions of images and allow the users to define a threshold for acceptable focus. The digitalisation of histological tissue section provides great possibilities for data sharing and anonymising data would be required for such a process. We have developed a simple to use application that removes any personal identifier from scans.

With robust ground tools, such as segmentation and image quality assessment, the possibilities are endless for transferring manual processes to automated ICT solutions. One example is the manual count of mitotic figures, a proliferation measure and an established prognostic marker in several cancer types. The counting is time-consuming, and the inter-observer variance is significant. We have developed a fully automated deep learning pan-cancer network for the mitotic count, that allows rapid identification and counting of mitotic figures in entire tumour regions. This work is under publication. Another example of an established pathology marker that we have automised using machine learning is the quantification of stroma fraction, which has been validated as a prognostic marker both in CRC and Pca (*Danielsen et al., Annals of Oncology 2018; Ersvær et al., International Journal of Cancer 2020*). These products



Scanned image of liver metastasis tissue with segmentation from our pan-cancer network for tumour delineation. Blue indicates segmented area.

are only a small selection of the many possibilities available to increase productivity and quality in the pathology field.

Today, we can offer several ICT solutions to ease the pathologists' workload. Virtual slides require software for viewing, and most scanners are supplied with their own software, but they are usually only limited to visual inspection. We have developed software where one can easily access the virtual slide and also perform the action needed. The product is named SeeMore and supports modular add-ons. Among available add-ons are anonymisation, mitotic count, focus score and stroma fraction. As one of the partners, the Norwegian eHealth Company DIPS, has implemented SeeMore into their product Arena, providing easy access for the hospitals.

From bench

to bedside

Developing systems with straight forward clinical utility has been a critical goal for the research activity in DoMore!. The focal point has been to bring methods and products to a level where they can be easily implemented in the clinic and to establish the structures and collaborations that enable efficient commercialisation

One of the products developed during the project, DoMore-v1-CRC, has successfully been brought from bench to bedside, and the groundwork for commercialisation has been broad-based.

International commercialisation often depends on patenting the products or key components of critical features. In the DoMore! project, two patent applications were filed in connection to Histotyping. While final development of market-ready products is naturally done in companies, early clinical testing requires easy-to-use applications. Thus, we have developed a software application (App), which can be run on Windows, Linux and Mac systems, making it available for use by clinicians independent of each particular clinic's platform. The output from the App is a report showing the probability of a poor outcome, with and without the pT and pN stage.

Commercialisation may be carried out either through cooperation with an established business or through the formation of new companies. We have followed both tracks by collaborating with the Norwegian eHealth company DIPS and through the establishment of the company DoMore Diagnostics AS (DMD). The company, established in 2020, was met with substantial interest and signed on investors for NOK 15 million.

DMD was fully operable in 2021 and license agreement on four products from the project; Histotyping CRC, Histotyping Prostate, Histotyping Lung and Automatic Mitotic Figure Count. The company has already successfully CE marked the product Histotyping CRC, and will bring the eventual commercialisation offerings to the market.

The potential benefits of histotyping are two-fold, both in identifying patients for whom the absolute benefit of adjuvant chemotherapy is low (a good prognosis assignment) as those that could benefit from prolonged or more intensive chemotherapy based on their poor prognosis assignment. This is also interesting from a health economics perspective. An evaluation conducted from a Norwegian Healthcare perspective by health economists showed that risk-stratifying stage II and III colorectal cancer patients using histotyping was cost-saving and more effective than the standard of care alone (*Kenseth and Kantorova et al., 2022, under submission*).

To demonstrate the feasibility of histotyping in a natural clinical setting, a clinical utility study will be conducted in collaboration with DoMore! partners Vestfold Hospital Trust and Oxford University.

With DoMore-v1-CRC, the establishment of DoMore Diagnostics and a health economic evaluation conducted, the framework for taking an algorithm from its development to its final product for the patient has been created. Future applications developed at ICGI will be able to follow this framework.

Photo: Terje Heiestad for CCB

Conclusions

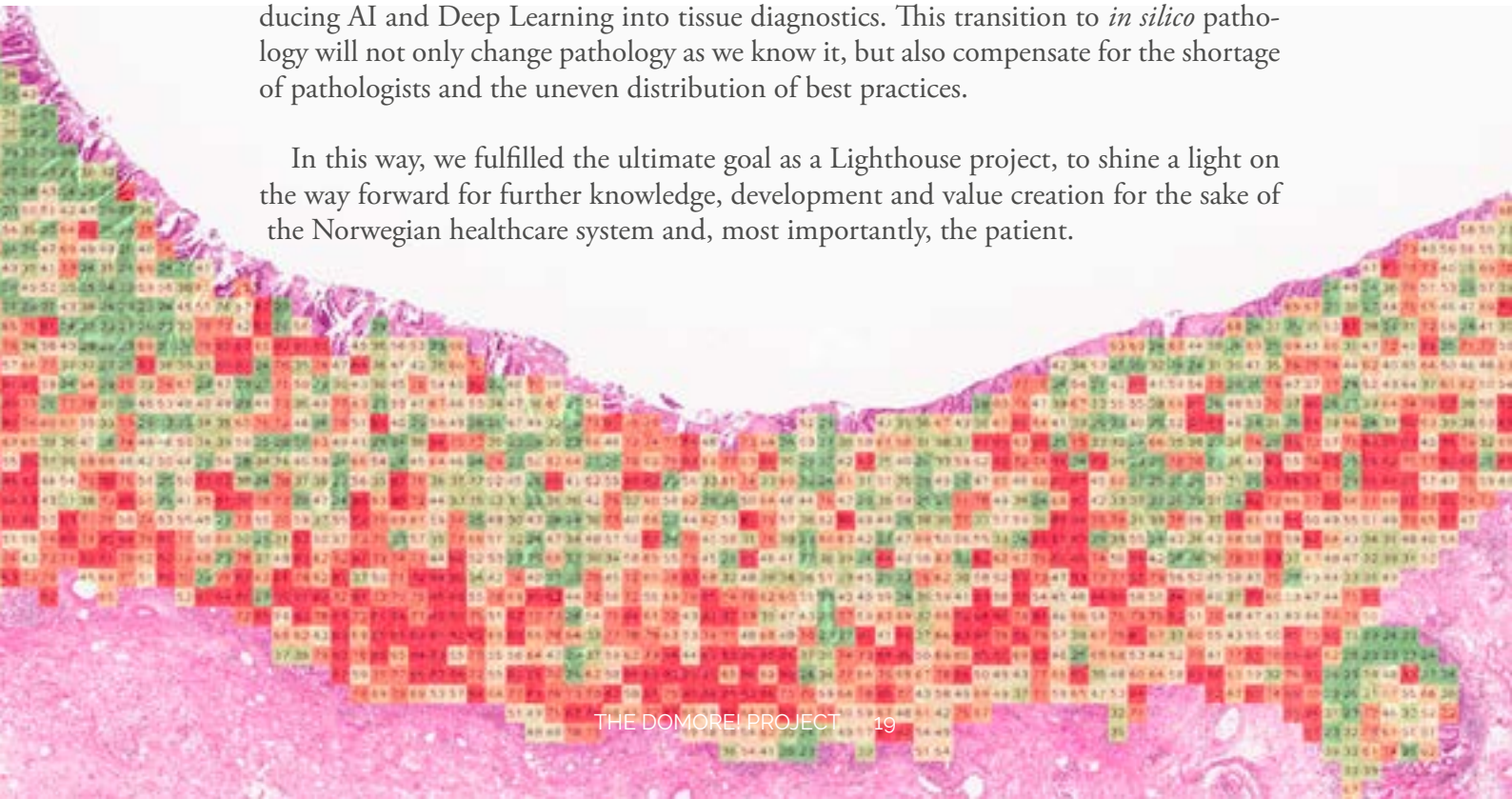
After five years of collaboration with users, public partners and commercial players, the DoMore! project concluded in 2021.

Through DoMore!, we developed generic and objective digital prognostic markers for prostate, colon, rectum and lung cancers using Deep Learning and Big Data. In doing so, we established more robust systems and ICT solutions to supplement or replace methods in pathology to increase productivity and quality, and hence treatment of cancer.

With the success of the automated methods and better prognostic markers developed within the project, we have been able to and adequately address the challenge of cancer heterogeneity and to "DoMore!" with the same amount of resources. Better prognostic markers will result in more personalised medicine with less over- and under-treatment. For patients to benefit from our research, we have established the company DoMore Diagnostics AS and provided the Norwegian eHealth Company DIPS with the necessary tools to integrate our products.

We are proud to have contributed to the digitalisation of pathology and paved the way for the transition from digital pathology to *in silico* pathology, in addition to introducing AI and Deep Learning into tissue diagnostics. This transition to *in silico* pathology will not only change pathology as we know it, but also compensate for the shortage of pathologists and the uneven distribution of best practices.

In this way, we fulfilled the ultimate goal as a Lighthouse project, to shine a light on the way forward for further knowledge, development and value creation for the sake of the Norwegian healthcare system and, most importantly, the patient.



DoMore! articles

2021

PTEN and DNA Ploidy Status by Machine Learning in Prostate Cancer
Cyll K, Kleppe A, Kalsnes J, Vlatkovic L, Pradhan M, Kildal W, Tobin KAR, Reine TM, Wæhre H, Brennhovd B, Askautrud HA, Skaaheim Haug E, Hveem TS, Danielsen HE
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EBioMedicine. 2021 Sep;71:103547

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2019

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Chromatin organisation and cancer prognosis: a pan-cancer study
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Beyond DoMore!

The need for digital tools and automatic methods have only been made clearer during the course of this project, and the following 6 projects have been launched during and after the DoMore! project to meet the demands;

Bench to Bedside

Norwegian Research Council

Ongoing Project

The project will develop a framework and tools that are useful for all deep learning-based methods from the DoMore! project. The Histotyping method, DoMore-v1-CRC, is used as an example and the first case, focusing on stain and imaging variation, robustness, product and clinical feasibility.

Learning from Deep Learning

Oslo University Hospital, Application under evaluation

Ongoing Project

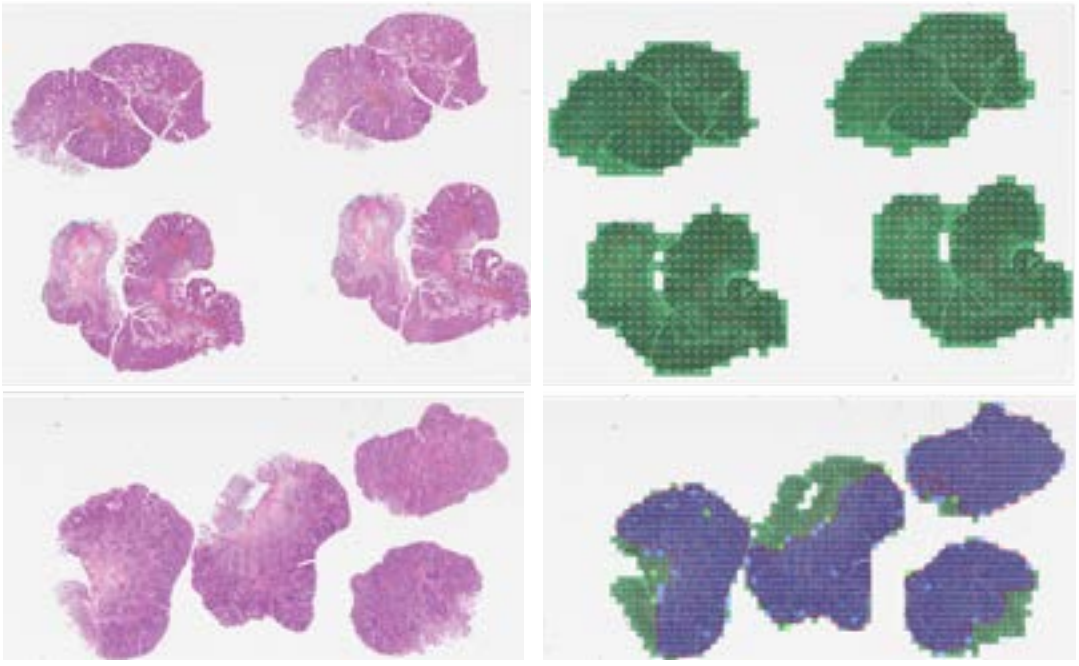
The DoMore-v1 classifier is a deep learning system for predicting patient outcomes in colorectal cancer. Using a combined biological and machine learning approach, we intend to provide methods to make our own and similar networks more transparent and thus easier for clinicians to use, as well as to improve our understanding of the biological mechanisms underlying metastatic disease.

Polyp Classification by Artificial intelligence

The Norwegian Cancer Society

Ongoing Project

Organised bowel cancer screening is implemented in several countries and is shown to reduce both incidences as well as mortality rates significantly. A faecal occult blood test is commonly used to identify patients that should undergo colonoscopy to examine the bowel for polyps. If polyps are identified during the colonoscopy procedure, these are removed and then evaluated by a specialised GI-pathologist. The vast majority of the identified polyps are low-risk adenomas, which seldom develop into adenocarcinomas over time, and require no further treatment when removed. Norway will begin screening in 2022, but implementation will require more endoscopists and pathologists, particularly specialised gastrointestinal pathologists with experience in histological polyp examinations. To reduce the workload for the pathologist, we aim to develop an automated risk classification of colon polyps using deep learning.



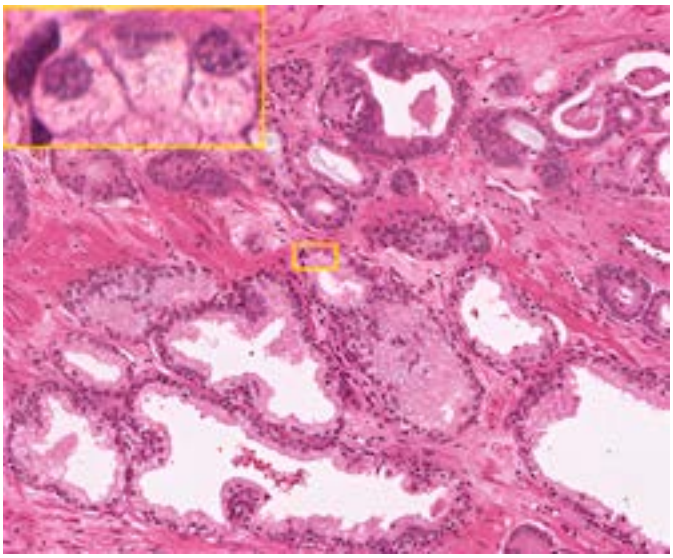
Polyp scans and heat-maps.
Low-risk polyp (top-left) and low-risk polyp with classification score (top-right)
High-risk polyp (lower-left) and high-risk polyp with classification score (lower-right)

HighRes Scanner

Oslo University Hospital

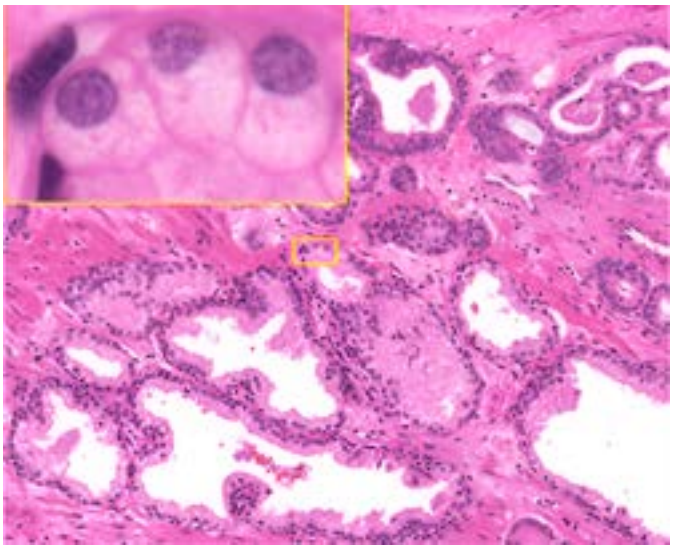
Ongoing Project

HighRes is a high-resolution, high-throughput digital pathology scanner developed by ICGI. The highly regarded status of visual observation has long set virtual limits for image quality in digital pathology. But whatever the trained pathologists' eyes can see no longer is the bleeding edge. Technologies from life science, augmented by AI, are entering the field. Focus on improving data at the source, rather than solving the data issues downstream, manifests throughout the industry in standardisation initiatives like DICOM and research of stain decomposition algorithms.



HighRes' mission statement is to maximise the image quality of scanners within the primary imaging modality of digital pathology (transmitted light), offer high quality in the high-throughput domain, and devise a flexible system adaptable to the ever-changing needs of the AI.

HE section scanned at maximum resolution (40x, na=0.7) with the Aperio AT2 scanner.



The same section scanned at maximum resolution (60x, na=1.4) with our proprietary HighRes scanner. Images in yellow at maximum tolerated magnification.

Active Surveillance Prostate

South-Eastern Norway Regional Health Authority

Ongoing Project

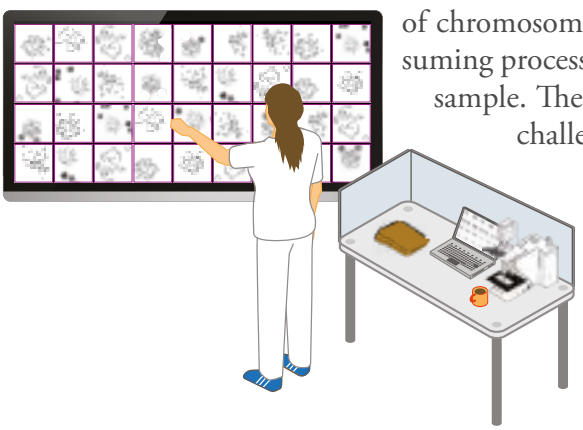
The incidence of prostate cancer has dramatically increased in the last 40 years, while mortality rates remain mostly unaltered. Unnecessary treatment is a challenge for both patients and healthcare systems. Patients with a low risk of aggressive disease should be included in active surveillance programs, where they are carefully monitored, and offered treatment of indicated disease progression. Unfortunately, criteria for inclusion and transition to treatment in active surveillance protocols rely on standard clinicopathologic characteristics that do not distinguish indolent from potentially aggressive disease, reliably which. Also, their assessment varies much between institutions.

We want to transfer and adapt the prognostic markers developed as part of the DoMore! Project to the active surveillance setting. Our objective is to improve the management of prostate cancer by providing clinicians with a tool that accurately and objectively distinguishes patients who would likely benefit from active surveillance and those who should receive immediate treatment.

CNN Karyotyping

Project not yet funded

Karyotyping is the process of ordering the chromosomes of an organism to provide a genome-wide snapshot of an individual's chromosomes. Karyotypes are prepared from mitotic cells arrested in the metaphase or prometaphase part of the cell cycle when chromosomes are in their most condensed conformations. Analyses of karyotypes reveal changes in chromosome numbers (aneuploidy) and more subtle structural changes such as chromosomal deletions, duplications, translocations, or inversions. Although samples from approximately 1200 new-borns and around 3000 cancer patients are karyotyped yearly at Oslo University Hospital (OUH) alone, this method's usability is limited by the fact that the visual interpretation of chromosomes requires specially trained personnel and is a time-consuming process that is carried out for only up to 25 cells for each patient sample. The limited efficiency of the method is now also becoming a challenge within the field of haematology.



A more efficient means of karyotyping is required, and we aim to automate the manual process of identifying and interpreting chromosome aberrations with artificial intelligence (AI).

In 2016 the Research Council of Norway selected DoMore! to receive funding as part of its ambitious Lighthouse Project scheme. As the name suggests, Lighthouse Projects were intended to be beacons, guiding and inspiring future projects to address large societal challenges using cutting-edge technology. Upon conclusion of the project in 2021, we are proud to have contributed to the digitalization of pathology and paved the way for the transition from digital pathology to *in silico* pathology, in addition to introducing AI and Deep Learning into tissue diagnostics.

The DoMore! project has been led by the Institute for Cancer Genetics and Informatics at Oslo University Hospital

Institute for
Cancer Genetics and Informatics

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