



# Big data management for the precise treatment of three patient groups



2018



Design, layout and print production of this report: ETN Grafisk  
BigMed visual identity: Melkeveien  
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# Table of contents

<b>Preface</b>	4
<b>Executive summary</b>	6
<b>About this report</b>	7
<b>What is precision medicine?</b>	9
<b>Current status for the BigMed clinical groups</b>	17
Rare diseases	18
Sudden Cardiac Death	26
Metastatic colorectal cancer	32
<b>Towards a more precise medicine</b>	39
<b>Overcoming the barriers to precision medicine</b>	43
Financial and political barriers	44
Legal and regulatory barriers	47
Organisational barriers	49
Barriers related to competence and knowledge	51
Technological barriers	54
<b>Tools and technologies enabling precision medicine</b>	59
<b>Regulatory framework for precision medicine</b>	83
References	88
Abbreviations	90
Appendix 1: BigMed partners and collaborators	91
Appendix 2: Overview of the Norwegian landscape	94

# Preface

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When the Norwegian Cancer Society and the Norwegian Heart and Lung Association were asked to join the BigMed project as user representatives, it was not hard for us to say yes. The healthcare services are facing a revolution in the use of digital tools to improve clinical decision making. This revolution will have great implications for the patient groups that our two organisations represent.

The development of precision medicine is an important trend in healthcare and a concept filled with promise. The goal of precision medicine is to offer precise and effective treatment for each person's individual disease while avoiding unnecessary treatment, thereby avoiding unnecessary risks and side effects.

Precision medicine will require the assembly and analysis of enormous amounts of data. Traditionally, health professionals could make diagnosis and treatment decisions using manageable amounts of knowledge and individual patient data. With precision medicine, the amount of information the physicians will have to consider is exploding. We are already reaching a point where the available information is too extensive for any healthcare professional to utilise sufficiently without the aid of proper technological tools for clinical decision making.

Precision medicine is a concept that will change the way healthcare services are delivered and it is essential to involve the users in projects building the platform for its implementation. We are therefore enthusiastic about our involvement in the BigMed project.



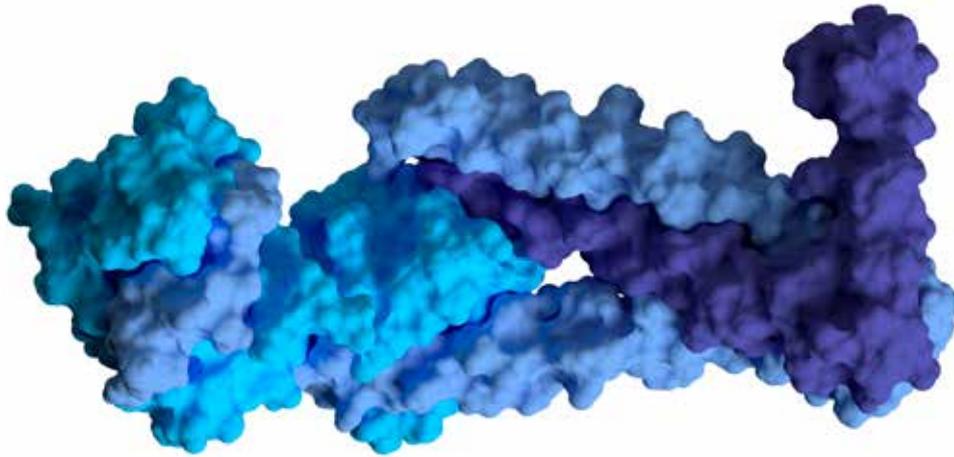
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Troponin: a biomarker for the detection of cardiac injury

BigMed includes highly relevant clinical cases. Colorectal cancer is a huge challenge, with more than 4,000 new cases annually in Norway and over 1,500 annual deaths. These patients desperately need new tools for disease management.

Sudden cardiac death accounts for approximately 5,000 deaths yearly in Norway. High-risk individuals can be offered life-saving therapies. Selection of patients for these therapies and prediction of disease are two of the greatest challenges in current cardiology. Thus, using patient-specific genetic data combined with clinical data is instrumental for new therapies and hope for patients.

Our expectation is that BigMed will provide the foundation for developing digital tools that healthcare professionals will find relevant and functional, enabling better and more individualised care for patients.

**The healthcare services are facing a revolution in the use of digital tools to improve clinical decision making. This revolution will have great implications for the patient groups that our two organisations represent.**



LHL



KREFTFORENINGEN

# Executive summary

Recent developments in technologies like informatics, biomolecular science, gene sequencing and medical imaging increasingly allow tailoring of clinical decisions, practices and products to the individual patient<sup>17</sup>. Beyond offering treatment based on averages from controlled studies, the patients can receive treatment based on experiences from the treatment of similar patients. This approach is achieved by collecting large amounts of data, from biomarkers to environmental factors, making them available for analysis and bringing the synthesis to the point of care.

Precision medicine is not just a technical venture, it also challenges traditional workflows in healthcare. Smart organization of knowledge and data is necessary for providing effective and safe healthcare services as the amount of new knowledge exceeds the individual capacity of clinicians and healthcare providers.

The necessary infrastructure must be developed to facilitate all aspects of data capture, analysis and application, including sharing and secondary use of data. Financial incentives must be adjusted to promote investments on all levels that provide an overall positive socio-economic effect, and the regulatory framework must be updated to balance healthcare outcomes with privacy risk in the current and future technological setting.

The transition towards precision medicine requires involvement of and contributions from a broad range of stakeholders, including politicians, practitioners, patient groups, academia and industry. In order to involve all these in the development and implementation of new solutions and smarter ways of working, there is a particular need for the establishment of secure platforms that can give external partners controlled access to de-identified data.

**Precision medicine is not just a technical venture, it also challenges traditional workflows in healthcare.**

# About this report

This report is produced as part of the BigMed project to document and distribute knowledge accumulated in the first phase of the project, identifying the challenges and obstacles the project aims to address.

The report consists of an introduction and three main parts; the clinical case descriptions, their next steps for implementing a more precise and individualized medicine and current barriers identified. Finally, a summary of enabling tools and technologies as well as the regulatory framework for precision medicine is provided.

Overarching barriers to implementing precision medicine and suggested actions for overcoming them have been identified through a series of workshops and discussions conducted with a variety of stakeholders in Norway, including patient organisations, clinicians, legal experts, research institutes, government institutions, ICT suppliers, and other health industry representatives. The basis for the discussions were situation reports from the three BigMed clinical groups at OUS.

The report does not provide a comprehensive description of precision medicine in all clinical areas or institutions in Norway. BigMed partners have contributed to the different sections of the report, but information provided does not necessarily represent the views of all partners.





The BigMed project is an ICT Lighthouse project funded by The Research Council of Norway to promote development and technology and services with advanced computer science. The project is managed and owned by the Intervention Centre at Oslo University Hospital, and includes a broad consortium of partners from several other departments in the hospital, three faculties at the University of Oslo, industry organisations and four patient associations.

The project aims to lay a foundation for implementing precision medicine and big data analytics in healthcare, and will do so through testing and developing of ICT solutions to support the implementation of precision medicine in three clinical areas: rare diseases, sudden cardiac death and metastatic colorectal cancer. When developing solutions, the cross-competence teams in BigMed will discuss barriers and identify actions to overcome them. The barriers for implementation of precision medicine include legal, ethical and social aspects that must be discussed and addressed.

[www.bigmed.no](http://www.bigmed.no)



# 1. What is precision medicine?

Precision medicine is a medical model that proposes the customisation of healthcare, with medical decisions, practices, or products being tailored to the individual patient <sup>[1]</sup>. Customization of medicine to individuals means including all relevant sources of information, from biomarkers to social attributes.

Traditional medicine has by necessity focused on averages and groups of patients, catering to the larger statistical groups but excluding the rare few. Technological advances are giving us the opportunity to evolve towards greater precision, but a paradigm shift is needed to capitalize on all opportunities.

## 1.1 "THE AVERAGE PATIENT" AND UNIQUE INDIVIDUALS

The aim of customising healthcare to the individual is not new. From the birth of medicine and surgery as practices, the goal has always been to treat the patient at hand, using the available knowledge about her condition. With increasing biological knowledge, practitioners gradually understood the common denominators for illnesses and called them diseases or medical conditions. These categories could be based upon common mechanisms by which the disease is caused (like malaria or a sunburn), or by symptoms (like pneumonia or arthritis).

Most clinical knowledge taught today is still based on these categories, and so is the way patients are treated. Looking at headings of clinical publications over the last 100 years confirms these perceptions, as most include the disease name and target a category of patients.

### DEFINITION OF PRECISION MEDICINE

Precision medicine is a medical model that proposes the customisation of healthcare, with medical decisions, practices, or products being tailored to the individual patient <sup>[1]</sup>.

Customisation of medicine to individuals means taking into account all relevant sources of information, from biomarkers to social attributes.

With the rise of evidence-based medicine, the clinical community has learned to understand the diseases and their subgroups, based on studies on strictly controlled patient cohorts. Evidence-based recommendations and guidelines are developed through systematic collection and ranking of results from controlled trials. The underlying statistical methods for hypothesis testing rely on an assumption that enough patients are similar with respect to phenotype (observable characteristics or traits), clinical history and potentially, genotype (genetic profile). And that the similarity is easily and objectively verifiable. Furthermore, the assumption is that a statistically significant positive outcome indicates that similar patients would benefit from the intervention tested.

There are some problems with this reasoning:

- Recommendations are not directly transferable to patients in real life as they generally cover only one intervention. Nothing is actually known for patients not included in the group investigated. Multiple interventions or multimorbidity can be handled only if included in the initial trials.

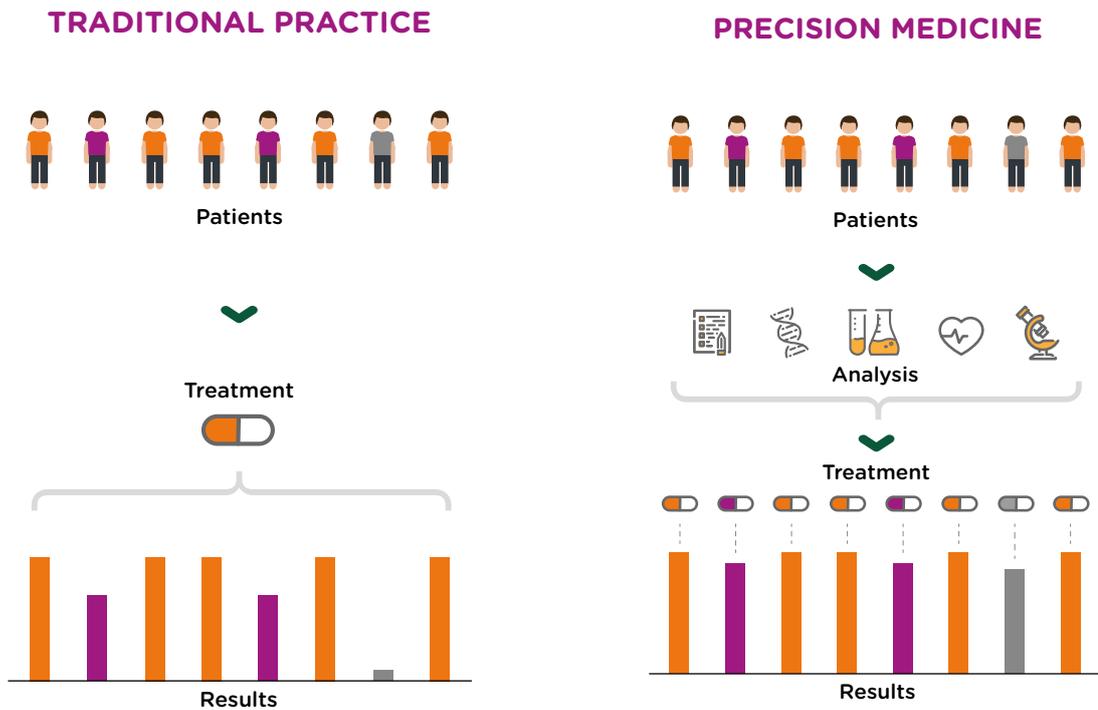


Figure 1 In precision medicine, analysis of data describing the individual patient's features helps tailor the treatment for higher efficacy and less adverse effects.

- A clinical question occurring in practice must perfectly match the research question leading to evidence in a trial.

Evidence based medicine has been a sound practice in the technological landscape medicine was operating until recently - it is better to treat a patient according to a statistical average of a group rather than on subjective clinical intuition alone. However, novel enabling technologies is about to change the clinical landscape significantly. This is described in section 5.

Diagnostic and interventional technology increases patient information and intervention complexity, leading

to smaller cohorts of similar patients, less evidence-based medicine power and narrower clinical recommendations, as illustrated in figure 1. Such technology also makes decision-making cognitively more challenging for clinicians due to complexity. This complexity can be compensated for by decision-support technology that enables model-based reasoning and abstraction, as shown in figure 2.

The practical challenges with traditional conditions-categorised evidence-based medicine is that, in a busy everyday clinical life, it is significantly easier to treat the conditions and not the patient. If the standard choice of drug for pneumonia is oral antibiotics, the doctor needs

## Complexities of clinical information and decisions

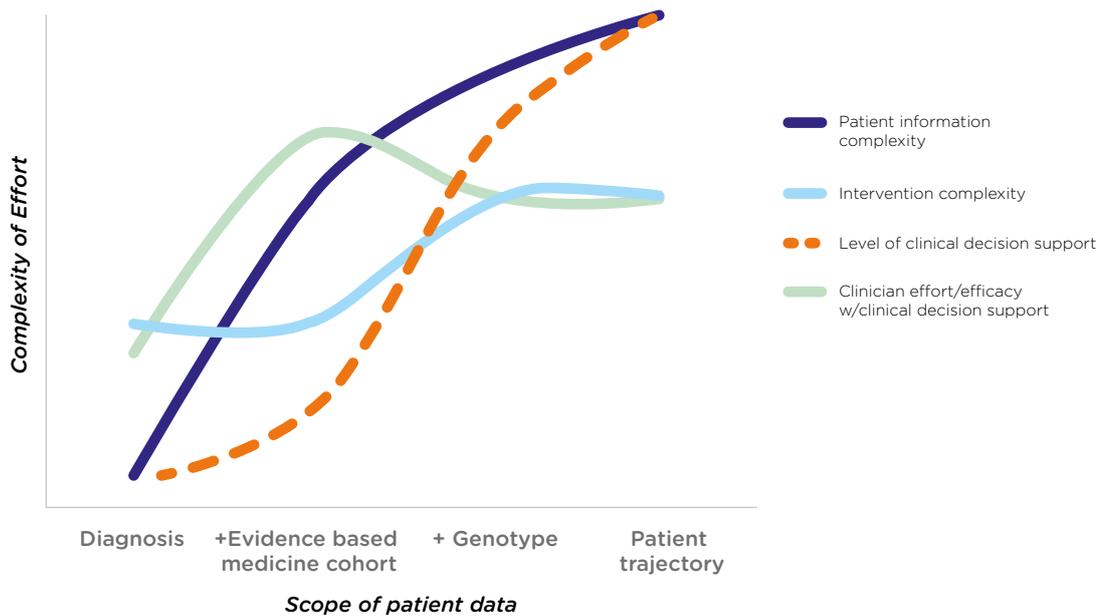


Figure 2 illustrates the dynamic relationship between technology, methods and clinical practice. As more information about the individual is known, the complexity increases and makes it harder for the clinician to make the right decision for the individual. With increased level of clinical decision support, this can be compensated for.

to ensure that the patient is capable and willing to take pills. She should ideally also have known if the bacteria are sensitive to the choice of drug. And there could also be a chance that our patient did have a genetic variant that made this particular drug more toxic for his kidneys. For reactive treatment like in this example, we have the possibility to monitor response and adjust our treatment strategy, but for preventive medicine, the advantage of hitting the target with more precision up front is even more important. If a patient has a stent in his coronary artery coated with an anti-trombotic drug that doesn't work for him [2], it doesn't help much that it has a positive effect on the "average patient".

The second and softer side effect is the preservative effect that categorisation has. Once a doctor has learned about, for example viral gastroenteritis and the ways to treat it, it is harder to teach her the specific traits of each of the viruses causing the disease and the consequences for treating each different one of them. Confined to each clinician's

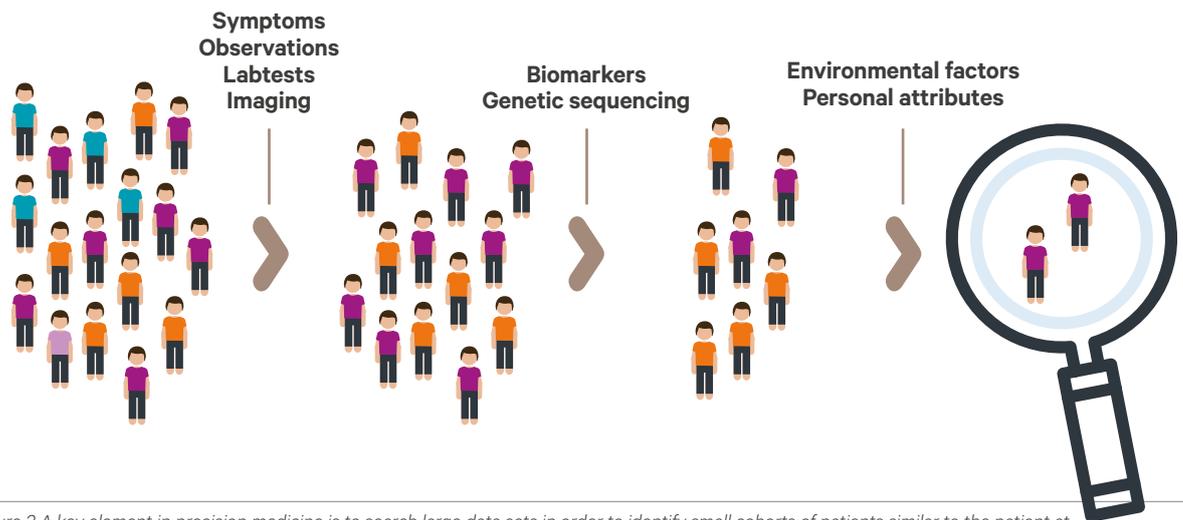


Figure 3 A key element in precision medicine is to search large data sets in order to identify small cohorts of patients similar to the patient at hand. The aim is to predict outcomes of different treatments by analyzing the patient trajectories in these smaller and more precise cohorts

capacity for remembering what she has read and experienced, the best she can do is to stick with categories broad enough for her to keep track of and narrow enough for patients to be treated as best as we can.

As described in this report, new technology can help us overcome these negative aspects of evidence based medicine and move into more precise medicine, should we be able to change the way we deliver healthcare.

## 1.2 WHAT IS NEEDED FOR MORE PRECISE MEDICINE?

Based on recent advances in technology, and in our knowledge of patient psychology and sociology, organisational research and other fields, one would expect rapid changes in health care practice. Yet adaptation of new methods and routines in Norwegian health care is slow.

The enabler of precision medicine, is the combination of medical advances and modern ICT. Data collection including novel biological tests, data analysis, and clinical

application of knowledge are the main components described in this report. Precision medicine, however, will also need new drugs and methods that target the new and more granular patient groups identified. This development is not within scope of this report.

Concerning data sources for precision medicine, we take the broad view. Figure 3 illustrates that many sources of information is needed to reach a clinically relevant stratification. The expanding knowledge of our DNA is perhaps the largest contribution to the relevant differences between each patient within the same category. If we add the DNA of tumours and the microbiology of both the agents we carry with us and infectious agents, the share is even larger. But it doesn't account for the complexity of biology, social factors, different personalities and preferences, or environmental exposure. In addition, modern imaging technology provides detailed information beyond pure anatomical data that can characterize the disease. Thus, to provide tailor made treatment all these data must be included in the

decision algorithms. “The whole data picture” challenges privacy concerns. Used improperly, such data collections, both on an individual level and on group and society levels, pose a potential threat to privacy and autonomy. Consequently, any such use has to be accompanied by developments in cybersecurity, ICT architecture, legislation, organisation and ethics to balance risks and benefits.

Making sense out of big data has emerged as one of the main challenges of organisations in our digitalised world. Transactions and interactions are leaving digital tracks that are revealing new knowledge daily. As big data are piling up, new methods for analysing them are emerging. These methods rely on infrastructure capable of state-of-the-art processing capacity and algorithms, and on having the right people to both initiate and perform the analysis. Organisations at the forefront of this development have built armies of data scientists who are not only able to write the code and get the results, but who also are able to dig through the data and find novel patterns previously unimagined. They combine skills that usually reside with scientists, programmers and consultants<sup>[3]</sup>. Within healthcare, we have just started to see the results of this development, but we cannot expect to see any significant development in big health data analysis without addressing both the technological and the competence perspectives.

The last, but just as important, piece in the technology puzzle is to bring all this new knowledge to the point of care. Traditional clinical decision support in clinical ICT applications is the main vehicle, but as more precise and rich knowledge becomes available, such tools will also target patients themselves to a larger degree. The last step in such a development is of course the automation of the entire process, bringing precision medicine into the algorithms of medical equipment, robots and wearables. Section 5 provides an overview of the different layers of technology needed.

### 1.3 PRECISION MEDICINE IN A NORWEGIAN CONTEXT

In Norway, as in many countries, precision medicine has until now often been interpreted as equivalent to the integration of genomics into medical practice. This has been a natural place to start, as it is the domain where it becomes most obvious that patients cannot be treated as averages in a large cohort. For rare diseases, precision medicine is the only medicine. In this context, considerable work in this field has been done in recent years on the governmental level. A review of personalised medicine in healthcare conducted 2013–2014 was followed by the release of the Norwegian Strategy for Personalised Medicine in Healthcare (2017–2021) in 2016<sup>[4]</sup>.

To bring precision medicine to other domains, however, we need to look beyond these plans. As this report shows, some of the main bottlenecks are in the ICT space. These must be addressed on all levels, from single departments and up to the international level. On the national level, there are two important processes ongoing.

One is the “One citizen – one record” strategy that aims to integrate information from different providers so that it is available not only for primary use in the care setting, but also for analysis needed for precision medicine<sup>[5]</sup>. The other important role of this process is the emphasis on functionality for clinical decision support in Electronic Medical Records (EMRs) – a vital component for providing clinicians with the right knowledge and recommendations at point of care. Closely linked to this process is the procurement of a new EMR in Helse Midt-Norge, “Helseplattformen”, where such functionality is part of the procurement requirements.

The other is “Helsedataprogrammet”, a programme aimed to address one of the main objectives of Norwegian

Health ICT, namely that “Data shall be available for quality improvement, health monitoring, governing and research” <sup>[6]</sup>. The programme is primarily looking at the National Health Registers, but the development of the programme is also relevant for healthcare providers in many ways, because it will create a national infrastructure aimed at analytics.

Most hospitals do use analytics, using data warehouse functionality either on hospital trust or on the regional level, but the large-scale use of clinical data for precision medicine purposes is not established. Necessary infrastructure like high-performance computing (HPC) is available for researchers only through universities or private vendors, and neither the organisations nor the clinical tools like the EMRs are rigged for integration of advanced analytics into routine clinical use.

In primary care, organisations are smaller (down to one doctor) and the EMRs are even more rudimentary <sup>[7]</sup>. Given the importance of the information from primary care for understanding the complexity of the whole patient pathway, it is crucial to integrate primary care data for use in precision medicine analysis.

The Research Council of Norway is funding several activities supporting Precision Medicine in Norway today, including the ICT Lighthouse projects BigMed, DoMore and Intromat as well as research infrastructures such as The Norwegian Consortium for Sequencing and Personalized Medicine and Elixir Norway. As appendix 2 in this report also illustrates, there are many activities ongoing and many parties engaging in developments within the field.



# Limitations and criticism of Precision Medicine

Precision medicine as described in this report, might at times seem like a solution to all of healthcare's problems. It is important to state that that is not the case. It is a way of evolving medicine from a group-based to an individual-based practice based on the use of technology, hopefully increasing clinical efficacy and decreasing unnecessary suffering.

Such change, however, is not without peril. First of all, a large part of the promise of precision medicine is still based on an extrapolation of technological development that still is not shown to work in real life, at least not at a large scale and implemented in live organizations. Secondly, used in the wrong way, there may be adverse side effects on both individual and on societal level.

Writer and physician Henrik Vogt rises these questions in his PhD thesis "Systems Medicine as a Theoretical Framework for Primary Care Medicine" <sup>[8]</sup>:

*A key finding is that the very concept of holism, which has previously been associated with a humanistic form of personalized medicine, is redefined in systems medicine and given a novel technoscientific meaning. The result is called a technoscientific holism. It is shown how this new holism brings substantial philosophical innovations for understanding and approaching whole persons (papers I and II). In particular, it is argued that the philosophy of systems biologist Denis Noble and the concepts of biological relativity and downward causation, might represent a significant contribution to conceptualizing the relationship between "bio", "psycho" and "socio" in the biopsychosocial model (paper I). However, despite these constructive theoretical developments, it is argued that systems medicine*

*cannot be expected to fully counteract fragmentation in medicine and become a genuinely holistic, personalized or humanistic medicine. Although it is promised as holistic, it can in practice be no more holistic than its computational and mathematical models. It also still involves a strong molecular focus and continued reductionism. It faces fundamental problems in conceptually and methodologically accounting for living wholes, in integrating all components of the complexity of human health and disease in its models, including what is called "mind" with what is called "body" (papers I, II and III). Concerning its clinical utility, the technoscientific holism of systems medicine corresponds to a "holistic medicalization". Each person's whole life process – however complex – is in theory defined in biomedical, technoscientific terms as controllable, pointing towards a situation in which this whole process is underlain a regime of medical control that is holistic as in all-encompassing. It is directed at all levels of functioning, from the molecular to the social, continual throughout life and aimed at managing the whole continuum from cure of disease, via mitigation of risk, to optimization of health. The participatory aspect of systems medicine involves an unprecedented self-medicalization (or "participatory medicalization") where each person is expected to perform the needed self-monitoring and self-control (paper II). This profound "holistic medicalization" comes with risks of waste and harm that have so far not been judiciously addressed by the visionaries of systems medicine. It is argued that there is a philosophical and scientific discrepancy between its promises of holism and a revolution in clinical utility on the one hand and the real world complexity, unpredictability and uncontrollability of human biology on the other (papers II and III).*



## 2. Current status for the BigMed clinical groups

The situation today at Oslo University Hospital (OUS) in the three BigMed clinical groups are described as dominated by systems that are largely paper based, with a number of manual processes and a general lack of ICT decision support. Clinicians struggle to access patient data in a format that efficiently assists their decisions. Decisions are made based on guidelines and reference knowledge, as internal systems for comparing with similar patients are not available. For rare diseases, the diagnostics part of precision medicine has come a long way, but has not led to a similar breakthrough in treatment for most of the patients. Furthermore, as the technology of high throughput sequencing is relatively immature, the examples below show a need for harmonization to ensure access to equal care.



## 2.1 Rare diseases

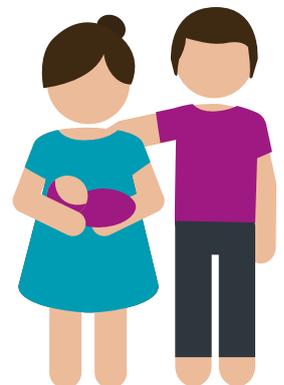
An accurate diagnosis is a crucial component of patient care for children with rare genetic diseases. Next-generation sequencing (NGS) is transforming the diagnostic odyssey for these patients, providing a molecular cause of disease for patients at an earlier point in the diagnostic workup than has been possible with other methods.

### 2.1.1 Patients with rare diseases

Rare diseases are defined as a large diverse group of life-threatening or chronically debilitating diseases, most of which are genetic-based and originate in early childhood<sup>[9, 10]</sup>. Rare diseases result mainly from inborn germline, de novo germline or acquired mosaic variation in chromosomes or single genes. According to the definition provided by the European Union (EU)<sup>[11]</sup>, rare diseases are those with prevalence values lower than 5/10,000, while in Norway, the current cut-off is 1/10,000<sup>[12]</sup>. Depending on the definition, there are between 5,000 and 8,000 rare diseases. According to the definition in the UK Strategy for Rare Diseases, there are 6,000 rare diseases and at least 80% of these have an identified genetic origin. 50% of all new cases are children<sup>[13]</sup>. The Norwegian rare disease definition is under review by the Norwegian Directorate of Health<sup>[14, 15]</sup> and a National Strategy for Rare Diseases is under development<sup>[16]</sup>. Though relatively rare, these diseases are collectively common and affect approximately 350 million people worldwide. Patients and families with a suspected rare genetic disease are confronted with significant obstacles along the diagnostic journey that includes not only laboratory and genetic tests, but also multiple specialist consultations, imaging studies, and invasive investigative procedures. Nevertheless, many patients go undiagnosed. Estimates suggest that up to 50% of patients with a rare genetic disease never receive a diagnosis. For patients and their families, the diagnostic journey is often described as a slow, costly, emotionally and physically exhausting venture<sup>[17]</sup>.

In Norway, approximately 3% of infants are expected to be affected by a rare disease<sup>[18]</sup>. For this group of patients, an early and accurate diagnosis is highly beneficial, with regard to precision intervention, tailored care, accurate genetic counselling of the family, and a reduced workup burden.

**Patients and families with a suspected rare genetic disease are confronted with significant obstacles along the diagnostic journey that includes not only laboratory and genetic tests, but also multiple specialist consultations, imaging studies, and invasive investigative procedures.**



**5–8,000**

identified rare diseases

**350 mill**

Approx. affected people worldwide

**3%**

of infants in Norway are suspected to be affected by a rare disease

**80%**

At least 80% of rare diseases have an identified genetic origin and 50% of new cases are children

**50%**

of patients with a rare genetic disease never receive a diagnosis

**50%**

# CURRENT SITUATION FOR RARE DISEASES

## Department Name

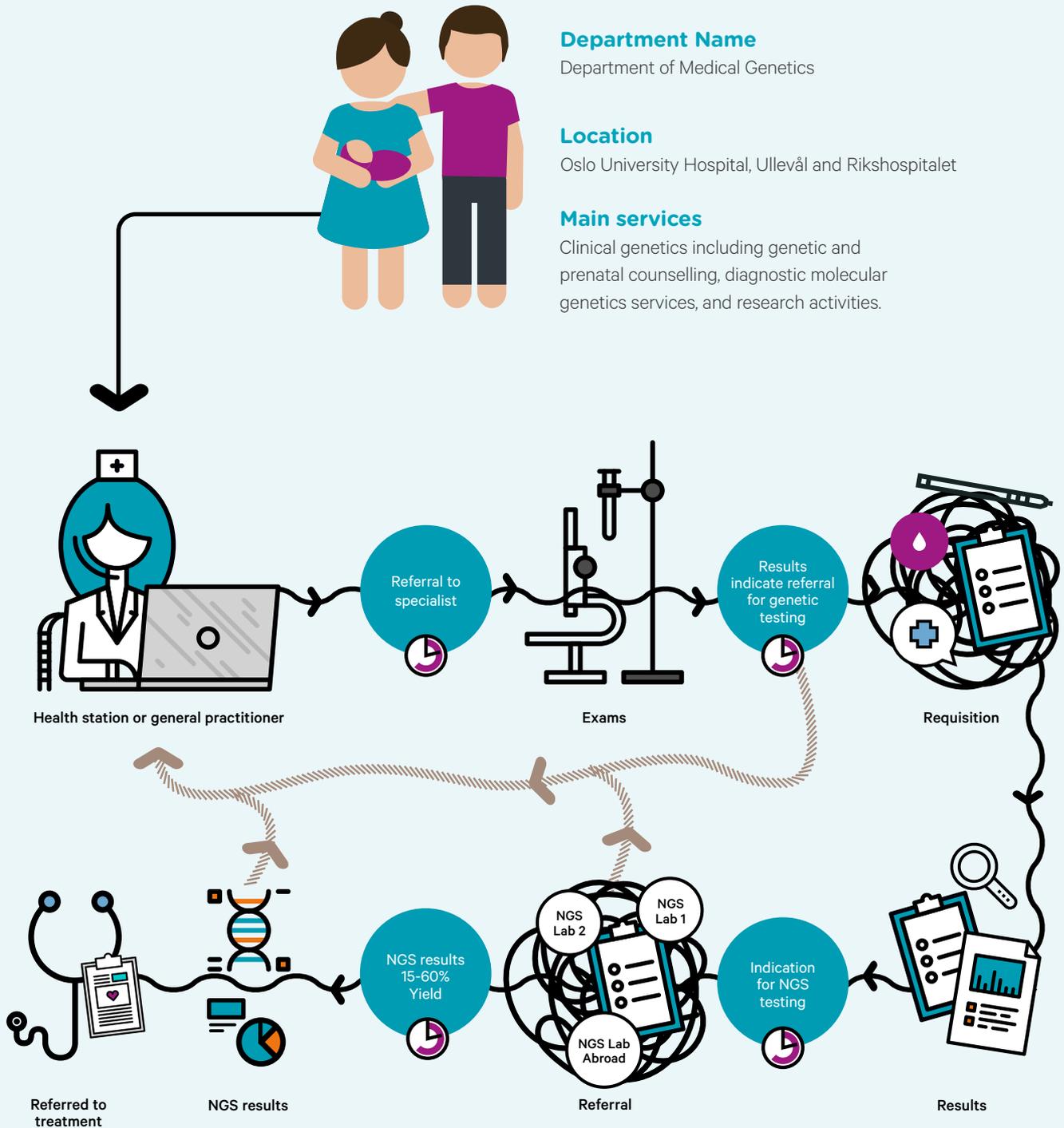
Department of Medical Genetics

## Location

Oslo University Hospital, Ullevål and Rikshospitalet

## Main services

Clinical genetics including genetic and prenatal counselling, diagnostic molecular genetics services, and research activities.



### 2.1.2 Current Situation for rare diseases at OUS

The diagnostic journey for infants and children with a suspected genetic disease in Norway varies greatly depending on the gravity of the signs and symptoms. For children with developmental delay, the parents' concerns may be presented to their general practitioner or local health station, resulting in referral for a diagnostic workup at an outpatient hospital clinic. Results may indicate the need for genetic testing. Information about available diagnostic genetic tests in Norway is available at "Norsk portal for medisinsk-genetiske analyser" [19] and at the internet homepages for the medical genetic laboratories. If a decision is made to order genetic testing at the Department of Medical Genetics at OUS, a blood sample is collected from the patient and shipped by mail, courier, hospital courier, or taxi to the laboratory at Ullevål. A paper requisition follows the sample.

The requisition form includes a field for free text to enter information related to the reason for referral, the desired test, and family history. The requisition form also includes an area for phenotype selection with 14 main categories to include development, behaviour, and main organ systems. The lab often receives requisitions from other genetic and non-genetic labs, old versions of a requisition, or simply a printout of the patient's name and sample type without further information. The paper-format requisition is registered in the laboratory information management system (LIMS) and is scanned and stored as a portable document format file. The requisition is not traceable in the EMR. The LIMS does not offer an electronically readable registration of patient phenotypes. Complex phenotypes are often incomplete, negative findings are not recorded, and the phenotypic information is static. A lack of information hampers the correct choice of analysis and assessment of the degree of urgency upon reviewing the requisition in the lab. Repeated analysis is often performed within the same

family because of a lack of family history and information about previous genetic testing on the requisition.

The most challenging part of the process for the lab today, is the interpretation of findings. When the required assays are run and the primary data analysis is done, findings need interpretation. The lab engineers filter and interpret the molecular effect of the identified set of genetic variants. Knowledge about the patient phenotype can help narrow the search, but the process is not designed for a dynamic dialogue between clinic and lab. Based on the lab results, lab doctors and clinicians evaluate any results in light of the patient phenotype. Variant interpretation is complex and relies on external sources of information (frequency databases, variant databases, medical literature), internal sources of information (observed variant frequencies in-house, previous variant classifications in-house), clinical information, results of supplementary testing of the patient (biochemistry, radiology, etc.), and family history. Medical doctors at the lab can obtain supplementary information for interpretation for OUS in-house patients from the OUS EMR, but the lab does not have access to patient records outside OUS. Results are reported on paper only to external referring physicians, and are also exported from the LIMS as an electronic PDF to the OUS EMR. The referring physician will review the results, inform the patient/parents and take action if a plausible cause of disease is identified.

**Repeated analysis is often performed within the same family because of a lack of family history and information about previous genetic testing on the requisition.**

For most cases, 1st-tier genetic test results are negative, and the referring physician will make a decision on further genetic testing and/or diagnostic workup, or refer the patient to another specialist. If analysis information is not passed on the specialist may order the same genetic workup as previously performed. Further genetic testing may include next-generation sequencing (NGS), or reanalysis of previously performed NGS. Further genetic testing requires a new requisition. If the referring physician chooses to perform further analysis in a different lab because of differing test offerings and turnaround times between medical genetic laboratories in Norway, the patient might be re-sequenced. There is no exchange of test results between labs, and no way for the lab to know whether the patient has undergone previous NGS if this information is not included on the requisition. Occasionally, the lab receives requisitions for a test that has previously been performed and where a molecular diagnosis has already been reached. Information is often lost between the local hospital and OUS AMG. The physician ordering genetic testing is often unaware of what information is required to facilitate the analytical process. Ordering physicians come from numerous specialties - GPs, medical geneticists, paediatricians, genetics, thoracic surgeons, etc. Even a well-educated physician will be unable to keep up with the advances in genetic testing and its applications for different patient groups. This inability results in cases of misordering and misinterpretation of results, both in the laboratory and in the clinic.

### 2.1.3 State-of-the-art for rare diseases

Technological advances have made possible the implementation of high-throughput sequencing that has transformed and enhanced the diagnostics and treatment of rare diseases<sup>[20]</sup>. Early diagnosis is becoming more feasible with significant reductions in sequencing and data analysis costs<sup>[21]</sup>. Bioinformatics has rapidly become an essential part of genomic medicine, resulting in a

growing range of software applications for the processing, analysis and storage of genetic data. No two labs are alike with respect to informatics solutions, and international guidelines and recommendations are scarce. Due to rapid technology development and the broad range of sequencing applications, it is difficult to define gold-standard recommendations for the content and pipelines of NGS assays. We will point out some main achievements and examples of ongoing initiatives which have been crucial for implementation of genomic medicine and which we believe will be defining for the future of the field in Norway.

#### Large, publicly available reference databases

Frequency databases are essential for separating between common and rare genetic variants and can therefore help to filter the many normal benign variants from analyses. The ExAC and gnomAD projects are led by international coalitions of investigators seeking to aggregate and harmonise exome and genome sequencing data from a wide variety of large-scale sequencing projects, and to make summary data available for the wider scientific community.

- Genotype-phenotype databases such as OMIM, Orphanet, Decipher, LOVD, ClinVar and others. ClinVar is a freely accessible, public archive of reports of the relationships between human genetic variation and phenotypes, with supporting evidence. ClinGen is a resource funded by the U.S. National Institutes of Health, dedicated to be an authoritative central resource that defines the clinical relevance of genes and variants for use in precision medicine and research<sup>[22]</sup>. These databases serve to centralize some of the crucial knowledge that would else be scattered across every lab and in medical literature and published articles, and can highlight differences in interpretation between different organisations, which can help to correct interpretation errors.

- Rare diseases are collectively significant, but the rarity of each individual disease means clinicians are unlikely to repeatedly diagnose the same genetic disease. Matchmaker Exchange is a protocol and data format for exchanging phenotype and genotype profiles to enable matchmaking among patient databases, to facilitate the identification of additional cohorts, and to increase the rate with which rare diseases can be researched and diagnosed [23].

A severe limitation of the databases used in clinical genetics is the lack of “clinical grade” curation. The databases have arisen as part of research initiatives, and all have been shown to include also erroneous data [24-26]. This has severe implications for medical genetics departments as the databases alone do not suffice to confirm a diagnosis, necessitating labour intensive manual inspection of variants and phenotypes. Further, many of the commonly used databases rely on public research funding, leading to uncertainties in terms of long term funding and maintenance (e.g. the OMIM database, which currently ask users for donations).

### Medical ontologies

There are several ontologies that can structure and standardise information in genomic medicine. For clinical genetics, the Human Phenotype Ontology stands out as a promising resource.

**Human Phenotype Ontology (HPO):** One challenge faced by medical professionals diagnosing rare or previously unidentified disorders is the need for accurate phenotypic information. Genetic data often makes sense only in the context of a patient’s symptoms because of incomplete penetrance, an interaction with the genomic background, or environmental factors. Phenotypic data can therefore be critical for the prioritisation and

**Bioinformatics has rapidly become an essential part of genomic medicine, resulting in a growing range of software applications for the processing, analysis and storage of genetic data.**



identification of probable causative variants. Also, consistent methodologies for describing patient phenotypes are essential for facilitating cross-disciplinary and cross-institutional communications, matchmaking, clinical data management, and maintaining patient archives.

For clinical genetics, HPO provides a standardised vocabulary of phenotypic abnormalities encountered in human disease. HPO has received considerable recognition over the past decade for its ability to connect genome biology and clinical medicine by providing bioinformatic resources for the analysis of human disease and phenotypes [27]. Numerous applications for utilizing standardised phenotypes in variant prioritisation have been developed [28], and while these technologies are unsuitable as a stand-alone strategy [29, 30] they are powerful when coupled with clinical expertise. HPO will likely be a driving force in the standardisation of phenotyping and implementation of a digital patient-twin in the future.

### **International consensus criteria for variant classification, interpretation and reporting**

High-throughput sequencing generates large volumes of data, and laboratories face challenges in developing, validating, and scaling NGS assays. While assays are available, the breadth of possible assays and the need to balance pipeline development with production mean that they are often inconsistently applied, and a common framework to facilitate adoption and the resolution of discrepancies in classification is needed to increase consistency within and between different laboratories. Some guidelines have been published for the development of NGS diagnostics and for the interpretation and classification of sequence variants, but are not uniformly adopted. An example is the American College of Medical Genetics and Genomics (ACMG) guidelines [31].

A major contributor to discrepancies in variant classification between laboratories is the different in-house databases. Two labs in the same country can be classifying two variants differently. If the information is not shared between the labs, the discrepancies can remain unidentified, leading to variations in diagnosis and treatment for patients, depending on what lab they are referred to for their analysis. Sharing of knowledge to increase quality of genetic analysis should be addressed as mandatory both in diagnostics and research. The Global Alliance for Genomics in Health (GA4GH) is leading the way and working for increased sharing of genomic data internationally [32].

Consortiums for rare diseases that are patient-centred, with national and international scope.

The International Rare Diseases Research Consortium (IRDIRC) brings together members that share common goals and principles and have agreed to work collaboratively within a multinational consortium [33]. IRDiRC teams up researchers and organisations investing in rare diseases research to achieve two main objectives by the year 2020, namely to deliver 200 new therapies for rare diseases and the means to diagnose most rare diseases.

The two programmes Care for Rare [34] in Canada and Deciphering Developmental Disorders [35] in Great Britain are examples of nationwide research programmes focused on improving diagnostics and treatment of rare diseases. Due to the sporadic nature of rare disease, such organisations provide critical support to patients and physicians who would otherwise be isolated, and are critical for an in-depth understanding of the mechanisms and best-practices for the diagnosis and treatment of particular conditions.



## 2.2 Sudden cardiac death (SCD)

### 2.2.1 Patients at risk of sudden cardiac death

Sudden cardiac death (SCD) is generally defined as an unexpected death without an obvious non-cardiac cause, occurring within 1 hour of symptom onset if the event was witnessed, or within 24 hours of the patient last being observed in normal health if the event was not witnessed. The European Union's and the United States' estimated annual incidences of SCD vary, respectively, from 50 to 100 cases per 100,000 persons. Rates are higher for men than for women. SCD accounts for around half of all deaths from cardiovascular disease and is the third-leading cause of death in the US.

The incidence of SCD increases with age, but deaths from SCD represent a larger proportion of all deaths in younger age groups, see figure 5. Deaths in younger age groups generally has greater socioeconomic impact. Although no data exist regarding SCD incidence in Norway, according to national registries, 11,613 deaths in 2015 were caused by cardiovascular disease <sup>[36]</sup>. Looking to international statistics, one can assume that half of these 11,613 deaths were caused by SCD, indicating an estimated 5,000 to 6,000 events per year.

Ventricular arrhythmia is the most frequent cause of SCD. Sustained ventricular tachycardia (VT) degenerates to ventricular fibrillation (VF), at which point the patient suffers circulatory collapse and loses consciousness. Thereafter, the heart rhythm degenerates to pulseless electric activity and finally asystole, when no electrical signal is discernible in the electrocardiogram (ECG). Both VT and VF are treatable rhythms that may be reversed by a high-energy electric shock through the heart muscle

# 5–6,000

Estimated events of sudden cardiac death in Norway per year

# 5–10%

Survival in out-of-hospital cardiac arrest is around 5-10%.

# 15–20%

Genetic cardiac diseases, structural heart disease, infiltrative and inflammatory heart disease, and primary heart muscle diseases are thought to cause 15–20% of SCD cases.

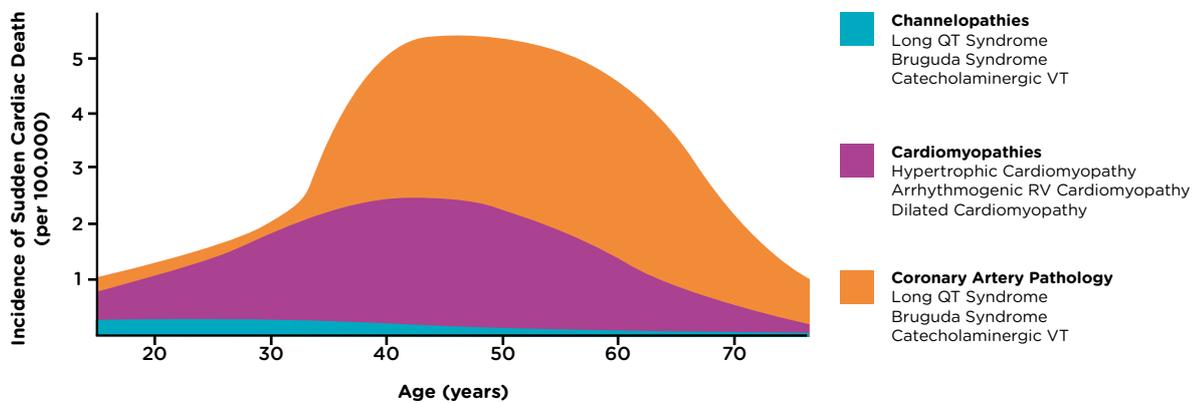


Figure 4 Age dependent changes in incidence and etiology of SCD [41]

via defibrillation. Resuscitation studies have shown that the earlier a patient is found after a cardiac arrest, the more likely it is that defibrillation will be effective, and that the survival rate is higher [37, 38]. However, survival in out-of-hospital cardiac arrest is around 5-10%. The sudden and often unexpected cardiac arrest requires lifesaving therapy with cardiac defibrillation within few minutes. This urgency highlights the importance of preventing cardiac arrest. Identification of patients at risk and of preventive measures in these individuals are of uppermost importance to reduce these events. To improve survival in cardiac arrest, significant effort is being put into reducing reaction time by teaching cardiopulmonary resuscitation techniques to as many people as possible and by making automatic defibrillators more widely available.

Public health initiatives geared towards improving cardiovascular health have resulted in a reduction in deaths from cardiac causes over the past several decades. Still, the burden of SCD is large, and there are limits to the kinds of preventive care that can be provided to whole populations.

#### Patients at risk for SCD

Unfortunately, for nearly half of SCD cases, cardiac arrest is the first symptom of cardiovascular disease [39]. For most patient groups known to be at risk for SCD, there is potential for improved preventive treatment. Coronary heart disease (CHD) is estimated to be the cause of around 75% of cardiac arrests in the western world. Patients who have had a myocardial infarction have a 10-fold higher risk of SCD than the general population does [40]. Although the absolute rate of SCD rises steeply with age, the proportion of deaths that

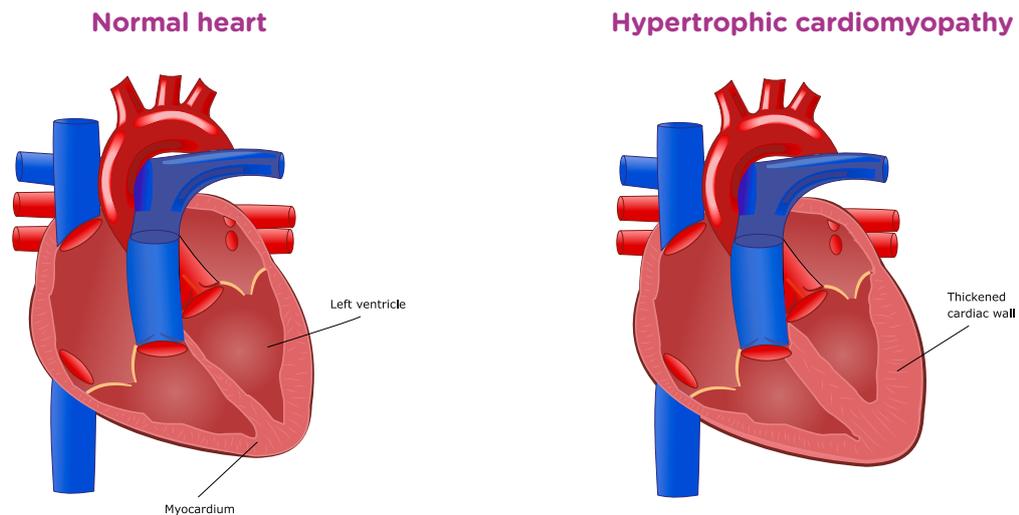


Figure 5 Hypertrophic cardiomyopathy compared to a normal heart. The heart wall muscle thickness may increase to several times normal.

are sudden has been found to be higher in younger age groups<sup>[41]</sup>. Genetic cardiac diseases, structural heart disease, infiltrative and inflammatory heart disease, and primary heart muscle diseases (cardiomyopathies) are thought to cause 15–20% of SCD cases, while around 5% may be attributed to electric disease such as long QT syndrome, Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia<sup>[42]</sup>. Despite being relatively rare, these diseases are the main causes of SCD in young adults.

### Hypertrophic cardiomyopathy (HCM)

Hypertrophic cardiomyopathy is the most common genetic heart disease, with a prevalence of 0.2–0.6%. A pathogenic mutation is found in approximately 60% of patients. In HCM, the heart wall muscle can increase to several times normal thickness, as shown in figure 6. This affects heart muscle contraction, increases risk of ventricular

arrhythmias, may obstruct blood flow through the heart, can impair oxygen delivery to the heart muscle itself, and cause formation of scar tissue inside the heart walls. For the patient with HCM, possible symptoms are chest pain during exercise, breathlessness, palpitations, dizziness, loss of consciousness, fluid retention and fatigue. Symptoms are not specific for HCM, and getting the right diagnosis can be challenging and time-consuming. Studies have shown that patients with HCM have a risk of ventricular arrhythmia, cardiac arrest, or SCD of nearly 1% per year.

### 2.2.2 Current situation for HCM at OUS

Due to the complexity of the disease, HCM can be difficult to identify. Initially, HCM may be suspected because of a heart murmur, positive family history, abnormal ECG patterns showing left ventricular (LV) hypertrophy, chest pain or heart failure symptoms indicating a need for echocardiography.

# CURRENT SITUATION FOR HCM AT OUS

## Department Name

Department of Cardiology, Unit for Genetic Heart Diseases

## Location

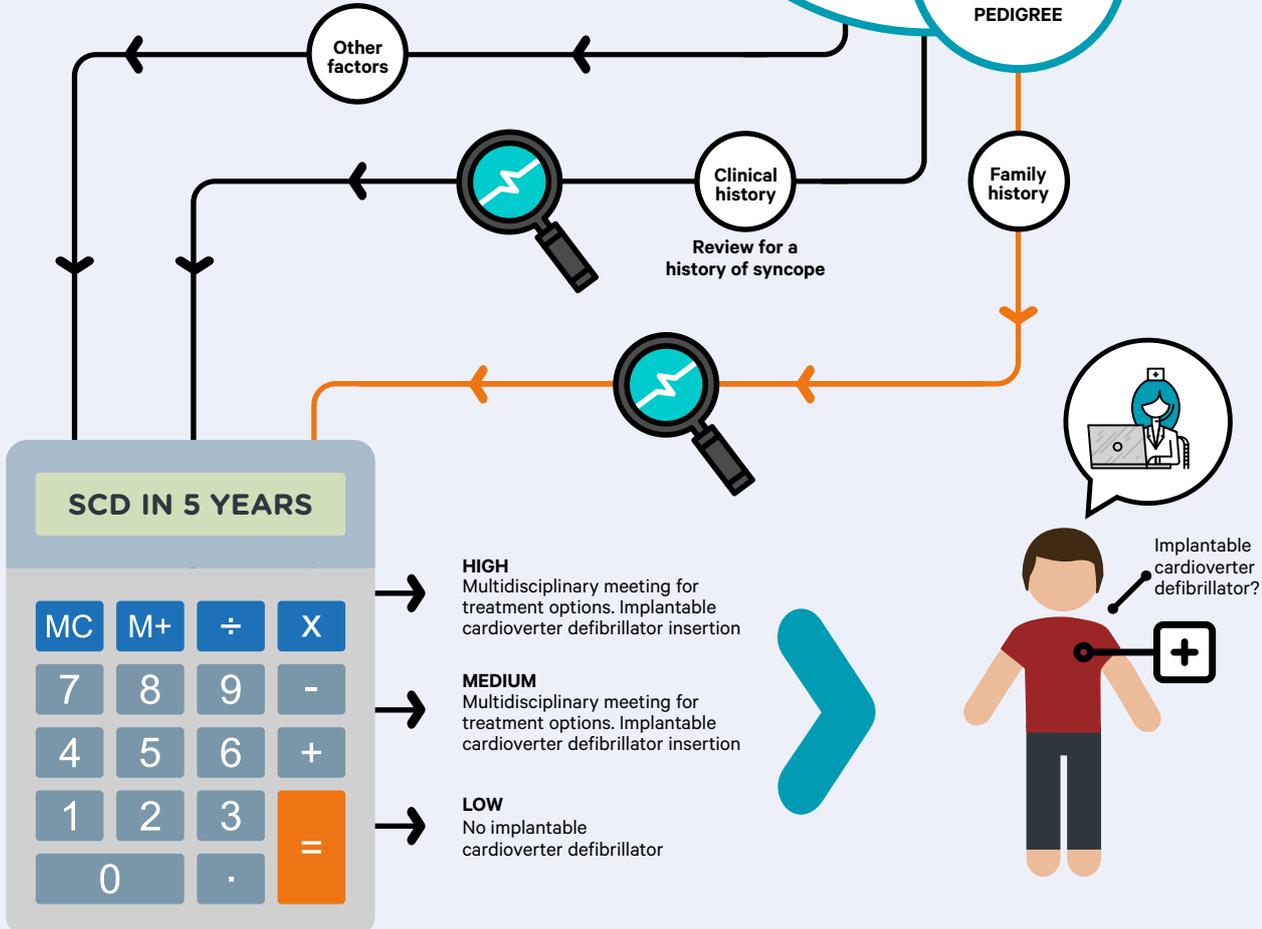
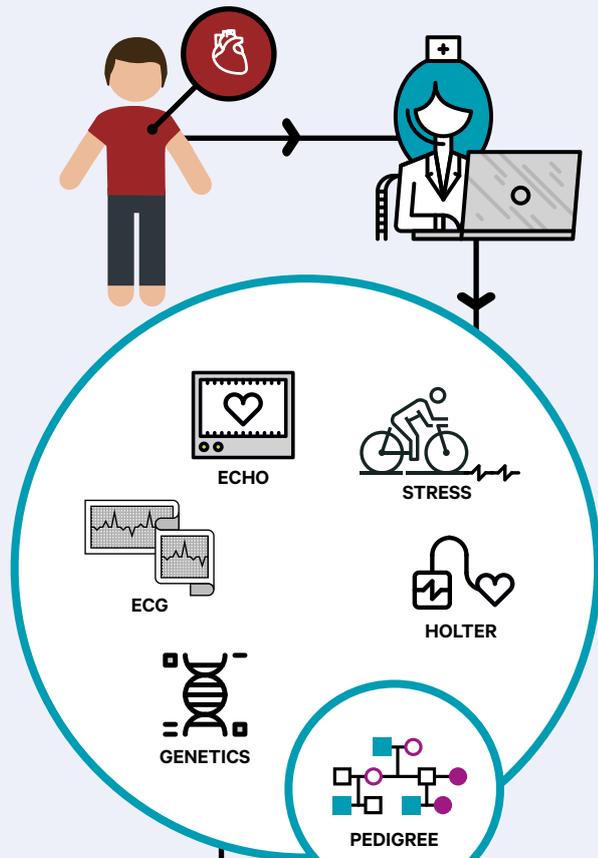
Oslo University Hospital, Rikshospitalet

## Main service:

Diagnosis, treatment and follow-up of patients with genetic (inherited) heart disease.

## Number of employees

1 associate professor and cardiologist,  
2 cardiologists, 3 nurses, 7 MD PhD fellows.



Patients are referred to the unit for Cardiac Genetic Diseases at OUS Rikshospitalet from other physicians and centres to confirm a suspected diagnosis or for second-opinion evaluations. A careful medical history is an important part of the evaluation and multiple sources are used to identify prognostically important information. Patients are examined with resting ECG, longterm-ECG (24h), stress ECG (e.g., by bicycle exercise test). In addition, pedigree mapping, genetic counselling and genetic testing are performed. A comprehensive echocardiographic examination is done, and in a large proportion of patients is supplemented with a cardiac MRI. Invasive studies of coronary arteries (coronary angiograms) are needed to exclude concomitant coronary artery disease, intra-cardiac pressures and shunts are measured, and heart muscle biopsies taken in cases in whom the diagnosis is unclear. Biochemical tests also provide additional diagnostic and prognostic information.

Genetic testing has emerged in the work-up of these patients during the last 15 years. Genetic testing allows a clear diagnosis and enables the possibility of genetic family screening. For genetically confirmed cases of HCM, first degree family members are offered genetic testing. Newly discovered gene carriers are referred for a comprehensive cardiological evaluation at the outpatient clinic. Patients with a HCM phenotype are followed annually, while healthy gene carriers are seen every 3-5 years, when a new complete examination is performed. Furthermore, a negative genetic test in a patient with HCM initiates further diagnostic measures and the search for specific rare diseases.

Some of the results of the above clinical evaluations feed into an online risk calculator made available by the European Society of Cardiology (ESC) to predict the patient's 5-year risk of SCD. More specifically, the current calculation bases the risk estimate on seven clinical parameters including the patient's age, a history of syncope (fainting), SCD in first-degree relatives, a diagnosis of non-sustained ventricular

tachycardia, maximal heart muscle wall thickness from echo/MRI, left atrial diameter, and the left ventricular outflow gradient. The calculation will determine a low, medium, or high estimated SCD risk which may indicate that treatment should be considered. A further review will be performed in a multidisciplinary department meeting. For confirmed cases of HCM, first-degree family members are offered genetic testing. Newly discovered gene carriers are referred for a comprehensive cardiological evaluation at the outpatient clinic. Patients displaying the HCM phenotype are followed annually, while healthy gene carriers are seen every 3-5 years, when a new complete examination is performed.

Today, this information is added manually to a calculator, following a manual and often labour intensive search through medical records and interview of the patient.

For the individual at risk of SCD, the most important decision in preventive care is whether to implant an implantable cardioverter defibrillator (ICD). An ICD is an advanced type of heart pacemaker that reacts to ventricular arrhythmias and can halt VTs before they degenerate into VF, or deliver a high-energy shock to terminate a VF if necessary. While ICDs may be considered the ultimate "safety net" for patients, there are downsides to their use. Implanting an ICD is a surgical procedure where leads are placed into the heart and there is an associated risk of complications. The battery must be surgically changed at regular 5- to 10-year intervals and the risk of infection increases with every surgery. There is also the possibility of inappropriate shocks. ICDs require lifelong monitoring and follow up. All in all, ICD therapy is resource intensive, and the risk-benefit assessment is difficult.

Since there is a well-known risk of SCD in HCM, treatment considerations include a comprehensive evaluation of the individual patient's risks and benefits of ICD implantation.

### 2.2.3 State of the art for SCD in HCM

In contrast to other patient groups at increased risk of SCD, for the HCM population a relatively well-defined risk model exists, and it allows individual SCD risk to be estimated.

In 2014, the European Society of Cardiology (ESC) made available an online tool that will calculate a patient's estimated 5 year risk of SCD using seven clinical parameters – age, a history of syncope (loss of consciousness), SCD in first-degree relatives, a diagnosis of non-sustained ventricular tachycardia, maximal heart muscle wall thickness from echo/MRI, left atrial diameter, and the left ventricular outflow gradient. High estimated SCD risk which may indicate further review in a multidisciplinary department meeting for treatment consideration and eventually the decision of implanting an ICD.

Since there is a well-known risk of SCD in HCM, treatment considerations include a comprehensive evaluation to the individual patient's risks and benefits of ICD implantation. The selection of these factors is based on registry data on more than 3,600 patients with HCM from five European countries.

The estimated 5-year risk is a helpful guide for clinicians caring for HCM patients, as it provides guidance as to whether the patient would benefit from ICD therapy. Patient cases with an intermediate or high calculated SCD risk are discussed in department meetings and treatment recommendations are reached by consensus. If ICD implantation is recommended, the decision comes down to patient preference.

Most SCD events in the general population are caused by coronary heart disease (CHD). CHD is highly prevalent, but the absolute SCD risk in CHD is relatively low. Several trials have attempted to identify which CHD patients benefit from

**Today, this information is added manually to a calculator, following a manual and often labour intensive search through medical records and interview of the patient.**

ICD therapy. The only subgroup of CHD patients in which ICD survival benefit has been proven is that of patients with severe heart failure. Other attempts at individualised risk estimation have so far not been successful and there is no current risk model for CHD similar to the HCM model.

Somewhat perversely, risk estimation may be easier in patient groups with a high SCD event rate because of the availability of more outcome data, and particularly difficult in populations with a comparatively lower absolute SCD risk. As a result, current techniques in individual risk stratification lack specificity. To illustrate this lack of specificity, figure 8 describes the distribution of the clinical statuses of individuals suffering from SCD. Obviously, better risk estimation tools are needed to prevent more unfortunate events.

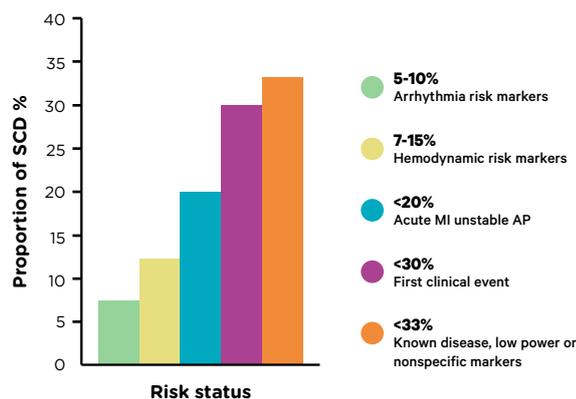


Figure 6 The distribution of the clinical statuses of individuals suffering from SCD. MI indicates myocardial infarction; AP indicates angina pectoris [43].

## 2.3 Metastatic colorectal cancer

### 2.3.1 Patients suffering from colorectal cancer

Colorectal cancer (CRC) is one of the most common cancers in the Western world. In Norway, approximately 4,200 patients are diagnosed with CRC each year <sup>[44]</sup>. The development of CRC is due to cellular injury, causing errors in the DNA (e.g., mutations, methylation and copy number alterations) <sup>[45]</sup>. The 5 year overall survival rate for CRC is 60–70% [44]. For patients diagnosed with CRC, 50% will develop metastases <sup>[46]</sup>. Most metastases will develop in the liver, but are frequently found in the lungs, or peritoneum (carcinomatosis) as well. Metastatic CRC (mCRC) is the leading cause of cancer-related mortality, where the best oncological treatment offers patients a median survival rate of 2.5 years <sup>[47]</sup>. Approximately 20–25% of patients can have metastatic lesions removed by surgical intervention <sup>[48]</sup>, where the prognosis is up to a 50% 5-year survival rate <sup>[49]</sup>.

### 2.3.2 Current situation for colorectal cancer at OUS

The Norwegian Gastrointestinal Cancer Group has formalised the investigation and management of patients referred with a possible diagnosis of CRC, and have outlined criteria for both pre-operative (neoadjuvant) and post-operative (adjuvant) oncological treatments. This investigation entails colonoscopy with biopsies to secure the diagnosis and location of the cancer for pre-operative planning. The level of a CEA (tumour marker) is measured from a blood sample. A clinical staging of the patient is mandatory and is performed by a computer tomography (CT) scan of the lungs, abdomen (to include the liver), and pelvis to locate possible metastatic deposits to visualise the anatomical location of the tumour. For rectal cancer,

# 4.200

In Norway, approximately 4,200 patients are diagnosed with CRC each year

# 60-70%

The 5-year overall survival rate for CRC is 60–70%

# 50%

Approximately 20–25% of patients can have metastatic lesions removed by surgical intervention <sup>[48]</sup>, where the prognosis is up to a 50% 5 year overall survival rate

a magnetic resonance (MR) scan is performed for better anatomical visualisation of the tumour. The investigation of patients with liver metastases includes an MR of the liver. A positron emission tomography (PET) scan can be used to find metastatic deposits outside the liver. When needed, organ-specific investigations are performed for patients with medical comorbid conditions of the heart, lungs, and endocrine that require a general anaesthetic.

Multidisciplinary team (MDT) meetings are advised for patients with mCRC and rectal cancers who are candidates for surgery. For CRC and mCRC, the MDT consists of gastrointestinal surgeons, radiologists, and oncologists who together form a treatment plan using results from pathology, clinical staging, response and tolerance to previous oncological treatment, mutation status and microsatellite status where appropriate. Treatment of mCRC requires a complex surgery with or without pre-operative oncological treatment. Currently, there are no best-practice methodologies for patient risk stratification. Consequently, multiple factors are used to estimate the patient's prognosis and fitness for surgery. This estimate may include a clinical risk score [50], derived from many of the parameters mentioned above and a response evaluation criteria in solid tumours (RECIST). Patients are then categorised into having a resectable or non-resectable tumour and are classified into being medically fit for surgery or not. If a tumour is found to be non-resectable or if the patient is deemed not medically fit for surgery, pre-operative oncological treatment or medical treatment is commenced to downsize tumours and optimise medical conditions influencing pre-, peri- and post-operative patient care. From neoadjuvant treatment,

12–13% of non-resectable patients can be made resectable [51]. Following this treatment, the patient is reviewed in an MDT meeting for a new assessment regarding surgery as a treatment option. Along with patient coordinators, the MDT facilitates the treatment plan. The development of an optimal treatment plan requires specific information that at times may not be available; if this is the case, the patient's treatment may be delayed or suboptimal. Figure 7 outlines the MDT decisions.

#### **The information required for a patient to be considered in an MDT meeting is the following:**

- Past medical/surgical/oncological history
- Current medical conditions
- Histology results
- Tumour information from radiological scans (CT, MR, PET)
- Results from genomic analysis

This information is obtained and printed from the patient's medical notes. The MDT meeting occurs on a weekly basis with a duration of approximately 2 hours for the review of 10–20 patients. Referrals that contain relevant clinical information from other hospitals to OUS for the MDT to facilitate decision making are often received in paper format by post/fax. Radiological images are either transferred on compact discs or directly transferred via a secure line. When missing information is requested, it is mostly retrieved from the referring hospital by fax. Other relevant patient information that is obtained via the patient's EMR is either printed or viewed on separate computer screens in the MDT meeting.

# CURRENT SITUATION FOR COLORECTAL CANCER AT OUS

## Name of clinic

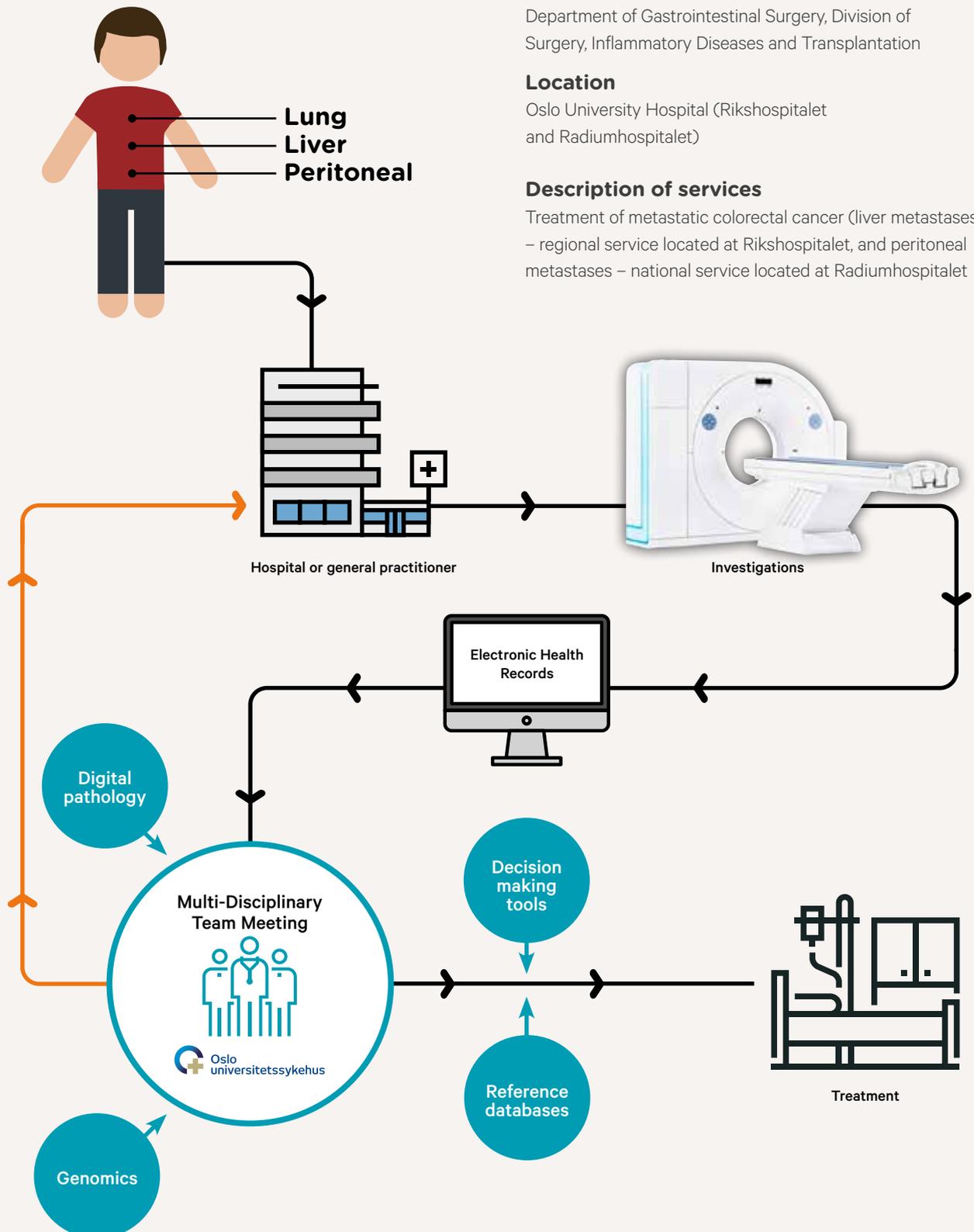
Department of Gastrointestinal Surgery, Division of Surgery, Inflammatory Diseases and Transplantation

## Location

Oslo University Hospital (Rikshospitalet and Radiumhospitalet)

## Description of services

Treatment of metastatic colorectal cancer (liver metastases – regional service located at Rikshospitalet, and peritoneal metastases – national service located at Radiumhospitalet)



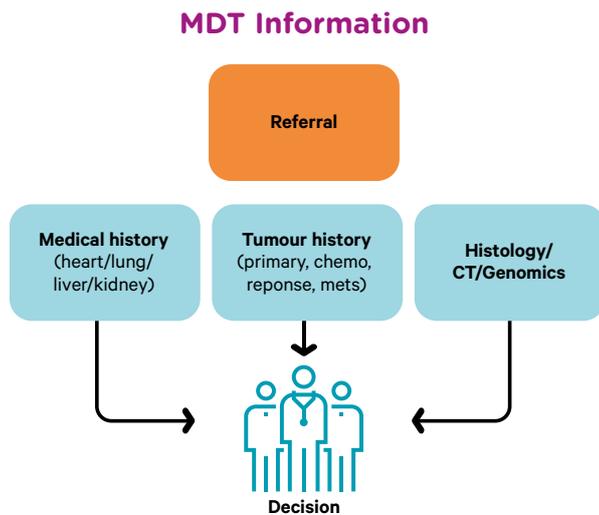


Figure 7. Technologies for clinical decision support both in and outside the MDT are today limited. Limitations in these technologies start with the referral process. Although clinical information is essential when forming treatment plans for patients with CRC, the Norwegian healthcare ICT infrastructure does not allow for information supply to MDT members at OUS in a way that is optimally efficient, precise, and reliable.

Currently, there are no effective ICT tools at OUS that enable the integration of data related to the patient's clinical details, tumour status, radiological and histological results. No tools are used to integrate structured information on molecular data, or to predict the outcome from patient treatment based on molecularly-guided data. Lack of clinical information can result in delayed decision making regarding the patient's treatment plan. For example, there are no current processes that provide physicians with the direct retrieval of patient information from the referring hospital. Important information regarding complications and prognoses related to different treatments is collected and stored in authorised registers or research databases. Such information is of great value for clinicians, but the current hospital ICT infrastructure and patient privacy regulations do not allow for flexible

information to be integrated into the MDT meeting. Information about the patient's wishes and life situation may be missing, and thus difficult to incorporate into the decision basis of the MDT meeting, as the treating physician who had the physical encounter with the patient often is outside of the organisation. The current ICT equipment used in the MDT meeting does not allow for simultaneous visualisation of images and text. The hospital's ICT infrastructure at OUS consists of multiple ICT systems and infrastructures with incompatible interfaces. These ICT bottlenecks require clinicians to manually retrieve patient information either via direct contact with the referring physician or by retrieving faxed documents from the referring institution. Ideally, the MDT meeting would entail the review of external registries, visual aids to demonstrate important patient information, timelines, and radiological images; however, this review requires access to different clinical systems that the hospital does not have access to. Therefore, physicians spend considerable time gathering and consolidating information. As complex data such as genomic information become more available and relevant in the MDT meeting, clinical interpretation of such data must be contextualised. There are many ways in which this can be achieved, but regulatory and technological bottlenecks may prevent innovative solutions that provide value to the patient.

To further develop precision medicine, the use of genomic data will be essential to understand tumour biology in a clinical context. At present, there are no possibilities for incorporating an interpretation of genomic data in the MDT setting. Currently, one does not know how to store this type of data or how to use scripts to compare genomic data with required external sources. Tumour data must be compared with normal variants to establish if a genetic aberration is a normal variant or is related to disease, and then one must relate these findings to patients and finally visualise results for clinicians.

### 2.3.3 State of the art for colorectal cancer

A comprehensive MDT meeting provides optimal management planning for the patient, but the current process presents considerable challenges to effective decision making.

At present, healthcare technologies within CRC are developed to improve surgical techniques, radiological imaging, digital pathology and genomic profiling of tumours. The term “precision oncology” is emerging, and implies prediction of which patients will likely respond to specific cancer therapies according to molecular diagnostics that are increasingly accurate as well as the mechanistic and functional understanding of individual tumours <sup>[52]</sup>. While molecular stratification of patients can be achieved through different means, NGS of tumour DNA and RNA has emerging clinical utility for treatment planning in CRC patients.

It is currently acknowledged that CRC is a heterogeneous disease with several molecular subtypes and currently there are three gene mutations (KRAS, NRAS and BRAF) that provide genetic information relevant for treatment planning in the MDT meeting. As the prognostic value of these markers is better understood and new markers are introduced, these biomarkers may have a greater impact on treatment. Currently, however, the impact on treatment is minimal due to limited pipelines for analyses, lack of bioinformatics support and lack of specialists trained in understanding the molecular biology of genomic markers <sup>[53]</sup>, as well as lack hospital ICT infrastructure and solutions to support these aspects. Sequencing of tumours can reveal genomic alterations that have clinical implications. Certain genetic alterations are shared across multiple histologic entities, raising the fundamental question of whether tumours should be treated by molecular profile and not by tissue of origin <sup>[52]</sup>.

General medical training can hardly keep up with the pace of increasingly complex genetic information and multiple test-platforms to choose from. Consequently, there is a rapidly growing gap between clinical knowledge and genetic potential in cancer care. Multidisciplinary molecular tumour boards (MTBs) have been suggested to address this disparity. MTBs can improve and increase the application of genetics-guided cancer care <sup>[54]</sup>. A survey by The American Society of Clinical Oncology concludes that tumour boards are commonplace worldwide, and that a majority of practicing oncology specialists attend them to obtain recommendations that result in changes in patient management <sup>[55]</sup>.

An increase in tumour genomic information available to clinicians creates a demand that access to more efficient and precise tools be made available to MDT members to aid in decision making. Surgical resection is considered the most optimal treatment for this patient group, but requires careful pre-operative planning to achieve complete resection without compromising vital structures. Tools to better visualise the anatomy (e.g., 3D imaging, fusion imaging, etc.) will aid in pre-operative planning. Selection of the correct patients requires an improved use of digital pathology, radiological imaging, genomic profiling, cancer drug screens and information connectivity in correlation with the patient's outcome for more efficient and precise decision making in the MDT meeting. Greater efficiency and precision will enable clinicians to tailor treatment more appropriately to each patient. Currently, some of these methods are costly and time-consuming to perform and interpret, like mutation- and gene-expression profiles.





### 3. Towards a more precise medicine

Technological advances are giving us the opportunity to evolve towards greater precision in the delivery of healthcare, tailoring treatment to the individual patient. The diseases and patient groups studied in this report are at different stages on the path towards precision medicine. The differences can to a large extent be explained by varying enablement of technology and differences in the knowledge of diseases.

An example; for genomics, the most important enabling technology for precision medicine, the picture is much simpler for rare diseases and SCD compared to cancer. For rare diseases and SCD there is commonly a one to one relationship between a disease-causing mutation and a phenotype, and the genome can for practical purposes be viewed as a static, non-changing entity throughout the life time of patients. In cancer there are numerous somatic mutations which together can influence phenotype and the tumors tend to acquire new mutations as the disease develops. Hence, the interpretation of genomic alterations is much more difficult and challenging in cancer compared to SCD and rare diseases. SCD on the other hand is more complicated than rare genetic disorders due to its commonly multifactorial causality.

As information grows more complex, there is a need for clinical decision support tools that collect and present contextual information. Automation of processes like information gathering will make better use of the health personnel time. Creating structured data from unstructured text in EMRs with Natural Language Processing is a focus in near future. New disciplines' input to clinical decisions can be facilitated through digital collaboration platforms. Clinical decision support will ideally be derived from secondary use of data, blurring the traditional line between research and the clinic.

### 3.1 RARE DISEASES: INCREASED SHARING AND QUALITY ASSURANCE

The Norwegian healthcare system has an ambition to offer its citizens good and equal access to a competent healthcare service. In the diagnosing of and caring for patients with rare inborn genetic disorders this ambition includes the access to relevant genetic technologies that are high in sensitivity and specificity. It also requires robust and consistent interpretation and reporting, and a rapid turnaround time from referral to diagnosis and treatment plan for patients who are critically ill.

Moving forward, developing technologies will bring -omics solutions from research to the patient's bedside in a safe and sustainable manner. Quality assurance of results and of interpretation will require a national healthcare ICT infrastructure that enables communication amongst providers and laboratories for the seamless exchange of information and data relevant to a patient's medical records. Inside each lab, software aided closer collaboration between lab technicians and the doctor will increase diagnostic yield and efficiency. This will result in patient care in rare diseases that is collaborative, dynamic, and patient centred.

#### Collaborative patient care requires:

- Public awareness of the burden of rare diseases, national networks for rare disease health professionals and a national strategy for rare diseases
- A national effort to identify and describe new genetic disorders [34, 35].
- A national variant database containing variant frequencies and variant classifications
- A national solution for electronic requisitions/referrals and patient consents
- A national real-time sequence-data repository and quality register for diagnostic purposes, where interpretation can be assigned to expert labs nationwide, and enabling equal, fast, flexible, and high-quality interpretation services with external quality control, regardless of where and when the patient has been sequenced. Cross-disciplinary, cross-institutional communications platform, patient archive/management system with user interface for interdisciplinary review of results before reporting

#### Dynamic patient care requires:

- Equal patient access to a wide range of diagnostic tools; from high-throughput full coverage genomes, combining technologies for calling structural rearrangements, copy number variation, sequence variation, repeated elements, mosaic variants, and mitochondrial DNA, to rapid, small-scale solutions for local/bedside use.
- Functional analysis as routine diagnostics to decipher the biological impact of genomic variation of uncertain significance (phenomics, metabolomics, transcriptomics, other).
- Real-time data exchange between medical genetic laboratories and open EMR platforms with archetypes for genomic medicine (genomic variation and clinical interpretation). Systematic data reanalysis, and reinterpretation when called for (with opt-out in dynamic patient consents).
- The interpretation of genetic variation in large data sets is not feasible without parental data or a defined patient phenotype to restrict the areas of interest in the genome. An electronically readable patient phenotype in a standardised format like the Human Phenotype Ontology will increase the precision and reduce the turnaround time for interpretation of genomic variation.

#### Person centred care requires:

- Further develop the organizations that support people affected by rare disease and establish and run a national register of rare diseases [56].
- Establish or further develop formal networks of multidisciplinary clinics for rare diseases.
- Patient and family involvement with increased patient autonomy and ownership of own healthcare data. Leave patients in control of their own health data – electronic communication, consents, identification of suitable research programmes, connect with rare disease programmes, etc.
- Genomic variation integrated in electronic medical records for secondary purposes such as pharmacogenetic analysis and simulation of planned intervention/treatment.

### 3.2 SUDDEN CARDIAC DEATH: AUTOMATED RISK MODELS FOR IMPROVED DECISION SUPPORT

Our near-term vision for Norwegian healthcare organisations includes the broad adoption of cardiovascular clinical decision-making tools that collect and present contextual information for SCD patients, in addition to the following:

- automated probable diagnosis and correlating information derived from evidenced-based research
- prognostic variables that can predict for clinical outcome and relevant therapeutic options
- focused patient data reports and summaries
- documentation templates
- enabled data sharing with relevant registries and research institutions

Advancements in clinical decision-making tools will facilitate precision medicine and individualised treatment by enabling big data methods for Artificial Intelligence (AI) and Machine Learning in healthcare. For the HCM case-study group, the future vision would enable an EMR system able to recognise an HCM genotype or phenotype from EMR data, automatically retrieve current (and future) ESC risk factors from physician notes and clinical systems, request missing diagnostic studies, and provide an individual SCD risk score.

Following this first step of using pre-processed examination data and small data results, a next step would be to employ machine learning and artificial intelligence (AI) technology directly on source data from clinical examinations such as echocardiography, MRI, lab data and ECG recordings. The goal would be to extract more clinically relevant information than manual evaluations have provided to increase our knowledge of the underlying disease mechanisms.

Successful implementation of more advanced clinical decision-support tools in an EMR system for HCM patients would provide the following opportunities:

Score models for individual risk. The system will automatically present the clinician with individualised risk estimates, and suggest treatments that are most likely to modulate risk. ECG, echo or MRI findings that could raise suspicion of HCM are flagged as alerts to the clinician at all care levels. “Risk events” in patients with HCM (i.e., cardiac syncope, ventricular tachycardia) generate alerts that can be extracted and flagged to the clinician. Furthermore, specific gene tests or broader genetic analysis may identify specific genotypes that confer higher or lower risk of SCD.

Higher Specificity. The system will recognise the patient’s disease entity, and automatically extract current clinical knowledge regarding the condition from online and/or local sources, and can present relevant practice guidelines. In cases of an indeterminate diagnosis, the system will suggest diagnostic procedures most likely to reduce uncertainty. Echocardiography and MRI are automatically analysed, and the most prominent components are automatically integrated in a risk calculation. In addition, wearables/private health monitors are integrated in the risk model, possibly giving early warning of events. An integrated risk calculation that shows the weight of the different components is presented to the clinician. Data from implanted devices (ILRs, ICDs) are collected and integrated as feedback into the decision algorithm.

Automated documentation, registry entry and quality assurance. The EMR will facilitate documentation of information gathered during the consultation, and automatically provide structured data to registries for quality assurance and clinical research.

### 3.3 METASTATIC COLORECTAL CANCER: ACCESS TO AND ANALYSIS OF CONTEXTUAL PATIENT DATA

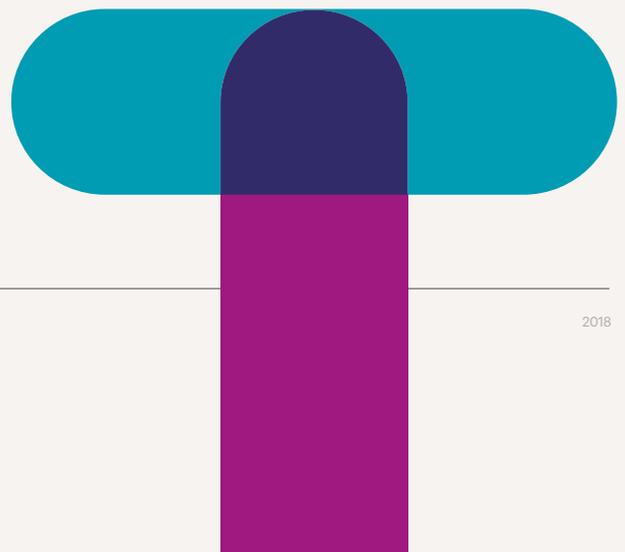
Precision medicine in cancer depends on a management strategy tailored to the patient's disease and needs. The use of genomic data will be essential to understand tumour biology in a clinical context. The MDT meeting is central to form the treatment strategy because it provides a forum to examine different important aspects of pathological and radiological information in relations to the patient's general health, to target treatment. The hope for the future is to enable precision medicine for patients with CRC by ensuring the adoption of modern applications within Norwegian hospitals that will enable the exchange of important information with MDT members prior to and at the MDT meeting.

To achieve this vision, the exchange of information at the MDT meeting between radiologists, pathologists, molecular pathologists, bioinformaticians, oncologists and surgeons must be processed and displayed by an ICT infrastructure with the following elements:

- A standardised referral process: incoming referrals will be standardised to include relevant clinical information that allows for the recognition of text.
- AI applications: radiological images, pathological images, and lab reports will be analysed by AI to enhance data quality and to enable identification of missing data, patient prioritisation, and identification of further medical investigation or treatment considerations before surgery is considered.
- Better understanding of biomarkers: The MetAction Trial funded by The Research Council of Norway demonstrated that through DNA sequencing using large gene panels, clinicians could characterise and understand tumour biology more thoroughly. This greater understanding opened possibilities for using targeted therapies based on more than one specific biomarker, giving more treatment options to end-stage cancer patients when all other options have been exhausted. At present, such

cancer services are offered only within clinical studies, and implementation of a wide sequencing of cancer patients will demand that a larger number of people with different specialties be involved <sup>[57]</sup>. Genomic data adds new aspects of information to patient treatment, including tailored oncological and surgical treatment, but also adds follow-up tailored to specific tumour subtypes. Such data are extracted from pre-treatment biopsies.

- Collaboration tools for bringing data about patients' situation, needs and preferences into the hands of the clinicians making decisions.
- Dashboard view: data presented in the MDT meeting via a dashboard view, including radiology images, biopsies, genetic results, retrospective images, and pathology reports from requisition to diagnosis that are automatically interpreted and connected on a real-time platform.
- Display of tumour information: 3D reconstruction of tumours and surrounding parenchyma and other vital structures to improve the planning of surgical resections.
- Logistics planning / patient flow: a direct overview of available out-patient clinics, radiology appointments and slots in operating theatres will aid the logistics and communication of treatment planning.
- Inclusion of AI based technologies that support the precision search for national and international clinical trials (Clinical Trial Matching) being performed that could be a relevant choice for the individual patient.
- Well-established pipelines for relevant genomic data, robust information on genomic information from tumour data (capturing the details and dynamics of the tumour in time and space) and relevant germline data, as well as deep knowledge reports for decision making.



## 4. Overcoming the barriers to precision medicine

This section highlights the overarching barriers impeding the successful implementation of precision medicine in Norway and recommended actions for overcoming these. While BigMed focuses on addressing technological and legal bottlenecks to the implementation of precision medicine, these are often interconnected with barriers of other natures such as financial/ political, competence/ knowledge and organisational. The barrier categories are shown in figure 11. Barriers and actions were discussed through a series of interactive workshops involving the extended BigMed network, based on situation reports from the three BigMed clinical groups.

Existing systems are not able to support an efficient shift towards precision medicine without substantial change. In the short term, technological and regulatory barriers must be addressed; there is a need for an adequate infrastructure for advanced analytics, and there is an imminent need for legal clarifications. On a longer term, development will be slow unless we overcome barriers in knowledge, organization and the financing of healthcare providers.

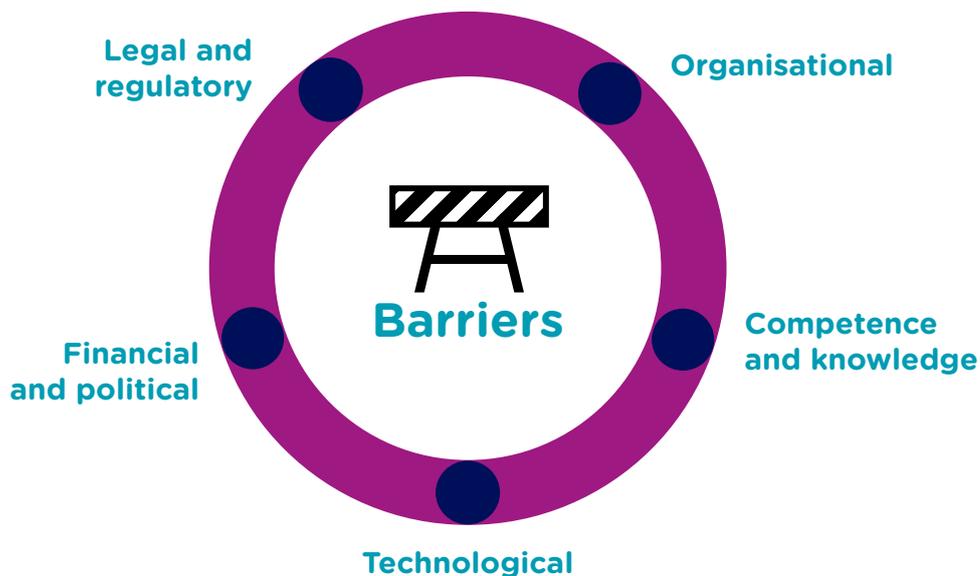


Figure 8: Categories of barriers to implementing precision medicine

## 4.1 Financial and political barriers

### BARRIER: Consensus model difficult for driving disruptive change

#### Barrier description

- Disruptive change requires strong leadership. Consensus-oriented processes are not ideally suited for areas where disruptive solutions or new actors are needed.
- Decision makers embedded in existing healthcare systems may tend towards maintaining status quo and protecting budgets while incentives to introduce new ideas, impulses and solutions, often through new actors, are not in place.
- The national strategy for implementation of personalised medicine has strongly prioritised building consensus among all health regions and professional groups nationwide.

#### Actions suggested for overcoming barrier

- Establish an organisation with a mandate and incentive to achieve disruptive change. Look to the Genomics England model whereby a state-owned enterprise has been created to drive transformational change and establish standards and quality guidelines.
- Implementation in healthcare ensured through financial mechanisms where reimbursement is provided only to laboratories adhering to the minimum requirements.
- Introduce funding mechanisms for innovation that encourage better and more industry involvement through public-private partnerships and innovative procurement processes.

### BARRIER: Inefficient incentives for innovation

#### Barrier description

- The current healthcare financing system provides hospitals reimbursements per activities rather than health outcomes which can lead to higher system costs and hinder improvement activities that may lower costs and / or improve outcomes. Investments in one part of the pathway may deliver saving or improvements in other parts of the pathway, potentially involving other entities and budgets. For example, limited access to data

across organisational entities at times results in repeated ordering of tests, which comes at a cost to society and patients.

#### Actions suggested for overcoming barrier

- Norway should aim to be best in Europe on value-based research, including use of patient experience data. This could provide a foundation for moving towards a more value-based reimbursement model.

## **BARRIER: Evidence supporting the relative costs and benefits of precision medicine lacking**

### **Barrier description**

- Cost is an issue in any health care system, whether it is private or public. The funding of both specialised and primary healthcare in Norway is based on a mixture of basic funding and activity based reimbursement. Introduction of any change in practice must be evaluated in this context.
- There is a concern that the tailoring of treatments to individuals may drive costs for healthcare providers. However, even if specialised drugs and implants may be expensive, they may reduce complications and the total number of days in hospital for patients, and so reduce the overall costs of care.
- The unit costs associated with precision medicine will decrease and the value increase as underlying technologies diffuse across specialities (e.g. as more people have their genome or exome sequenced), and we can utilise data on a broader scale.
- The current economic models are based on measuring group outcomes based on the one size fits all model. The current models of health technology assessments are less well suited for assessing technologies that can lead to transformational changes of whole systems.

### **Actions suggested for overcoming barrier**

- In the long term, a value based healthcare should be the core foundation for funding and political prioritisations.
- To fully evaluate the impact of precision medicine, targeted health economic research should be performed. Value based research tools like quality of life, economic, organisational and ergonomic outcome studies should be implemented.
- Research projects should be initiated to develop new economic models.
- Data and evidence on effects of precision medicine should be collected as the basis for a cost-benefit analysis for applying new economic models.
- Documentation of the value of precision medicine for the patient and for society should be provided.
- The cost of the loss of human life or of reduced health, such as by applying models and thinking from road safety analysis, should be quantified.

## Examples: Financial and political barriers

### Example 1

The principal performance indicators tied to financial gains for laboratories and clinics are number of patients and turnaround time. These are perverse incentives as they can incentivise healthcare providers to prioritise in a manner that is not always to the best of the patient.

There are no incentives for providing state-of-the-art services, to the detriment of patient groups with rare diseases. As an example, a medical genetic lab

is not reimbursed to perform a re-interpretation of sequence data. To account for new findings in the medical literature or the diagnosis of similar cases elsewhere, international guidelines recommend the re-interpretation of NGS data as standard care when a molecular diagnosis is not reached for a patient with a suspected genetic disorder. Currently, clinical genetic laboratories in Norway who are delivering this standard of care are doing so in spite of – and not because of – the system.

### Example 2

Cost is a predominant issue when launching new drugs. With a smaller patient target group for the drug but similar development costs as a blockbuster drug, the cost is likely to be higher. At the same time, there is an increasing understanding that thousands of patients today are receiving non-tailored therapies that may have reduced or even adverse effects due to genetic factors. These could have been revealed through an initial gene sequencing.

One example is the drug Clopidogrel, a platelet inhibitor given routinely to patients having been treated with angioplasty and stents. The drug's oxidation is mainly dependent on the cytochrome P450 enzyme 2C19 (CYP2C19) which is important to activate the drug. Patients with certain genetic variants in CYP2C19 have been found to have lower levels of the active metabolite, less platelet inhibition, and greater risk of major adverse cardiovascular events such as heart attack, stroke, and death <sup>[58]</sup>.

Genetic factors influence the metabolism and transport of thousands of drugs. The U.S. Food and Drug Administration (FDA) regularly publish an updated list of drugs where they recommend genetic sequencing before administration due to their potential for adverse effects (<http://genelex.com/clinical-guidance/fda/>). The drug labelling must include drug exposure and clinical response variability; adverse event risk; genotype-specific dosing; mechanisms of drug action; and polymorphic drug target and disposition genes. Pharmacogenetic testing is not widely implemented in Norway today, leading to unnecessary incidents of reduced or adverse effects that could have been avoided through genetic testing.

Tailored treatments may drive direct costs for healthcare providers, but may in turn reduce overall societal costs if they are more effective and reduce overall complications and days in hospitals for patients. Just avoiding one single incident of acute myocardial infarction by giving the right dose of Clopidogrel, or choosing a different drug that is effective, will amount to savings of several hundred thousand kroner.

## 4.2 Legal and regulatory barriers

### BARRIER: Privacy concerns trumps value of data sharing and secondary use of data

#### Barrier description

- To fully realise the potential of precision medicine, many parties require access to broad sets of patient data, and this data must be made available for secondary use.
- While research appears to support the idea that citizens are generally positive to the idea of sharing healthcare data for the common good, legal barriers constructed to protect privacy are making data sharing a challenge.

#### Actions suggested for overcoming barrier

- Sharing of health data for clinical purposes can be facilitated using informed consent as a legal basis. The administrative burden of managing consent at the scale required for precision medicine is significant without smarter solutions.

- Administration of consents should be uncoupled from the providing of healthcare services to remove pressure on patients.
- An alternative approach would be to modify regulations so that the consent for sharing of specified deidentified patient data is the default as part of the social contract for a national healthcare system. This could include the possibility for patients to “opt out” of data sharing.
- Establish a one-stop shop for information, guidance and legal advice to secure harmonised interpretations and practices, and equal quality of care across institutions and regions.
- The operational leadership of each healthcare provider entity must take the final responsibility for weighing privacy and patient safety considerations against each other.

### BARRIER: Segregated regulation of research activities and healthcare services

#### Barrier description

- Clinical practice and research activities are regulated separately today. The use of genetic analysis as the basis for precision medicine challenges this regime because genetic analysis generates information about a patient beyond the primary purpose of diagnosis and treatment. Reaching a diagnosis may also require the exploration of data, making each patient a research project within the healthcare delivery, creating a grey zone between research activities and healthcare service delivery.

#### Actions suggested for overcoming barrier

- Rapidly evolving clinical disciplines and the use of genetic information challenge the segregation of research and clinical use and will force a different organisation of diagnostic processes. A formal framework must be developed where testing, diagnostics, and research are integrated.

## BARRIER: Regulations do not facilitate big data research

### Barrier description

- Big data analysis has the potential to extract correlations from big datasets that are not easily perceived by the human observer. An initial hypothesis of the analysis may not be clear. To realise the value of big data analysis such as AI approaches in healthcare, there is a need to explore massive amounts of data combined from multiple individuals and sources.
- Per privacy regulations, the basic principle for access to health data is patient consent. Administration of large volumes of consent is a practical challenge (see above). According to regulations and current practice, processing of health data must be explicit for specific research purposes.

- The current privacy practices emphasise the principle of data minimisation, including limiting cohort size, data categories and data sources to be combined, limiting the opportunities to take advantage of big data technology advances in healthcare research.

### Actions suggested for overcoming barrier

- Within the boundaries of international regulations, there is a need for national regulations and guidelines that unleashes the potential of novel big data methods such as machine learning.

## Example: Legal and regulatory barriers

As the field is constantly evolving and interpretations of genetic variants differs between practitioners, there is a need to learn about and resolve conflicting interpretations. Sharing of information about variants and their relevance to disease is important for quality assurance, patient safety and diagnosis accuracy.

Today, it is not clear if a genetic variant should be considered anonymous or not per definitions in Norwegian and EU regulation, and if sharing of variant information can take place without patient consent. This clarification is needed before medical genetic departments can share information about interpreted variants between Norwegian labs and with international resources.

## 4.3 Organisational barriers

### **BARRIER: Healthcare organisations are complex and adverse to change**

#### **Barrier description**

- Healthcare organisations are focused on productivity and incentives are misaligned with resources for the innovation required to implement precision medicine.
- Changes threaten existing culture because they challenge current organisation, hierarchy, professions, medical specialties and power structures. There is resistance to changes in roles and procedures, which makes implementing changes difficult.

#### **Actions suggested for overcoming barrier**

- Development and implementation of precision medicine must be driven by political leadership and top hospital management. An ambitious national vision for precision

medicine as defined in this paper should be developed, and the implementation must secure precision medicine as an integrated task in a cross-disciplinary organisation.

- Establish clear and accountable roles in the provider organisations for managing data, such as the CMIO (Chief medical information officers).
- Sufficient resources required for innovation and implementation must be allocated, including test facilities for new technologies. Innovation needs to be measured using indicators that are broader than academic publications.
- Major performance indicators should be derived from patient outcomes rather than activities.

### **BARRIER: Structures and mechanisms do not facilitate sharing of information between healthcare organisations**

#### **Barrier description**

- Structures and mechanisms do not facilitate the cross-disciplinary and cross-sectorial cooperation needed for successful implementation of precision medicine. Having structures and mechanisms in place may in turn influence the culture in a positive manner, to promote a culture of capture, use and sharing of data.

#### **Actions suggested for overcoming barrier**

- Reinforce the fact that the patient owns her data and therefore should be able to share them with whoever she wants.
- Establish Nordic and other international collaborations, such as sharing of variant and classification databases.
- Establish electronic medical record system that facilitates interaction and sharing at a national level.
- Establish solutions and procedures for automatic collection of consent for data sharing and secondary use of data when patients encounter the healthcare system.

## BARRIER: Scepticism to industry involvement

### Barrier description

- Looking to global trends, industry is taking a leading role in technology development. There are clear political policies in Norway stating that industry must be involved in healthcare innovations. Furthermore, there are explicit expectations in the national strategy for personalised medicine to the need of industry partners to contribute to the development of innovative products and services linked to precision medicine.
- Nevertheless, industry struggles to engage decision makers and establish productive projects or innovation partnerships to meet the needs of the healthcare system. Industry actors report that they experience a tendency that healthcare organisations want to develop own solutions rather than purchase commercially available products.
- This could partly be because there is little tradition for industry involvement in healthcare innovation, partly because public employees have little competence in the possibilities of innovative procurements, and partly because there are little incentives for budget holders to involve industry.

### Actions suggested for overcoming barrier

- Focus innovation on areas where good solutions are not commercially available.
- Address current culture of industry scepticism from a political and top management level.
- Acquire and test available solutions and technologies to a larger extent than currently practised.
- Where commercial technologies are available these should be tested for use in the Norwegian healthcare system rather than developed locally.

## Example: Organisational barriers

Molecular tumour boards, where genetic information is included in MDT meetings, is becoming common practice in many countries but not yet in Norway.

The MetAction Trial funded by The Research Council of Norway demonstrated that including DNA sequencing information in MDT meetings provided more treatment options for end stage cancer patients also for patients at OUS.

Implementation of broad genetic sequencing of cancer patients will require involvement of a larger number of people with different specialties <sup>[57]</sup>.

The process is resource-intensive and requires a clinical genetic pipeline for cancer and inclusion of new competences such as bioinformaticians and molecular biologists to interpret the information in the clinical decision making process.

Clinical implementation of the resource-intensive practice of molecular tumour boards is delayed as 1) the organisation at OUS is not rigged for the logistics it entails and 2) the health economic benefit remains to be demonstrated.

## 4.4 Barriers related to competence and knowledge

### **BARRIER: Lack of relevant competences (data scientists and bioinformatician) within the healthcare system**

#### **Barrier description**

- Data scientists and bioinformaticians are expected to play an increasingly important role in clinical decision making, and a lack of access to these competencies could slow the implementation of precision medicine. For many areas, this competence need to be available close to the front line of medicine, and should not be organised as standard operational ICT support backend. The need for local data science competence must be balanced with the need to sustain large enough groups to build attractive and competent work environments.

#### **Actions suggested for overcoming barrier**

- Build on existing well-functioning ICT groups at hospitals with critical mass and give them access to modern infrastructure. This would improve recruitment and retention, and create pan-group competence networks for ICT and data scientists.
- Create an understanding of the need for complementary competencies by demonstrating gains in efficiency and quality.
- Increase focus on development of relevant competences in the education system. Funding of more industry PhDs within the data science and biomedical disciplines with joint supervision from clinics and industry, establish professor II positions within the same disciplines (biomedical, ICT), and finance relevant scholarships, internships, and exchange students.
- Increase status and salaries for data scientists and bioinformaticians at hospitals.
- Ensure availability of data scientists and bioinformaticians close to the clinical front line. These competencies should not be organised as backend ICT support.
- Raise awareness in the population and at the political level to recruit more ICT personnel, such as bioinformaticians, into healthcare.

## **BARRIER: Lack of the cross-disciplinary understanding (clinical, informatics, legal, data science, etc.) that is necessary to use data for clinical decision making**

### **Barrier description**

- Implementation of precision medicine requires collaboration between different competence groups such as clinicians, informaticians, data scientists and legal staff. This collaboration will challenge the traditional organisation of the healthcare system which is sectioned based on medical specialities.
- Current strategic decisions will shape the future health system, and principal decision makers should be informed about needs related to infrastructure, technology, competences and knowledge, as well as about optimal organisation of processes and competences relevant for implementing precision medicine.
- Create cross-disciplinary advisory reference groups at HF or RHF level that can build a knowledge base and act as core organisation and advisors for development projects. Include external advisors from industry.
- Encourage hospitals to establish local ICT data science teams with closer ties to medical specialities.
- Establish knowledge hubs for dissemination of knowledge across entities and geography. These hubs should be tied to registries, patient and healthcare systems, and to international resources for sharing of data, and should also be available to researchers.
- Speed up the effort to recruit clinicians into ICT and hire ICT-competence close to the clinic
- Include the digitalisation of health care into the curriculum of medical school and other clinical curriculums

### **Actions suggested for overcoming barrier**

- Norway could take learning from other countries such as the UK, the USA and Denmark and from other industries in developing public-private partnerships for collaboration on innovation and development of operational excellence, learning and sharing.

## **Example: Competence and knowledge barriers**

A young patient was experiencing arrhythmia, but doctors could not identify any issues. A genetic test could have identified an inherited genetic disorder of muscular dystrophy resulting in dilated cardiomyopathy – the growing of her heart. Unfortunately, this genetic disorder was not identified as a possible cause by her doctors and the test was never requested.

For many years, the patient's health declined. She frequented the ER with symptoms of arrhythmia, but felt labelled a hypochondriac and even admitted to psychiatric care for imaginary symptoms. The patient remained undiagnosed until suffering cardiac arrest. At this point the heart was so damaged the only option was a heart transplant. Only three years after the transplant did a dedicated doctor identify the underlying genetic issue.

## BARRIER: Lack of awareness among patients and clinicians about the benefits of precision medicine

### Barrier description

- The clinical uptake of precision medicine currently depends on the awareness and motivation of healthcare personnel and on the demand from patients and patient organisations.

### Actions suggested for overcoming barrier

- Develop and implement solutions for joint decision making, involving both clinicians and patients.
- Increased patients' involvement through e-learning, research projects, educational electronic consent solutions and clinical studies.
- Enable the inclusion of patient-generated data in healthcare, spanning from information on patients' and their families' knowledge of disease history to information from wearables.
- Increase the effort to make transparent the results and methods from different healthcare providers to strengthen the patients' position when choosing healthcare provider.
- Involve and empower patient organisations to drive changes.
- Create and disseminate new knowledge derived from biobanks and registries to provide a better basis for decision making.
- Improve the knowledge model to make new studies on patient groups and specific cases available more quickly.
- Systematic teaching of new knowledge to health personnel.

The patient's family was then followed up and offered the symptom-delaying treatment that the patient did not receive until it was too late.

There is generally low awareness about rare diseases among patients and caregivers. The role of genomics in healthcare expands and the rate of new diagnoses accelerates, increasing the need to train physicians, genetic counsellors and medical geneticists to provide correct and relevant information to

peers, and to provide genetic counselling of patients and their families to allow for informed decision making. Still, there are no individual clinicians who can have a full overview of all rare inherited diseases. Continuous inclusion of information on genetic diseases in a clinical decision support tool could enhance systematic distribution of knowledge to clinicians.

***The patient has consented to sharing this story in this report.***

## 4.5 Technological barriers

### BARRIER: Lack of modern, open and flexible ICT infrastructure platform

#### Barrier description

- ICT infrastructure and processes of the Norwegian healthcare system are not capable of supporting the implementation of precision medicine.
- Currently, no suitable infrastructure for bioinformatic applications exists in hospitals. The Service for Sensitive Data (TSD) at Oslo University is today preferred not only as a platform for high-performance computing (HPC), but also as a general platform by Oslo University Hospital researchers and innovators.
- ICT and clinical decision support (CDS) are critical for achieving implementation of precision medicine. The pace of development with many specialised applications and data sets means that a modern platform environment is required. Without it, there is nowhere to run modern applications, and the cost to test, develop and maintain new technologies is too high.
- No suitable platform for health Internet of Things (IoT) is available outside the traditional medical technical unit (MTU) space. Today it is not possible to connect different applications and data sources, such as outcomes of whole-genome sequencing, with other clinical results and findings.

#### Actions suggested for overcoming barrier

- Establish overall ICT architecture for precision medicine
- Move from current monolithic ICT infrastructure model towards a platform-based flexible and user-centric solution. This entails central control of data-layer and API, allowing for local adaptations in the overlaying structure – microservice and self-services.
- Invest in modern digital platform (“platform as a service”) that allows development, use and management of applications, and to which all relevant stakeholders will have controlled access and can communicate.
- Provide access to HPC capabilities inside the hospital environment (for example by connecting TSD with the HSØ network or through a national joint solution for research and healthcare.)
- Create an environment for the testing needed for development of the innovative technologies and solutions required to support the implementation of precision medicine.
- The test environment should include test versions of EMR and other crucial systems, with access to both dummy data and real production data.
- Demand that all clinical systems should support flexible functionality for clinical decision support
- Ensure that the ICT governance allows flexibility and local adaptations to facilitate innovation and reduce time to implementation.

## BARRIER: Primary clinical data is not captured or made available for analysis

### Barrier description

- Clinical decision support systems often require access to structured primary data. Primary clinical data are not captured or made available, neither for big nor small data analysis.

### Actions suggested for overcoming barrier

- Integrate medical-device data in future ICT infrastructure and write primary data to accessible data lake.

- Medical device procurement requirements should include a plan for data management to ensure availability and transparency.
- Establish quality indicators and assurance requirements to incentivise reuse of data in future analysis.
- Establish opportunities for clinical research to incentivise secondary use of data.
- Invest in ICT tools and equipment for daily clinical work.
- Preserve the raw data generated f. ex in ECGs
- Capture treatment outcomes and funnel back to the system for future learning and quality improvement.

## BARRIER: No direct communication between ICT systems

### Barrier description

- The lack of standardised application programming interfaces (APIs), protocols and data formats in critical applications, such as EMRs, hinders the exchange and reuse of data between systems, internally within the hospital, between health regions and systems, and internationally.
- One example today is that the EMR solution in HSØ does not allow integration of pharmacogenomic reports in any meaningful format except as scanned pdfs.

### Actions suggested for overcoming barrier

- Adopt an API-economy view of systems integration and define a national standard for healthcare API's in cooperation with the other Nordic countries. A modular

system with APIs that facilitates connections and sharing could provide smooth user interfaces and access to necessary information across data sources and allow for flexibility in future developments. This will also allow for private sector adoption as the market potential for API investment in their solutions is attractive.

- Include procurement requirements to ensure that clinical applications have open APIs towards 3rd-party suppliers and equipment.
- Favour open systems with standard data models and strive to separate data and access to data from applications
- Increase the capacity for systems integration.
- Build increased capacity inside the health maintenance organisation (HMO) for ICT systems integration.

## Examples: Technological barriers

### Example 1: Access to patient data across health entities

Patients with rare diseases are typically followed up regularly at two locations: a local hospital and a university hospital. They are typically tested 4–12 times per year for various indicators. Treating physicians at both hospitals need access to the test results in time for further processing, and they need the information to be complete. There are no digital solutions in place today to facilitate the access to test results, and communication is through polyclinical notes or epicrisis. Investigating missing information by phone is time-consuming, and the patient cannot be expected to carry this information.

Test results may also be important in annual status reporting, and for registration in quality registers if the patient has consented. Most health registers are based on manual entry of data. The quality of the registry is reduced if the information is incomplete. Following up through email and by phone to gather missing information from the different hospitals and treating physicians is time-consuming.

### Example 2: Loss of data

In HSØ, ninety-five per cent of medical records are digital <sup>[59]</sup>, but the data formats are unsuitable for digital processing. For example, ECG data are digital, but at OUS they are stored in the EMR as images after having been printed out and scanned for storage. This process renders the source digital data inaccessible for later analysis.

### Example 3

OUS ICT does not provide an infrastructure for secure high performance data processing and storage. Consequently, genomic analyses for clinical use are performed in the secure infrastructure of the University of Oslo (TSD). This infrastructure is not designed for such use and does not provide 24-7 user support and availability. Furthermore, working on separate infrastructures hinders efficient solutions in genomic analysis for both variant interpretation, crossdisciplinary workflows and for the integration of genomic data back in the EMR.



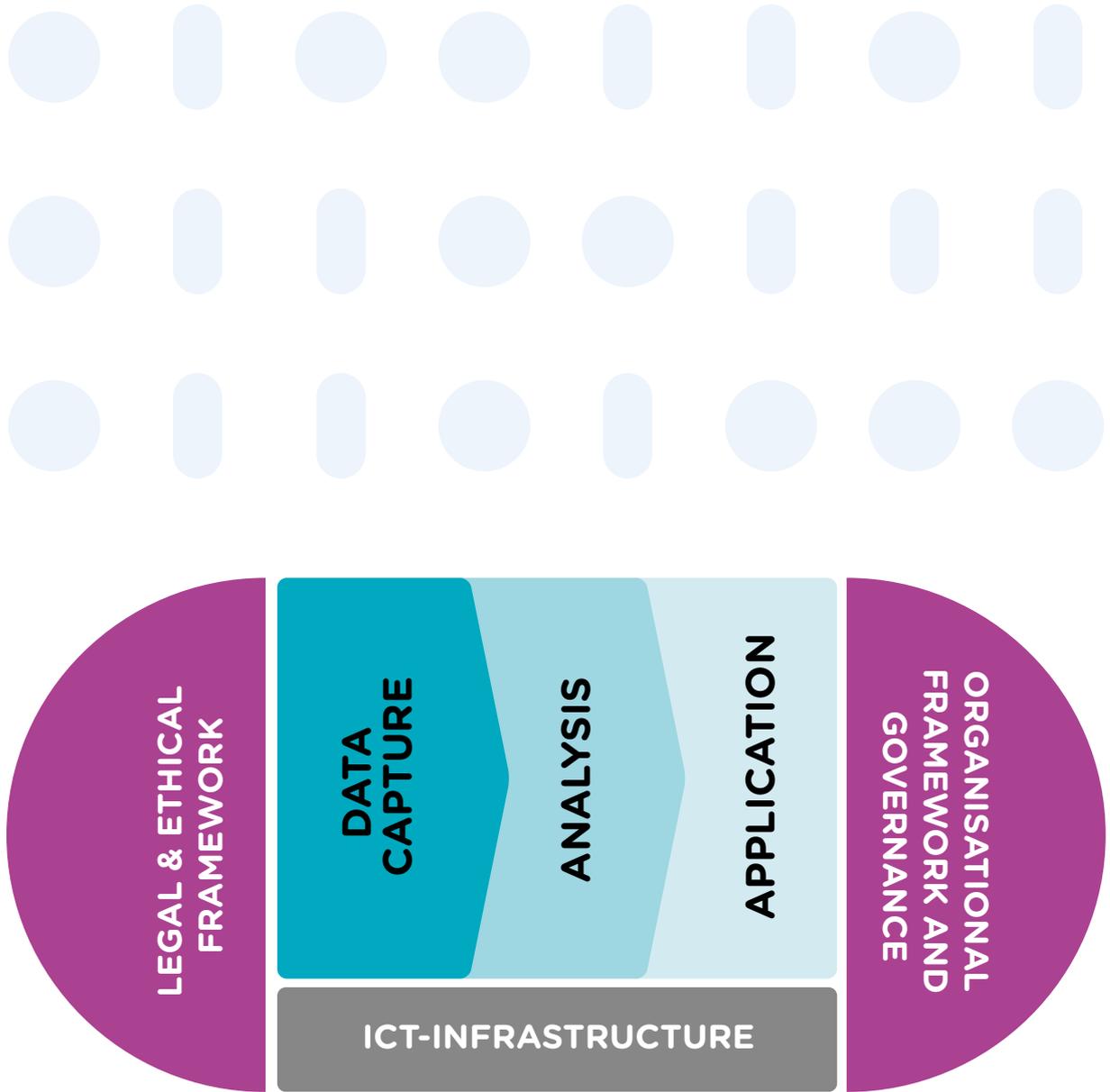


Figure 9: Generating knowledge from advanced analysis of data to improve diagnosis, prediction and choice of intervention requires broad data capture and well-functioning ICT infrastructure. Technologies enabling precision medicine are used within current legal and ethical frameworks, and within current organisational capabilities and governance models.

## 5. Tools and technologies enabling Precision Medicine

The focus of this section is ICT as an enabler of precision medicine. First discussing how we can use ICT as a tool at the point of care, then working our way back through analysis and into the initial data capture. Finally, we describe the infrastructure enabling the whole process. Figure 9 summarises the capabilities that is needed in order to advance further.



### 5.1 APPLICATION

The true value of precision medicine practices is correlated with our ability to infuse the clinical practice with the knowledge generated from advanced analysis of our data. By “application”, we mean the ways that knowledge affects the services offered to the patient, either indirectly through research, guidelines and clinical decision support, or directly through devices or software.

International studies show that the time from the emergence of new knowledge through research until it has become standard procedure 17 years on average <sup>[60]</sup>. In a precision medicine paradigm, new knowledge must be available to clinicians and patients as soon as evidence is sufficient.

The digitalisation of healthcare offers new ways of bringing knowledge more directly into the hands of clinicians, healthcare workers and patients. This section gives an overview of the means and tools that are driving this field.

#### 5.1.1 Clinical decision support

Clinical Decision Support Tools are one way to quickly transfer results from clinical research to practice at the bedside <sup>[5, 61]</sup>. The idea is that through using modern EMRs and other digital tools, users have information available to them provided through different ways of clinical decision support (CDS). The range of different ways CDS can work is broad, from forcing users to make certain choices to light nudging by informing them about best practice. The effect of CDS on clinical outcomes, however, depends on the way the system is designed, and varies from highly positive to highly negative <sup>[62]</sup>.

The easiest way of implementing CDS is to integrate it into the tools that clinicians use daily. Modern EMRs are becoming more than archives of paper documentation, and now support work flows and are designed to provide decision support at the point of care <sup>[7]</sup>. This includes CDS functionality for users and for the provider organisations to develop and manage the CDS rules. CDS can also be delivered as independent software, for example in web interfaces, but such software requires the user to switch windows and actively choose to use the service.

In modern ICT architecture, the right way to think about such decision support is to develop standard ways of communication between the front end the user sees, the CDS motors, and the data the CDS uses to generate rules

or models (where these are data driven). This requires common standards, both technical and semantic that are not in place today. The industry is working on developing such standards, which will open the playing field for more actors and help accelerate the development of knowledge needed to create good CDS solutions.

As large organisations are starting to implement 3rd-generation EMRs with CDS functionality, they learn that the challenges to implementation are largely about setting up their organisation such that the new functionality is used in a way that is best for patients. Centralising clinical decisions through CDS requires that experts who are to develop and manage the rules or models work together in new ways and be willing to embed their knowledge in digital tools <sup>[63, 64]</sup>.

Longer term, increased use of CDS also potentially enables significant task shifts in healthcare provisioning both within and outside organisations. Within organisations, CDS can enable clinicians and healthcare workers to perform tasks that today require greater expertise. Within the radiology field, some of the “easier” tasks of describing musculoskeletal x-rays have in some departments been handed over to handpicked and trained radiographers, although not without resistance from radiologists. Given CDS tools that help radiographers interpret images, one could imagine that it would be easier to hand such tasks to other, more available personnel.

### 5.1.2 Patient-oriented decision support

For many patients with chronic diseases, managing their own disease is a goal which both frees up time and enables the patient to “own” their challenges to a larger degree, making it easier to live with them. Such patient empowerment is one of the goals in the political ambition of creating patient centred care.

The interface of decision support systems can have many forms. Mobile applications may be a major interface, but not the only one. Digital assistants in the form of chatbots or avatars are already doing a lot of customer support in other industries, and what works well in other industries will also be welcomed by patients if the advice provided is trustworthy.

From a precision medicine perspective, one of the great advantages is that such technologies can increase information bidirectionally, both to and from the patient. A self-learning system will then be able to collect and digest the input and improve the model for giving advice to the next patient. Depending on the type and amount of input the patient gives to the system, the system will not only be able to improve the models incrementally, but might also give rise to new hypotheses and factors affecting treatment.

One of the interesting questions concerning patients-facing clinical support tools is to what degree they will be provided by today’s public healthcare providers or by other commercial or not-for-profit providers who will reach out directly to patient groups. Given the slow speed of digitalisation in the public provider space today, there is a significant chance that many other players in the field will have a head start. Such a development can be both good and harmful, depending on the quality and reach of the services offered.

### 5.1.3 Intelligent medical devices

The most automated use of the tools presented in this section is in the automation and embedding of intelligence directly into devices and equipment used to diagnose and treat patients. The most typical example is an “intelligent” insulin pump where self-learning algorithms govern the release of insulin directly into the blood flow using not only continuous blood sugar measurement, but also other input like physical activity and nutrition intake. The first

# Machine learning in clinical decision support

As the rules behind CDS move from being manually developed to being automatically generated based on machine learning and big data, considerable work has been done on how to implement such functionality safely and securely. One of these initiatives has come from The CDS Coalition, a group of software developers and medical device manufacturers in the US <sup>[65]</sup> who have devised five steps that developers of machine learning could follow to be transparent <sup>[66]</sup>.

Explain what can be explained. Don't make the problem bigger than it has to be. If the software is a blend of expert systems and machine learning, and if a particular recommendation is based on expert systems, such as simply looking up the drug allergy in the patient's EMR, following a simple computational model, or recommending a treatment because it is cheaper, the recommendation ought to reveal that reason.

Communicate the quality of machine-learning algorithms. When the source is truly machine learning, the software must reveal that source, along with information that will help the user gauge the quality and reliability of the machine-learning algorithm. Through a page in the user interface that can be periodically updated, the developer could explain to the user the extent to which the system has been validated and the historical batting average of the software. That context helps the user understand the software's overall reliability.

Describe the data sources used for learning. Providing a thorough explanation of the data sets used to feed and test the machine can provide important context and assurance to the clinician.

State the association as precisely as possible. With machine learning, really what we are seeing is an association when something in patient-specific information triggers an association to what the software has seen in other cases. Although the software can't articulate exactly what it is about the data that triggers the association or even what features it looked at, that doesn't make it any different than a radiologist who points to a place on an image and says, "I've seen that before, and it's been malignant". Much of what we "know" in medicine is in reality just associations without a deeper understanding of a causal relationship. Software built on machine learning needs to explain that it has spotted an association, and state as precisely as it can the details of that association.

Convey the confidence level. While software based on machine learning does a miserable job of explaining the clinical logic it follows, machine learning excels at communicating its confidence level in reaching a particular recommendation. And that capability is quite valuable. That information helps the user decide how much deference to give a particular recommendation.



generations of such technology is already available and will act as prototypes for the next and more “intelligent” devices <sup>[67]</sup>. This is generally coined as edge computing, where central deep learning can be implemented on the edge devices because of highly efficient algorithms and increased processing power in the devices.

The next frontier of such automation is the robots and other equipment used in the OR. Even if it is a long way from routine clinical use, this is a field to watch as data become more available and algorithms become better.

#### 5.1.4 Improved research

Precision medicine techniques will also affect traditional research. The improved infrastructure, data capture and analysis described in the previous sections are providing researchers with a new and better arsenal of tools. A good example is how researchers in a recent study combine genetic knowledge, laboratory experiments and big data registry analysis to show the probable positive effects of a well-known asthma drug on Parkinson’s disease <sup>[68]</sup>.



## 5.2 ANALYSIS

The objective of all precision medicine analysis is a simple one: to predict what available treatment

will best benefit the patient at hand. Reaching this objective using the different data sources mentioned in section 5.3 requires different techniques, tools and competences, depending on the patient at hand and available information. The availability of big data has spurred interest in new and promising techniques such as machine learning that complements traditional statistics.

### 5.2.1 Big data – statistics and machine learning

At the end of the previous millennium, the New England Journal of Medicine celebrated the most important medical developments of the past thousand years: together with fundamental inventions, like anaesthesia and the discovery of cells and their substructures, the journal lists “applications of statistics to medicine”. The typical tasks where statistics is fundamental are those comparing conditions, understanding effects and predicting processes in uncertain situations.

Statistics is the instrument needed to quantify evidence for a theory when we do not understand the underlying biomedical processes and mechanisms. The association between smoking and lung cancer was established statistically long before the mechanisms involved were described. Today, statistics is still essential for progress in medicine by delivering methods needed at all stages, from randomised clinical trials to high-throughput genomics, from medical instrumentation to prediction of survival.

The use of Big data in health challenge traditional statistical methods. For example, when looking for biomarkers which are predictive for a certain trait, one repeatedly tests thousands of potential biomarkers, to find the very few which are useful. In such a case, the traditional 5% significance level must be abandoned, as it would lead to a much too large number of false discoveries, in favour of much smaller significances, controlled by false discovery rates.

Besides statistics, machine learning has established itself as a very important tool for discovery and prediction. Machine learning learns to predict a clinical trait (output), say, by using previous examples of relationships between clinical variables (input) and the output. A model of the relationship between input and output is improved gradually, by testing how the model produces outputs given inputs, by comparing the model to the truth, and by correcting the model sequentially. Statistics is usually not using data sequentially, but all data together at once.

Both sciences allow to (i) classify, (ii) cluster, (iii) estimate associations, and (iv) predict. Classification is the task of assigning units, such as a sample, patient, gene, or drug, to one of the classes in a list of possible classes. Labelled/classified training data are used to estimate a model and to train an algorithm, so that it can infer the label for a new (unlabelled) case. The SPAM filter in your laptop classifies every email you receive as either SPAM or not SPAM, and its efficiency depends on how well it has been trained on labelled emails. In clustering, the classes to which the units will be assigned are unknown. Units in the data are not labelled and we wish to divide them into groups, so that within a group data are similar, and between groups they are different. For example, one may wish to divide a group of breast cancer patients into separate clusters, according to the gene expressions of each patient. In each cluster, some features are shared. In estimation and prediction, for example, when one wishes to predict time to recurrence in cancer-based on clinical and genetic covariates, the aim is not to assign a label to each unit. Data are a collection of observations (covariates, time to recurrence) and the algorithm implements a statistical rule that predicts the value of a new sample, where only covariates are known and not time to recurrence. Covariate selection is an important task, answering the question of which of the covariates are truly responsible for an outcome.

To quantify the uncertainty of the prediction, it is important not to reuse information as this would artificially reduce the variance and thus lead to falsely precise predictions. Bayesian approaches are particularly interesting for integrative analysis. Overfitting is another important phenomenon seen when models are trained to be wonderfully precise on training data, but fail on test data. There are various statistical approaches to control overfitting, using the cross-validation method, which iteratively leaves part of the training data out when fitting the model.

**The objective of all precision medicine analysis is a simple one: to predict what available treatment will best benefit the patient at hand.**



It is possible to distinguish between machine learning and statistical approaches which are purely data driven or model based. Data-driven methods do not require specifying a data-generating model, which is estimated from the data themselves. For example, functions can be estimated non-parametrically using flexible splines or wavelets expansions, rather than assuming a specific parametric form, as would be the case in model-based approaches. Reinforcement learning, for example, is a way to estimate an unknown loss function by trial and error, assuming that an algorithm which is told of its mistakes and successes can learn how to avoid the former. Deep learning is a very popular data-driven approach for prediction which works well in cases where large training data are available, which is not always the case in medicine. Model-based approaches require the availability of a good statistical model which describes the important features of a process.

For example, to predict the risk of an infection in a patient, one would need to determine how this risk depends on the patient's conditions: her treatment, properties of the environment, etc. It is not necessary to design the correct model; it is enough to express a first-order approximation, which captures the main effects and is precise enough for the prediction one wishes to make. There are many advantages of model-based approaches. Models have a certain internal solidity, and they can be discussed, criticised and improved. They allow one to compute the uncertainty of the prediction because they describe how data can vary around a null model. Because they are mechanistic, models can be used to simulate the outcome under various hypothetical conditions, and such simulation allows one to determine optimal interventions in silico.

### 5.2.2 Small data from big data – similarity analysis

Another way to look at the task of predicting the

best possible treatment for the patient at hand is to consider match making from a small-data perspective, that is, to find the few patients in a large cohort that have the same traits and use those traits to predict the right treatment for the patient.

As described in section 1.1, the gold standard for evidence based medicine is randomised controlled studies that can show improved results compared to control groups in large cohorts of patients. This approach, however, is merely a proxy for addressing the objective of predicting the best possible treatment for the patient at hand <sup>[73]</sup>. To overcome this barrier and move to precision medicine, one method commonly used in the field of rare genetic diseases is match making (see information box on genomics and bioinformatics)

On the simplest level, similarity analysis is about creating an infrastructure which allows locating patients with the exact same condition as your patient. The task might seem trivial at first, but it requires tedious work in work processes, standardisation of data elements, secure sharing of data and a governance model that allows for sharing patient information when the match making is done. The richer the data, the more information we can extrapolate to our own patient.

In almost all other clinical domains, the aetiology and dynamics of disease are more complex than in monogenic, rare diseases. To bring the same thinking to such fields, we must understand the different patients in an automated and scalable manner. Dealing with structured data is dependent on different analysis methods described in section 5.2.1, but the tradition in medicine is to describe the patient through a narrative told in plain text. Therefore, the automatic analysis and understanding of such narratives

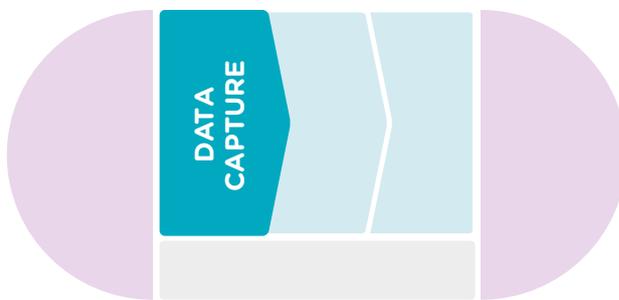


## Machine learning in image recognition

One of the most compelling applications of machine learning on structured health data is automatic image recognition. Feeding self-learning algorithms with large amounts of pictures has proven useful in other domains, and optical character recognition, facial recognition, and image-based search are now standard functionalities in many applications. The same methods used in healthcare are on the verge of reaching clinical usability because, for example, it has been shown that such methods can support radiologists in their interpretation of pneumonia in lung x-rays <sup>[69]</sup>. In Norway, the Lighthouse project DoMore! <sup>[70]</sup> seeks to improve diagnosis by utilising Big Data and software-driven automation of pathology.

The potential seems to be huge. Beyond the support of and eventual automation of the interpretational work done by humans today, algorithms have the potential to perform image analysis that the human brain is not capable of. One example is to interpret the underlying data from equipment such as MRIs that are not possible to display in a good way for the human eye. Another is to put several layers of information “on top” of each other to find patterns that we humans cannot see. Within radiology, the field of radiomics is emerging as such a domain <sup>[71, 72]</sup>.

have become major tasks in advanced health analytics [74], see information box on natural language processing.



### 5.3 DATA CAPTURE

The essence of precision medicine is knowledge: knowledge about the patient, her health, and her particular condition. The more knowledge we can capture and process, the closer we can come to true precision medicine. And with today's medical technology and all the data generated by it, combined with digitalised capture and storage, we have vast amounts of data. But herein also lie the challenges because an ever-increasing amount of data also adds to the complexity and to the challenges of making all these data available for analysis.

There are several well-known difficulties with extracting knowledge from health data, the first being a lack of standards that keep up with the data generated. Modelling the extremely complex coordination of our biology and all the factors that add up to what we call our lives is no doubt harder than modelling a financial transaction or the flow of oil through a refinery. Modelling difficulties are the main reason healthcare is lagging behind other industries in standards development and dissemination. Slowly, however, international standards are emerging

and being agreed upon. Driven mainly by the need for exchanging information between users and systems, we can at least to a certain degree say that we now have a fairly comprehensive toolbox of internationally recognised standards for the large bulk of health information we are capturing. Nevertheless, comprehensively applying these standards to the data captured takes significant time.

Second, the most common architecture today involves storing data within applications where they are generated. There are exceptions, for example in the radiology field, where vendor-neutral archives are replacing the applications as the main place for storing the data. But overall, data are still stored within applications, according to the data model in the application, and are dependent on either standard interfaces like APIs or custom-built integrations to be transported out of the application to be reused and analysed for other purposes, such as precision medicine purposes.

#### **An ever-increasing amount of data adds to the complexity and to the challenges of making all these data available for analysis.**

The third challenge, but perhaps the hardest to overcome, is the difficulty with data quality. "Garbage in –garbage out" is a highly relevant description, also in the healthcare data space. The core issue is that data captured for one purpose are used for other purposes. When users or sensors or algorithms do not have secondary use and analysis "in mind" at the point of capture, the risk is that the data are just not fit for it. When the Summary Care Record solution ("Nasjonal kjernejournal") opened its data for all Norwegian inhabitants to see what was registered in the National Patient Register about their visits to specialist healthcare, the solution was widely criticised in media, because people saw that the information was not necessarily correct or complete [78].

# Natural language processing (NLP)

Semantically explicit knowledge representations and domain models have been used in information systems many times, but have reached a new level of maturity with the advent of semantic web technology. Essentially, such technology involves logic-based representations of commonly shared knowledge about the world, work, science, and information, and it has revolutionised the natural sciences as well as engineering.

The field of natural language processing deals with automated processing of natural language data, such as text and speech, in important application areas such as search, information extraction, and machine translation. The subfield of clinical NLP focuses on the application of NLP techniques to clinical data and has made significant progress over the last decade.

Clinical data typically consist of patient electronic medical records<sup>1</sup> collected over short or long periods. Clinical NLP can, for instance, be used to predict the risk of occurrence of a disease by automatically analysing patient records through task-specific rules and applying machine-learning techniques. Moreover, clinical NLP can also consist of extracting relevant parts of the EMR or summarising an EMR for use by the medical practitioner to diagnose a disease.

General challenges for application of NLP include <sup>[75]</sup>:

- Lack of big data
- A lack of common standards for presenting EMR across countries
- Unedited text (i.e., text which is not clean)
- Longitudinal data (collected over time)
- Short documents (consisting of a few hundreds of words)
- Ungrammatical text showing domain-specific abbreviations

In summary, the text is “noisy”, and typical NLP systems trained on clean data might not perform so well on EMR data. Therefore, significant effort goes into tailoring a standard NLP system for a specific task.

Today, most NLP tools are language-specific and little exists in terms of clinical NLP tools for Norwegian. Clearly, a real need exists for adapted NLP tools for clinical Norwegian.

The problem, however, was the quality of data in the underlying National Patient Register. A positive aspect, however, is that this example shows that opening up our health data establishes the necessary feedback loops to correct the data and hopefully improve the capture process. This mechanism will gradually increase data quality as more and more data become available, but along the way, we should be extremely careful about trusting data of unknown quality.

### 5.3.1 Electronic medical records

The electronic medical records (EMRs) were originally the electronic version of the log that every physician used to document patient consultations, whether in a GP office or an outpatient clinic, or in a bedside consultation in a ward round. These systems have over time grown and become the main digital tool of all health personnel, also encompassing the patient administration system (PAS), specialist modules, nurse documentation, radiology and laboratory information systems (RIS and LIMS). The most modern systems also incorporate functionality that exceeds documentation alone, and give users process support, clinical decision support (CDS), and advanced analytics capabilities as described in sections above.

The main core of the data captured in the EMR is still the same as in the original paper record and in the early EMRs – descriptions of what the clinician observes during a patient consultation. Originally, this information was a more or less prosaic description, formatted as free text. Over time, the need has arisen for including more structured elements in the record. Such structured elements serve several purposes. One is to ensure that the data are captured for primary purposes: data is better collected when you use a structured registration of symptoms in cancer patients <sup>[79]</sup>. Furthermore, structured data are the basis for most analytical methods. Capturing the information in a

structured form is therefore the preferred way for everyone concerned with secondary use of data. Structure is also, at least with today's technology, a prerequisite for using data in clinical decision support and process support. These benefits argue for an increased use of structure in EMRs, but there is a trade-off. The field of interest for clinical personnel is not merely the easy-to-format information like "has the patient urinated or not?" and "is this a clinical depression according to the MADRS score?" Relevant information like the patient's feelings, the vague description of an unusual light-headedness, or her relationship to her deceased mother cannot easily be captured as structured data, at least not without a significant loss of richness in information. Another common and relevant criticism is that structured data often takes a lot longer to enter, and that increasing granularity leads to overwhelming amounts of choices (again leading to "garbage in" when clinicians give up). That complexity, along with tradition and culture, is why clinicians are sceptical of replacing the prose with tables and checkboxes.

The governmental "One citizen – one record" project in the Directorate of e-Health <sup>[5]</sup>, and the documentation from it, presents a very thorough picture of the status and challenges of today's EMRs in Norway. The directorate of ehealth has created an overview of health data sources in Norway, see Figure 13. As part of the documentation, a description of the maturity of the solutions was written by Gartner <sup>[7]</sup>. The main finding is that although Norway was an early adopter of EMRs, our systems have not evolved into the modern EMR era, but are still advanced versions of the paper record, merely adding some process functionality like PAS, RIS, and being able to show lab data. Combined with very little structured data input, most of the available data from EMRs is prose and needs NLP in order to be digitally analysed.

	Reference knowledge	Patient data from own healthcare entity	Patient data from other healthcare entities
Unstructured	<ul style="list-style-type: none"> <li>Peer reviewed literature etc.</li> <li>Guidelines</li> <li>Procedures</li> </ul>	<ul style="list-style-type: none"> <li>Electronic Medical Record</li> </ul>	<ul style="list-style-type: none"> <li>Electronic Medical Record</li> </ul>
Structured	<ul style="list-style-type: none"> <li>Decision support rules and algorithms</li> </ul>	<ul style="list-style-type: none"> <li>Digitalised test results</li> <li>Connected medical devices</li> <li>Patient-generated data</li> <li>Patient context data</li> </ul>	<ul style="list-style-type: none"> <li>Digitalised test results</li> <li>Connected medical devices</li> <li>Patient-generated data</li> <li>Patient context data</li> <li>Health registries</li> <li>Open research data</li> </ul>

**Table 6** Data sources contributing to the basis for clinical processes (own analysis)

### 5.3.2 Digitalised test results

The other traditional main source of information about a patient’s status is what we refer to collectively as test results. In a broad sense, these include everything that we can measure by performing different tests in laboratories, in radiology departments, in electrophysiology and many new methods to examine a specific feature of the patient and her condition.

From a data perspective, the principal advantages of such results are that they are 1) mostly structured and at times in standardised formats, 2) more reliable because they are more or less automatically captured through equipment and processes with no or little room for human variation, and 3) easier to anonymise and thereby less risky from a privacy perspective.

Throughout the last century, the different types of equipment, methods and modalities available in modern facilities have multiplied, and daily we have access to new measuring methods that give us new insight into each

person’s health. The flip side of this development is that it is hard for the information models and the standards to keep up, and new modalities will inevitably be introduced storing information in different formats. Eventually, consolidation and standardisation catch up, but in the meantime, we must live with a fragmented information model where different providers, applications, and equipment store and handle the structured information in separate ways.

Two of these structured data types play special roles in personalised medicine: genetics because of the particular potential for understanding individual differences due to genetic variation, and all the radiology and pathology images because of the recent advances made in image recognition.

### 5.3.3 Connected medical devices

The structured data described in the previous section can be manually entered after, for example, counting the number of breaths per minute, giving respiration rate, or it can be harvested directly from medical equipment,

the latter being more and more abundant in the clinical work space. Most patients in hospital have their simple vitals measured by electronic devices, and if patients enter the ICU, everything that can be measured is measured through a sensor, either on the patient herself, or on the equipment we use (e.g., an infusion pump).

The nature of this data is generally that they are simple measurements, very frequently collected along a timeline. The data are usually stored within each device, and then further funnelled into a software application through a wireless or wired network. The application can be either a proprietary application for the device, or the EMR or a more designated general system for collecting structured data, like the “electronic charting” systems commonly in use in Norway today.

#### 5.3.4 Registries

The data we have described so far are health data captured for primary use by clinicians working directly with patient care. The challenge with these data is that they are not specifically designed for analysis and secondary use.

This challenge has traditionally been solved by establishing registers tailored to such use. Helsedatutvalget, a committee appointed by the Norwegian Ministry of Health, points to three categories of such registries:

- **Central health registries** are national registries regulated by general or special legislation, and the purpose is often population health monitoring. Collection of data is mandatory and to some degree automated. The coverage and quality of such registries are on a high level, but access and use can be challenging <sup>[81]</sup>.
- **Quality registries** are central or local registries designed to ensure quality in the services delivered. These can be used for monitoring new methods or comparing outcomes for different methods.

The input varies from thorough manual input by every department within a certain clinical field to automatic extraction of data by a single clinician to monitor her own patients during a period. The management of these registries is mainly overseen by the trusts.

- **Population-based health surveys and research biobanks** are data sources managed by large projects and programmes with a specific cohort in mind. The data are often characterised by a broad spectrum of different sources per patient, but lack completeness within each targeted cohort.

All these sources represent a great potential in precision medicine, especially when combining them with the primary sources. Such combining, however, poses challenges regarding privacy and secure and controlled access.

#### 5.3.5 Patient-generated data

By patient-generated data we mean all the medical data that are generated in one of these three ways: 1) by medical equipment issued by clinical staff that the patient uses outside the hospital or doctor’s office (e.g., a heart rate monitor issued by a cardiologist), 2) personal devices that generate clinical-relevant data that are possible to use for analysis, like a pulse monitoring smart watch, or 3) manually recorded digital patient data, like patient-reported outcome measures (PROMs) or patient-reported experience measures (PREMs).

The first group can be seen as an extension of the connected medical equipment data covered in the previous section. The equipment is designed to capture structured clinical data. It uses, to a certain degree, common standards and the interfaces necessary to transfer the data into more usable infrastructure. The equipment can either be carried by the patient, like the heart rate monitor, or installed in the patient’s home, such as a digital weight or pill dispenser.

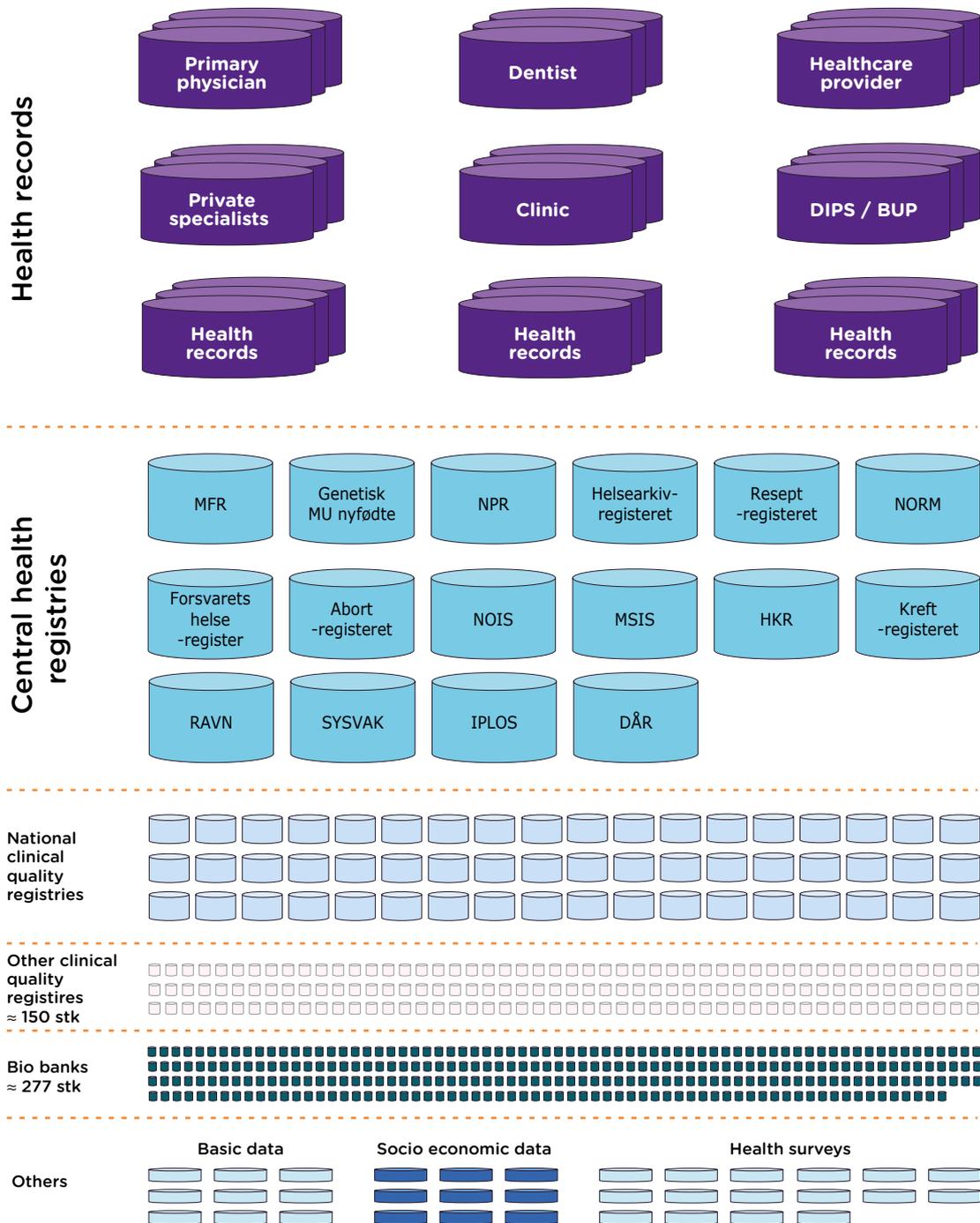


Figure 10: Overview of health data registries and other sources of aggregated health data in Norway [Adapted from 80]

The personal devices in the second group have had an explosive growth and coverage since 2014, as illustrated by smartwatch unit sales depicted in figure 14.

The problem with data captured by these devices is the data's availability for clinical use. These types of data are usually stored in cloud environments at each technology provider (Apple, Garmin, Fitbit, etc.), and it is not a trivial task to transfer the data into the EMR or an environment where they can be available for secondary use. Some global EMR vendors have started working on integrating such data into their applications<sup>[83]</sup>, but in general, physicians are confined to merely looking at their patients' smart phones to get the information.

Since the days when patients had to fill out long paper forms, the input of manually recorded health data has become much easier given the possibility to use web forms and applications, either on phones, tablets or PCs, to get structured digital input. Collection of PROMs and PREMS from digital sources is used in research in several places<sup>[84]</sup>, and primary clinical use of such input is on the rise<sup>[85]</sup>.

### 5.3.6 Patient context data

In the narrowest perspective, precision medicine can be reduced to tailor prediction, diagnostics, and treatment to the biological substrate of our bodies. The complexity of our bodies and minds, however, restricts the knowledge we get from analysing these basic biological building blocks. Even with all the biological data at your fingertips, you cannot predict whether your patient will take his prescribed medicine, nor can you accurately predict which of your patients will commit suicide in the next year. These limitations point to the notion that to come closer to true precision, we should also be able to tap into other sources than those of a purely biological origin.

These sources can contain either data related to a single person or general context data that have a causal relation with the patient and her condition.

Data about every one of us is abundant. Through digitalising communications and transactions, we leave digital tracks of value in a precision medicine context. It has been shown that voice analysis may predict depression<sup>[86]</sup>, and by developing personalised marketing, other industries have shown that tracks we leave can be used for very precise segmentation and prediction of behaviour like voting preferences<sup>[87]</sup>. Whether such information also should be used in a clinical setting is a subject of discussion, and the right to privacy is the principal consideration.

From a privacy perspective, using general and publicly available data is easier. A large study looking at social media posts and weather data could show what we have always thought – nice weather makes us happier<sup>[88]</sup>. Our exposure to weather cannot always be controlled, but other elements in our exposome can be of even higher relevance, like pollution and infection outbreaks.

### 5.3.7 Open data and peer-reviewed information

All the data we have been describing so far have been representations of different phenomena directly influenced by or influencing the patient at hand. But this is only half of the input needed to make more precise models, predictions and decisions regarding our patients. The other half is what we can call general knowledge of health and disease that we can use to interpolate to the single patient or groups of patients at hand. Such sources can include<sup>[65]</sup>:

- Peer-reviewed medical literature, either individual articles curated for this purpose or commercially available databases of such literature

## Smartwatch unit sales worldwide from 2014 to 2018

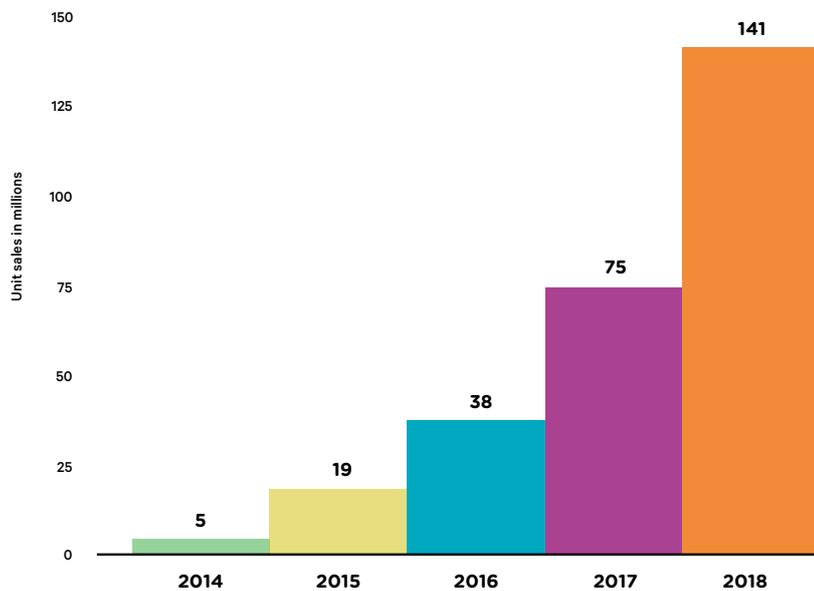


Figure 11 Smartwatch unit sales worldwide from 2014 to 2018 (in millions) <sup>[82]</sup>.

- Medical abstracts from meetings
- Consensus clinical guidelines from medical societies
- Institution-specific clinical guidelines
- Expert medical opinions from individual professionals
- Medical insights gleaned by software using machine learning, through digesting raw medical data from a given population of patients
- The knowledge behind proprietary algorithms and calculators developed by drug or medical device companies
- Clinical trial results not vetted through peer reviewing

- The knowledge used by commercial clinical resources that aggregate and synthesise medical research and evidence

Furthermore, there is a strong movement among the international medical society, especially in the US, promoting the openness of data from clinical studies. Some journals are now demanding access to the underlying data for doing peer review. Transparency of such data is contributing to quality and reproducibility, but poses privacy questions that are still unanswered.

Given the enormous amount of general medical data, their use in personalised medicine comes down to the level of automation we are able to achieve in reading, understanding and using such data. Some vendors have specialised in such automation <sup>[89]</sup>, but recent findings have shown that the task at hand might be more difficult than some have thought <sup>[90]</sup>. Tools must be able to distinguish good quality from bad, but also in a good way show how the data are fed, read, and used in the specific setting.



## 5.4 INFRASTRUCTURE

The capacity and capabilities of modern ICT infrastructure are two of the main enablers for the large-scale adaptation of precision medicine. Secure and effective capture, analysis, and presentation of large amounts of information are possible only if the ICT infrastructure is designed to perform such operations. On a technical level, such operations require scalable storage and high-performance computing. From a security and privacy perspective, such operations require state-of-the-art cybersecurity and relevant access control measures. And from an architectural point of view, such operations require an architecture on all levels that is designed for reuse of data.

### 5.4.1 Storage

The amount of collected data in healthcare (section 5.3) follows an exponential growth curve, a prime example being the availability of genetic data following the dramatic drop in sequencing costs illustrated in figure 15 <sup>[91]</sup>. Together with other fast-growing data sources like imaging, this growth poses serious challenges to today's infrastructure which is not readily scalable. Whether this infrastructure will be delivered as a service from one provider or in more or less proprietary data centres, it will need to be both designed to scale according to the data available, and have the right architecture to support the reuse of data.

### 5.4.2 Processing capacity

Analogously to the requirements for storage, the processing capacity needs of precision medicine are also challenging today's capacity. Genetic pipelines, microbiome analysis, radiomics, digital pathology and a range of new technologies require high-throughput computing that is not available in hospitals today. In Oslo University Hospital for example, such computing is today being done on the infrastructure of the University due to the lack of options inside the clinic, and clinical data has to be transferred to a secure site at the University. Novel analysis tools, like deep learning, which are expected to be used in many medical fields in the future, will increase the need for such capacity even more.

In addition to purely capacity requirements, dedicated software and hardware solutions are being rapidly developed, and efforts must be made to continually monitor and implement them as necessary. As a concrete example, cutting-edge NGS-specific hardware installed at the University of Oslo has significantly reduced the time required for secondary analysis of sequencing data, a major bottleneck in the bioinformatics pipeline. This again makes it more feasible to do rapid whole-genome sequencing analyses, for example of sick infants.

# Data integration and the role of ontologies

An approach to data integration is to use ontologies to model the data and the context / metadata. The links or mappings between data sources can then be expressed in terms of these formal models. Using formal languages like ontologies adds the possibility of using automated reasoning in your integration. Depending on the expressivity of the language, such reasoning can help with detecting or avoiding certain errors or incompatibilities in your data. Making the links between data checkable and reusable is important, since making such mappings can be tedious, error prone, and often demands very specialised competence.

In the EU project Optique, the partners from IFI-LogID gained experience with using ontologies for data integration, using a paradigm called Ontology-based Data Access. In this paradigm, the end user interacts with the data through a single model, called an ontology, made with the end-user group in mind. Each of the underlying data sources (In the case of Optique, relational databases) is connected with small mappings to each concept in the ontology.

A different aspect of integration is that of relating multiple ontologies which cover overlapping domains. Automatic tools for aligning ontologies were also developed in Optique. These techniques may become very valuable in the health domain, since there are many ontologies in use, and connecting, for example, phenotyping and disease ontologies may be valuable.

## BETTER, CHEAPER, FASTER

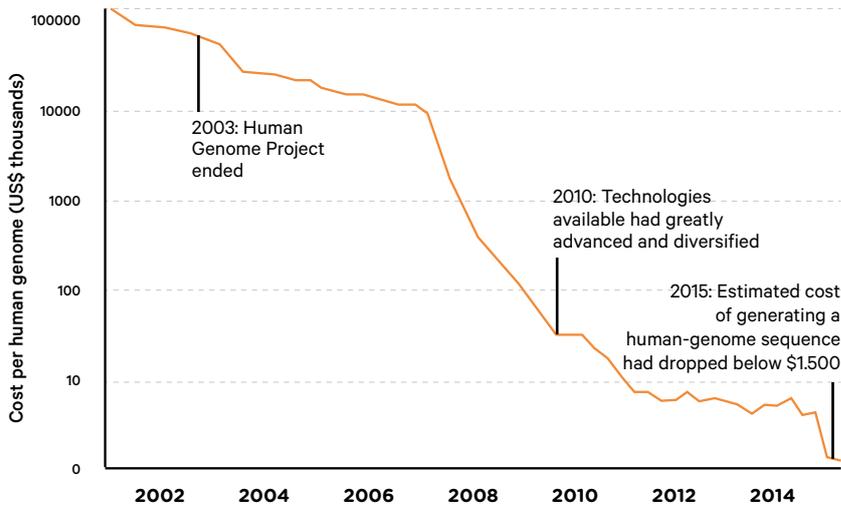


Figure 12 The cost of DNA sequencing has dropped dramatically over the past decade, enabling many more applications [91].

### 5.4.3 Networking and transmission

Along with the increased capture of data from devices and the Internet of Things, networking and transmission capabilities are becoming increasingly important. Such capabilities include not only fast and encrypted transmission, but also a flexible architecture that allows for devices and users to move within hospitals and between the hospital and home. Higher requirements for example for transmission speed can have consequences for example for how close a data center must be placed the clinical facility it is serving.

### 5.4.4 Information security and privacy

Maintaining data confidentiality, availability, and integrity as health data are exploding is no easy task. With the rise

of cybersecurity attacks, along with increased awareness of possible privacy breaches in hospitals [92, 93], there can be no talk of infrastructure without information security.

We will not comprehensively discuss the different measures of modern information security here, and the overall challenges of privacy are described in section 6. Main components include cybersecurity defence, access control, logging and monitoring of access, and use to detect and avoid both external breaches and internal anomalies. And basic infrastructure measures like backup, archiving, and georedundancy are crucial, too. All these technological measures must be accompanied by governance and processes that do not compromise the information security.



## Benefits of a data lake architecture <sup>[94]</sup>

- A user must go to the source systems only once. When a process is set up to extract data from the source system, he never has to touch that source system again for analytical purposes.
- Health system leaders don't know all the future analytics needs of their organisations. Analytic needs in healthcare are fluid—with standards and vocabularies evolving rapidly—which means that many new questions will arise in the future that they will want to use data to answer. A flexible architecture enables analysts to respond to any and all future needs. In a Data Lake, the late-binding architecture allows for this.
- Users can scale the size of an Enterprise Data Warehouse easily with this architecture by using traditional database tools. The team can start small and lean, pulling into the source marts only the data needed to address a specific use case, and then add more data when able to.

### From the nature of the data source

Such a data lake will also be the best possible solution as analysis methods of unstructured text is becoming more available (see information box on natural language processing).

The handling of clinical information from patients is dependent on trust from the patients that the providers can keep the information safe, and security breaches can deal fatal blows to this trust.

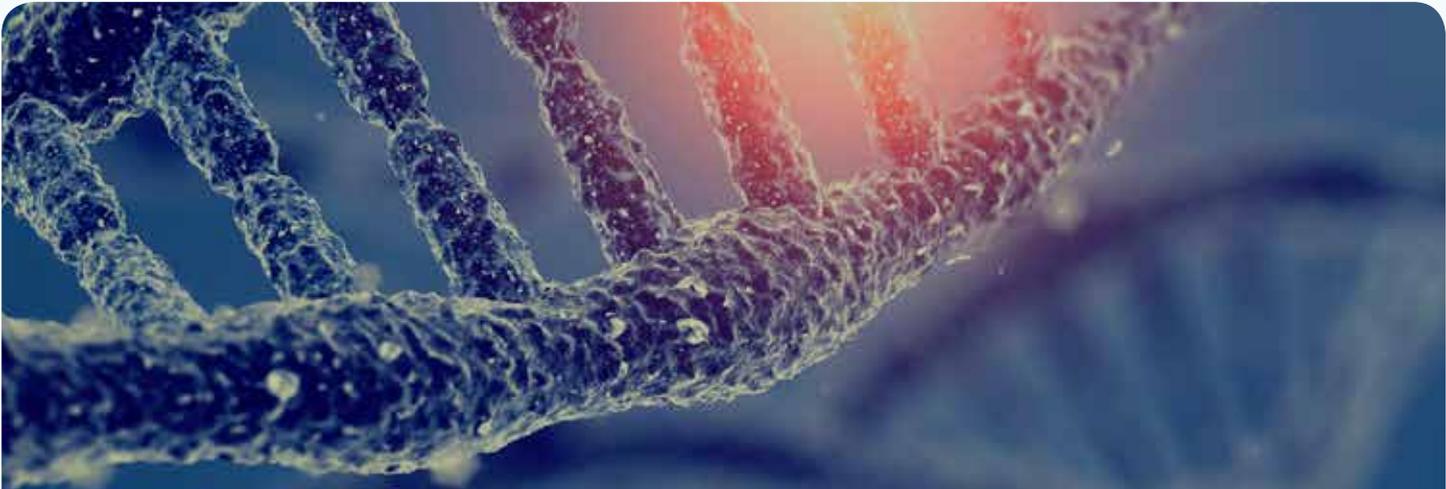
#### **5.4.5 Architecture for data use and reuse**

Today's patient journeys through the healthcare system often cross organisational boundaries. To truly implement the idea of providing the right treatment to the right patient, a prerequisite would be for healthcare workers to have access to relevant data on the patient as a basis for their decisions, meaning open interfaces for communication across units.

Reuse of data for analytical purposes requires another way of access to data than through the primary use or production systems. Therefore, healthcare providers, like other organisations eager to use their data for such purposes, have started thinking of ICT architectures that support this use. Such architectures involve streaming data from production systems into a secondary storage where they are available without increasing the strain on the production systems.

Traditional data warehouses extract data from production systems, transform them into usable data ("early binding"), and load them into a system where they are available for analysis. Such data warehouses have been used for decades in other industries, but have had only limited use in Norwegian Healthcare.

Due to several limitations with traditional data warehouse solutions, it has become increasingly common to delay transforming data until one knows the use ("late binding"). Such practice leads to less structure in the data stored for secondary purposes, and the result is often called a "data lake". Data lakes need other solutions for access control and metadata governance, but because of their flexibility, they are the favoured solutions today, even in healthcare.



# Genomics and bioinformatics

Genomic sequencing is arguably the technology with the most potential to transform the way healthcare is delivered in the next twenty years. While genomics is expected to be an integral part of many clinical areas in the future <sup>[76]</sup>, today it is most relevant for patients with rare diseases, cancer, or infectious diseases. Genomics can speed up and improve the diagnostic yield for patients with rare diseases, ending what today is often a long and costly diagnostic journey. It can give cancer patients predictive information, and allow for targeted therapies. In the context of infectious diseases, it can guide clinical management and help combat treatment resistance in pathogens.

Looking to the future where genome sequencing of both healthy individuals and patients could be the norm, many opportunities beyond these clinical cases can be realised. Genomics can contribute to a safer and more effective healthcare system that is tailored to individuals' genetic makeup. Pharmacogenomics will predict how individuals metabolise specific drugs, and whether they are likely to develop side effects, thus informing the choice and dosage of drug. Knowledge of one's genome sequence will identify susceptibility to common diseases such as diabetes and cardiovascular disease, allowing screening and other intervention strategies to be implemented.

In the context of rare disease diagnosis, the process of identifying the disease-causing variant(s) is commonly likened to looking for a needle in a

haystack. Firstly, the individual's unique set of variants must be identified through the process of variant calling, which compares an individual's genome to a reference genome. To identify the proverbial needle, or the disease-causing variant, this unique set of variants then must be compared to a collection of all previously observed genetic variation. A commonly found variant is unlikely to be the cause of a rare genetic disease. Ideally, this dataset would encompass as wide as possible a range of human genetic variation. Finally, the subset of variants in genes related to the phenotype observed in the patient must be compared to databases of well-curated variant-phenotype-diagnosis relationships. Today, the available datasets might be of variable quality and must therefore be applied with care in clinical decision making. In the absence of such known causative genes, international initiatives such as Matchmaker Exchange can facilitate the identification of additional cases of overlapping phenotypes with a deleterious variant in the same gene, which may provide sufficient evidence to identify the causative gene <sup>[77]</sup>.

In the context of rare disease diagnosis, the process of identifying the disease-causing variant(s) is commonly likened to looking for a needle in a haystack. The general steps in the clinical application of genomic sequencing, challenges and future needs are outlined on page 80.



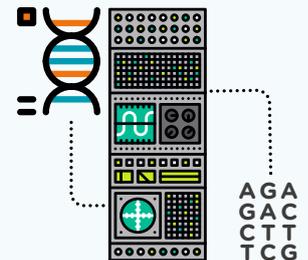
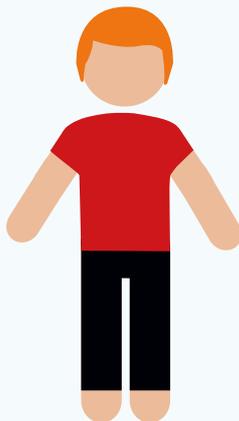
# General steps: Genomic sequencing

## Challenges

Highly variable knowledge among doctors of the opportunities that genomics can offer

Current paper-based requisitions often fail to provide enough information to select an appropriate genetic test and inform the subsequent data analysis.

Explosion in volume of tests ordered and carried out and resulting data



Patient meets doctor in a rare disease, cancer or infectious disease context. Establish if genomics analysis may be useful.

The treating physician will order genetic testing for diagnostic purposes if there are suspicions of hereditary disease, or for prognostication or tailoring treatment in the case of cancer.

Patient DNA is sequenced. Technology development is exponential, continuously driving down costs.

## Future needs

- Increased knowledge about the availability and utility of genomic testing among doctors and patients
- Standardised protocols/guidelines on when to order genomic tests
- Solutions for dynamic consent

- Standardised formats for referrals and sharing of information: Electronic requisitioning that: **1.** gives a good overview of available tests and criteria for ordering them; **2.** supports structured phenotype description; **3.** enables dynamic communication between the referring doctor and the genomics lab to gather missing information.

- Further automation of lab processes and scale-up of operations and infrastructure to secure substantial economies of scale.

The general steps in the clinical application of genomic sequencing are derived from examples from the BigMed clinical cases. For rare disease diagnosis and cancer prognostication and treatment, each step is linked to needs and challenges for implementation in the future.

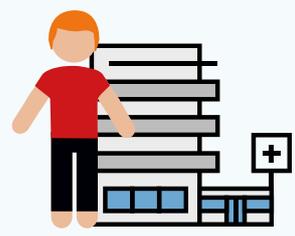
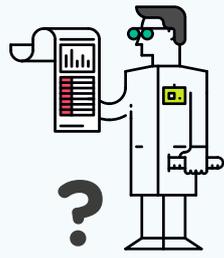
For rare diseases, genetic testing is ordered for diagnostic purposes if suspicion of genetic disease is raised by the patient's symptoms or family history. Health services also increasingly offer genetic testing of tumours for prognostication and to tailor treatment, given tumour-specific mutations.

Isolated HPC infrastructure, lack of bioinformaticians and data scientists

Most challenging, labour-intensive step of the process, including comparison of variants found against a knowledge base

Interpreted results and translation to actions must be available at clinical decision checkpoints.

Referring doctor must understand implications of results to guide clinical management



Sequencing data is processed with bioinformatic pipelines on high-performance computing infrastructure

Identification of relevant variants and their effect

Communicating of findings to the clinic

Translation of results to actions in the clinic



- A high-performance computing infrastructure connected to the rest of the healthcare network to enable effective integration of data sources.
- Bioinformaticians to develop efficient analyses for increased case volumes through automation and standardization

- A learning healthcare system that can compare data across patients through secure data sharing.
- Decision support systems that help curate reliable and standardised databases.

- Lab systems that directly deliver results to structured EMRs and other consumers of genomics results.

- Vehicles for communication of consequences of the results to both patients and the referring doctor.



## 6. Regulatory framework for precision medicine

### 6.1 A CHANGING HEALTHCARE IS CHALLENGING THE REGULATORY FRAMEWORK

New knowledge, specialisation and technological advancements with increased digitalisation are changing healthcare services in terms of content, work processes and organisation. Due to the increasing complexity within diagnostics and treatment planning, multidisciplinary teams have evolved. Preparing healthcare professionals to deliver patient care as members of an interdisciplinary team requires access to health information and coordination of healthcare services and patient information. The use of genetic information opens new opportunities. Genomics provides new knowledge about genetic variations and their relevance to diseases and treatments, and we have yet to explore its full potential in diagnostics, treatment and research.

In Norway, clinical practice/healthcare and research activities are regulated separately. In cases where standardised care pathways are not established, the diagnostic process must be organised as clinical research even if it is part of the healthcare delivery. Rapidly evolving clinical disciplines and the use of genetic information challenge this segregation and will force a different organisation of diagnostic processes. Future developments in healthcare services and research must take place within a formal framework where testing, diagnostics, and research are integrated.

### 6.2 CURRENT REGULATORY STRUCTURE AND FRAMEWORK

The Norwegian state, represented by the Parliament, uses legal and economic means to govern<sup>[95]</sup>. Healthcare is a main societal priority and access to healthcare services is regarded as a fundamental right for the state's citizens. Healthcare is regulated through comprehensive legislation.

Medicine is constantly evolving to provide better opportunities for diagnosis and treatment, and healthcare is subject to continuous discussions on prioritisation and distribution. A premise for healthcare services is that they must be necessary and appropriate<sup>[96, 97]</sup>. The health administration has detailed this premise further through priority guidance for the specialist health services<sup>[98]</sup>.

#### 6.2.1 Patient rights and consent

Patient rights were established in the 1980s and corresponded with the contemporary view of the individual's interests, rights and legal protection. The purpose was to improve the balance of power, limit the variations in individual judgment by professionals and ensure predictability.

A basic principle for healthcare services is informed consent, which in healthcare regulations refers to a consent based on the consenting person being

adequately and sufficiently informed about a situation to be able to take a decision on consent <sup>[99]</sup>.

If the patient is unable or unwilling to provide consent, it is still legal to provide treatment under certain conditions. Consent is normally not formalised, because it is presumed that the patient, when seeking healthcare services, will accept the help provided. In certain cases, consent may be secured to verify that the patient has received certain information or accepts the disadvantages of certain medical procedures. In cases where there is a legal requirement for written consent, its purpose is to emphasise the importance of a situation in addition to verifying that information is received.

Other important aspects of patient healthcare rights and duties embodied in Norwegian law are related to:

- Health personnel's duty of confidentiality, patients' rights of privacy and of protection of data;
- Patients' rights to information about their health and medical care;
- Patients' rights to participation in the choice of accessible and appropriate examination and intervention; and
- Patients' rights to access to patient records including rights such as making corrections and deletions and blocking information in their patient records.

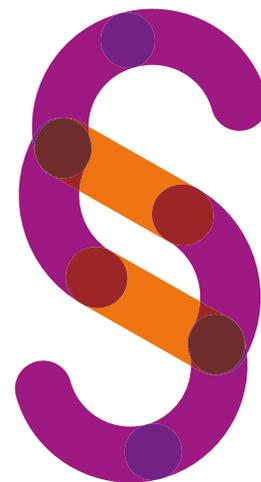
### 6.2.2 Digitalisation of health data

Digitalisation of health data has implications for the duty of confidentiality, the requirement to document and the respect for the patient's integrity and right to privacy, as multiple users are storing and re-using information. Increased use of health information, including genetic data, requires more involvement of the regional health authority and healthcare provider in managing health data, including ICT systems for access control and protection against cybercrime.

### 6.2.3 Research and secondary use of data

Patient health data originating from examination and treatment can later be used for secondary purposes, including research. The legal mechanism for research participation and access to patient data is documented consent. Research participants will usually sign a document confirming that they have received information related to the research study and that they voluntarily consent to their participation per specified procedures, such as donating a blood sample, testing a drug or responding to a questionnaire.

The consent must be detailed and explicit for the clinical research or trial with a defined purpose and method. Under certain conditions, it is possible to give a broad consent to participation in a research study that may evolve over time, where details on methods and hypotheses cannot be provided in advance. Research participants can freely withdraw their informed consent at any time.



**The purpose of the regulation is to provide a set of standardised protection laws across all the EU member states for citizens to understand and control how their data is being used and to facilitate sharing of data.**

Although the withdrawal may not extend to the data already obtained while the participant was enrolled in the study, in some cases, the participant may retract any biological material that was provided but that has not yet been analysed, and that can be isolated or retrieved. Solutions for digital dynamic consent are being considered for management and administration of consents.

With the exception of research conducted on data stored in health registries, which is regulated through the Health Registry Act <sup>[100]</sup>, clinical research must be pre-approved by the regional committees for research ethics (REC) <sup>[101]</sup>. There are some exceptions to the requirement for informed consent for research on health data. Under certain conditions, RECs can approve that health data can or shall be provided for research by health personnel, without being hindered by professional secrecy.

#### 6.2.4 Anonymised data

Anonymous information is information which does not relate to an identified or identifiable natural person or personal data rendered anonymous in such a manner that the data subject is not or no longer is identifiable <sup>[102]</sup>. For anonymised data, privacy of the patient is no longer a concern and regulations regarding health data do not apply. There are currently discussions regarding what data are to be considered anonymous and if re-identification is possible for certain data even if name, ID number and other identifiers are removed.

#### 6.2.5 Aggregations of data

For both healthcare and research, digitalisation has led to increased data generation and data aggregation. Registries and databases are established for storage, accessibility and retrieval for various uses within the healthcare system. The electronic medical record is specially regulated in terms of its function and duration. There are also regulations for registers used for the administration of healthcare services and registers set up for research and quality improvement. In addition, there are registers that have combined purposes: starting out as healthcare registries, but later used for research. The legal basis for all these aggregations of data requires assessment of need, purpose, duration and access to data.

Within genetic diagnostics and treatment, databases of genetic variations are used as reference data for genetic analysis.

The methodology requires access to reference information and sharing of data for the benefit of other patients. Neither the Health Registry Act <sup>[103]</sup> nor the Patient Record Act <sup>[104]</sup> addresses the assembly of genome data from multiple individuals for research, quality assurance or as reference data. There is a need for clarifications regarding the legal basis for genetic databases.

#### 6.2.6 Individual integrity and the General Data Protection Regulation

There are several international conventions and provisions in the constitution of the kingdom of Norway that affect how legislators and courts shall handle the rights to healthcare and privacy protection. With the European General Data Protection Regulation (GDPR) <sup>[105]</sup> entering into force in May 2018, new rights and duties must be investigated. The purpose of the regulation is to provide a set of standardised protection laws across all the EU member states for

citizens to understand and control how their data is being used and to facilitate sharing of data. Individuals will have easier access to personal information and to information about how their personal data is stored, accessed and processed. The goal is to strengthen the conditions of consent, purpose and proportionality as a basis for processing of personal data. When individuals withdraw consent, the regulations include the right to be forgotten, that is, their details must be permanently erased and not just deleted. The legal responsibility for healthcare providers and other organisations handling personal data is tightened.

### 6.3 LEGAL STRUCTURE AND FRAMEWORK FOR PERSONALISED MEDICINE

Today's legal structure and framework are suited neither for handling today's knowledge and technology, nor for handling opportunities arising from personalised medicine or future healthcare delivery. The historically separated regulation of clinical care and research does not handle the current trend of these disciplines merging.

With personalised medicine, large-scale genetic analysis is introduced in healthcare processes. Employing methods such as whole exome and whole genome sequencing generates information beyond the primary purpose of analysis, such as risk factors related to other diseases. Only information relevant and necessary for the primary purpose of the analysis is allowed to be documented in the patient's health records.

Aggregation of this surplus information from variant calling and interpretation of genetic variants could be used as resources in further genetic analysis, but such patient data registries and databases must then have a separate legal basis.

Current regulations are not suitable to facilitate medical diagnostics that balances between healthcare and health research, and which is directly based on aggregations of health data and secondary use of health data. The legislation distinguishes between healthcare and health research, and the value of healthcare is to a very limited extent reflected in the detailed regulation of health data. This segregated regulation limits the opportunities for realising the potential of big data analysis and small data matching as enablers of the implementation of personalised medicine. A legal basis for the relevant activities must be discussed and suggestions for necessary changes to regulations should be put forward.



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## Abbreviations

<b>AI</b>	Artificial intelligence	<b>PREMs</b>	Patient-reported experience measures
<b>APIs</b>	Application programming interfaces	<b>PROMs</b>	Patient-reported outcome measures
<b>CDS</b>	Clinical decision support	<b>REC</b>	Regional Committees for Research Ethics
<b>CHD</b>	Coronary heart disease	<b>RIS</b>	Radiology information system
<b>CRC</b>	Colorectal cancer	<b>SCD</b>	Sudden cardiac death
<b>CT</b>	Computer tomography	<b>TSD</b>	Service for Sensitive Data at Oslo University
<b>DNA</b>	Deoxyribonucleic acid	<b>VF</b>	Ventricular fibrillation
<b>ECG</b>	Electrocardiogram	<b>VT</b>	Ventricular tachycardia
<b>EMR</b>	Electronic medical record		
<b>ESC</b>	European Society of Cardiology		
<b>GDPR</b>	European General Data Protection Regulation		
<b>HCM</b>	Hypertrophic cardiomyopathy		
<b>HMO</b>	Health Maintenance Organisation		
<b>HPC</b>	High-performance computing		
<b>HPO</b>	Human Phenotype Ontology		
<b>HSØ</b>	Southern and Eastern Norway Regional Health Authority		
<b>ICD</b>	Implantable cardioverter defibrillator		
<b>ICT</b>	Information and communications technology		
<b>IRDiRC</b>	The International Rare Diseases Research Consortium		
<b>LIMS</b>	Laboratory information management system		
<b>LV</b>	Left ventricular		
<b>mCRC</b>	Metastatic CRC		
<b>MDT</b>	Multidisciplinary team		
<b>MR</b>	Magnetic resonance		
<b>MRI</b>	Magnetic resonance imaging		
<b>MTBs</b>	Multidisciplinary molecular tumour boards		
<b>NGS</b>	Next-generation sequencing		
<b>NLP</b>	Natural language processing		
<b>OUS</b>	Oslo University Hospital		
<b>PAS</b>	Patient administration		
<b>PET</b>	Positron emission tomography		

## Appendix 1: BigMed partners and collaborators

Organisation	Precision medicine related activity/ focus in Norway	Link to website	Contact person	Partner
DIPS	DIPS aims to enable data collected in the DIPS record, including genomics data, to be processed and analysed to support precision medicine under the BigMed project.	<a href="https://www.dips.no/">https://www.dips.no/</a>	Finn Harald Stokland, CPO fhs@dips.no	Consortium partner
DNV GL	Quality assurance and data governance body linked to clinical genomics to enable trust between stakeholders and an Initiator for Nordic Alliance for Clinical Genomics in sharing trustworthy data.	<a href="https://www.dnvgl.com/">https://www.dnvgl.com/</a>	Stephen McAdam Global Healthcare Director stephen.mcadam@dnvgl.com	Consortium partner
Norwegian Armed Forces, Joint medical Services	Supporting BigMed activities by learning from current initiatives in Norwegian military medicine in using big data methodologies for medical challenges in cold weather and arctic operations.	<a href="https://forsvaret.no">https://forsvaret.no</a>	Dag Hjelle	Consortium partner
IBM	IBM Watson Explorer Content Analytics (WEX CA) uses natural language processing to transform unstructured text to structured, analysable information elements. In BigMed, WEX CA extracts relevant patient information from unstructured EMRs and provide this information as a service.	<a href="https://www.ibm.com/no-no/">https://www.ibm.com/no-no/</a>	Loek Vredenberg, CTO IBM Norge loek.vredenberg@no.ibm.com	Consortium partner
Karolinska Institutet/ SciLifeLab	The Clinical Genomics facility provides a dedicated research infrastructure for projects utilising massively parallel / next generation sequencing technologies. The facility serves as a competence center assisting the translation of genomics-based tools to routine clinical care.	<a href="https://www.scilifelab.se/">https://www.scilifelab.se/</a>	Valtteri Wirta, Head of unit Clinical Genomics Facility valtteri.wirta@scilifelab.se	Consortium partner
Kunnskapsforlaget	Kunnskapsforlaget provides tools for extracting knowledge from unstructured and structured texts, and to resolve ambiguity and prepare texts for language technology analysis and output.	<a href="https://kunnskapsforlaget.no/">https://kunnskapsforlaget.no/</a>	Thomas Nygaard, Publishing Director thomas.nygaard@kunnskapsforlaget.no	Consortium partner
The Norwegian Heart and Lung Patient Organization (LHL)	LHL closely follows up patients with heart and lung disease and their relatives before, during and after treatment through research, political influence, public awareness, and professional treatment.	<a href="https://www.lhl.no/">https://www.lhl.no/</a>	Are Helseth, Medical Director are.helseth@lhl.no	Collaboration partner
Norway Health Tech	An organisation to support and accelerate the development of new medical technology and e-health products, services and innovative solutions for the Norwegian and global healthcare markets.	<a href="http://www.norwayhealthtech.com/">http://www.norwayhealthtech.com/</a>	Kathrine Myhre, CEO kathrine.myhre@oslomedtech.no	Consortium partner
Norwegian Cancer Society (Kreftforeningen)	Supporting and funding of research. Advocacy and participation in different kinds of boards such as Oslo Cancer Cluster, "One Patient, One Journal" and seed funding companies providing software in precision medicine and pharma.	<a href="https://kreftforeningen.no">https://kreftforeningen.no</a>	Kirsten Haugland, Avdelingssjef Forsknings- og forebyggings-avdelingen kirsten.haugland@kreftforeningen.no	Collaboration partner
Norwegian University of Science and Technology (NTNU), Faculty of Information Technology and Electrical Engineering, Department of Computer Science	Conducting research in the fields such as artificial intelligence, big data, computer architecture, computer graphics, computer security, databases, human computer interaction, information systems, operating systems, and software engineering.	<a href="https://www.ntnu.edu/idi">https://www.ntnu.edu/idi</a>	Øystein Nytrø, Associate Professor nytroe@idi.ntnu.no	Consortium partner

Organisation	Precision medicine related activity/ focus in Norway	Link to website	Contact person	Partner
Oslo University Hospital, Department of Medical Genetics)	The Department of Medical Genetics is the largest medical genetic department in Norway studying hereditary diseases and performing research on genetic causes of disease.	<a href="http://www.med.uio.no/klinmed/om/organisasjon/klinikker/laboratoriemedisin/medisinsk-genetik/">http://www.med.uio.no/klinmed/om/organisasjon/klinikker/laboratoriemedisin/medisinsk-genetik/</a>	Dag E. Undlien d.e.undlien@medisin.uio.no	Consortium partner
Oslo University Hospital, Institute for Cancer Research, Department of Tumour Biology	Engaged in basic and translational cancer research all the way from experimental research on model organisms and human materials to clinical trials for advanced medical research across sciences, including genomics and bioinformatics, for individualized diagnostics and treatment for cancer patients.	<a href="https://www.ous-research.no/tumorbiology/">https://www.ous-research.no/tumorbiology/</a>	Eivind Hovig, Professor ehovig@radium.uio.no	Consortium partner: OUS
Oslo University Hospital, the Interventional centre	Multidisciplinary centre to develop new treatment methods for patients, for example, new algorithms for processing and understanding complex, large amount of data for high precision diagnosis, treatment and follow-up.	<a href="https://oslo-universitetssykehus.no/avdelinger/akuttklinikken/intervensjonsenteret">https://oslo-universitetssykehus.no/avdelinger/akuttklinikken/intervensjonsenteret</a>	Erik Fosse, Group leader of interventional centre, OUS erik.fosse@medisin.uio.no	Consortium partner: OUS
Oslo University Hospital - legal department to OUS CEO			Randi Borgen Legal director UXRARG@ous-hf.no	Consortium partner: OUS
OUS ICT			Arve Kaarese akaarese@our-hf.no	Consortium partner: OUS
Oslo University Hospital - OCBE	Develops and applies statistical and machine learning methodology and algorithms to (i) extract understanding from clinical and genomic data and (ii) make predictions of future events/ conditions. Biomarker discovery, Patient safety monitoring based on electronic health records.	<a href="https://www.med.uio.no/imb/english/research/centres/ocbe/">https://www.med.uio.no/imb/english/research/centres/ocbe/</a>	Arnoldo Frigessi arnoldo.frigessi@medisin.uio.no	Consortium partner: OUS
PubGene	Patented biomedical research text mining (Coremine) for mining evidence for better diagnoses and possible treatments for every single patient.	<a href="https://www.pubgene.com/">https://www.pubgene.com/</a>	Odd Arild Lehne, CEO oal@pubgene.com	Consortium partner
Sykehuspartner	Provide a data platform and data provisioning service for the BigMed project.	<a href="https://sykehuspartner.no/">https://sykehuspartner.no/</a>	Arild Jacobsen arjaco@sykehuspartner.no	Consortium partner
The Norwegian Association for Children with Congenital Heart Disease (Foreningen for Hjertesyke Barn)	The Foundation aims to improve the overall quality of life of children with heart defects by supporting research addressing physical, psychological, social and spiritual aspects towards an integrated approach.	<a href="http://www.ffhb.no">http://www.ffhb.no</a>	Marte Jystad Special Adviser marte@ffhb.no	Collaboration partner
University of Oslo, The Faculty of Law			A.K. Befring a.k.befring@jus.uio.no	Consortium partner: UiO
University of Oslo, Institute of Health and Society			Melberg h.o.melberg@medisin.uio.no	Consortium partner: UiO
University of Oslo, Services for Sensitive Data (TSD)	TSD is an infrastructure which meets the strict requirements of the law for the treatment and storage of sensitive biomedical (and other sensitive) research data.	<a href="http://www.uio.no/english/services/it/research/sensitive-data/">http://www.uio.no/english/services/it/research/sensitive-data/</a>	Gard Thomassen, Assistant Director - Department for Research Computing gardot@usit.uio.no	Consortium partner: UiO

Organisation	Precision medicine related activity/ focus in Norway	Link to website	Contact person	Partner
University of Oslo, Department of Informatics	Project coordinator in EU project Optique, a platform to connect end users and data sources and utilise data to solve scalable data access relevant for precision medicine activities.	<a href="https://www.mn.uio.no/ifi/">https://www.mn.uio.no/ifi/</a>	Arild Waaler, Professor arild@ifi.uio.no	Consortium partner: UiO
University of Oslo, Department of Informatics, Language Technology Group (LTG)	Language Technology comprises theoretical and applied Informatics that seeks to enable computers to 'make sense' of human language. LTG performs data-driven linguistic analysis of text using machine learning and HPC.	<a href="https://www.mn.uio.no/ifi/english/research/groups/ltg/">https://www.mn.uio.no/ifi/english/research/groups/ltg/</a>	Lilja Øvreid, Associate professor lijao@ifi.uio.no	Consortium partner: UiO
University of Oslo, Department of Informatics, Logic and Intelligent Data (LogID)	The work in LogID is based on well-established methods from logic, which they extend and enhance to tackle tomorrow's challenges in fields like Semantic Web and Big Data.	<a href="https://www.mn.uio.no/ifi/english/research/groups/logid/">https://www.mn.uio.no/ifi/english/research/groups/logid/</a>	Martin Giese, Professor martingi@ifi.uio.no	Consortium partner: UiO

## Appendix 2: Overview of the Norwegian landscape

Implementation of precision medicine requires a joint effort from many different players to build the knowledge base and develop the tools and methodologies needed. Below we have gathered a list of organisations and groups with employees in Norway that are involved in (pre)commercial activities, research and/or clinical activities relevant for precision medicine. The list includes academia, clinical departments and groups and a wide spectre of industry organisations,

from start-ups to global players.

This will hopefully be a resource for forming of new partnerships and collaborations. These list holds examples of current entities, and is not a complete representation of the Norwegian landscape. A minority of entities have reserved themselves from being included in this list.

### ACADEMIA

Entity	Precision medicine related activity/ focus in Norway	Link to website
Høgskolen i Oslo og Akershus, Senter for velferds- og arbeidslivsforskning, Velferdsforskningsinstituttet NOVA	One of Norway's largest social science research institutes focused on welfare research and studies of the life cycle from childhood to elderly.	<a href="http://www.hioa.no/Om-HIOA/Senter-for-velferds-og-arbeidslivsforskning/NOVA/Om-NOVA">http://www.hioa.no/Om-HIOA/Senter-for-velferds-og-arbeidslivsforskning/NOVA/Om-NOVA</a>
Høgskulen på Vestlandet, Avdeling for Helse- og Sosialfag, SimArena Simuleringscenter	SimArena is a new modern and well-equipped simulation center consists of 35 laboratories and state-of-the-art medical equipment for teaching, research and development.	<a href="https://www.hvl.no/om/organisering/avdelingar/avdeling-for-helse-og-sosialfag-bergen/">https://www.hvl.no/om/organisering/avdelingar/avdeling-for-helse-og-sosialfag-bergen/</a>
Høgskolen i Oslo og Akershus, Fakultet for Helsefag (Oslo and Akershus University College of Applied Sciences, the Faculty of Health Sciences)	Research focused on the development of knowledge-based health services utilising cooperation between the different health professions within health promotion, prevention, diagnostics and treatment of illnesses, rehabilitation, care and human behaviour.	<a href="http://www.hioa.no/">http://www.hioa.no/</a>
Midt-Norsk Sepsis Senter, Norges Teknisk-naturvitenskapelige Universitet - NTNU, Institutt for Sirkulasjon og Bildediagnostikk - ISB (Mid-Norway Sepsis Research Group, Norwegian University of Science and Technology - NTNU, Department of Circulation and Medical Imaging)	The PEST project is focused on personalised medicine for sepsis patients by looking at the interaction between the patient's genes, physiological response to the disease and microbial genetics.	<a href="https://www.ntnu.no/isb">https://www.ntnu.no/isb</a>
Nasjonalt senter for e-helseforskning (Norwegian Centre for E-health Research)	Expertise in developing advanced statistical methods to extract information from large datasets for quality improvement, health monitoring, management and research, while safeguarding privacy and trust of patients and health workers.	<a href="https://ehealthresearch.no/">https://ehealthresearch.no/</a>
Norges Arktiske Universitet, Institutt for Medisinsk Biologi (The Arctic University of Norway, Department of Medical Biology)	Research focuses on fundamental biomedical on various types of cancer, cardiovascular diseases, the body's immune system and resistance to antibiotics, marine bioprospecting and in the development of new medicines.	<a href="https://uit.no/om/enhet/forsiden?p_dimension_id=88110">https://uit.no/om/enhet/forsiden?p_dimension_id=88110</a>

Entity	Precision medicine related activity/ focus in Norway	Link to website
Norges Miljø- og Biovitenskapelige Universitet (Norwegian University of Life Sciences).	A hub of expertise within life sciences, environmental sciences and in the arena of sustainable development.	<a href="https://www.nmbu.no/">https://www.nmbu.no/</a>
Norges Teknisk-Naturvitenskapelige Universitet - NTNU, Fakultet for Medisin og Helsevitenskap, Institutt for Klinisk og Molekylær Medisin - IKOM.  (Norwegian University of Science and Technology - NTNU, Faculty of Medicine and Health Sciences, Department of Clinical and Molecular Medicine)	Working on basic, clinical and palliative cancer research, immunology and mechanisms of infection, population-based studies of human disease, as well as research within some aspects of internal medicine.	<a href="http://www.ntnu.edu/ikom">http://www.ntnu.edu/ikom</a>
Norges Teknisk-Naturvitenskapelige Universitet - NTNU, Senter for Omsorgsforskning  (Norwegian University of Science and Technology, Centre for Care Research)	To collect, produce and disseminate knowledge about care, caring and care work and a professional meeting place to share knowledge of care and care.	<a href="https://www.ntnu.no/omsorgsforskning">https://www.ntnu.no/omsorgsforskning</a>
Norsk konsortium for sekvensering og persontilpasset medisin (Norwegian Consortium for Sequencing and Personalized Medicine)	Research infrastructure funded by The Research Council of Norway and regional health authorities. The infrastructure is providing next-generation sequencing services to the Norwegian research communities and facilitates novel diagnostic tests using next-generation sequencing. University hospitals and universities in Oslo, Bergen, Trondheim and Tromsø are partners in the infrastructure, which is led by OUS.	<a href="http://www.norseq.org">http://www.norseq.org</a>
Norwegian Bioinformatics Platforms	The infrastructure develops solutions and offers assistance and education for the analysis, storage, organisation or visualisation of biological and medical data.	<a href="http://www.bioinfo.no">http://www.bioinfo.no</a>
Universitetet i Bergen, Det Medisinske Fakultet, Centre for Cancer Biomarkers - CCBIO (University of Bergen, The Faculty of Medicine, Centre for Cancer Biomarkers – CCBIO)	Working on new cancer biomarkers and targeted therapy, how cancer cells are affected by the microenvironment in the tumours and its significance for cancer proliferation and poor prognosis.	<a href="http://www.uib.no/en/ccbio">http://www.uib.no/en/ccbio</a>
Universitetet i Bergen, Det Medisinske Fakultet, Institutt for Global Helse og Samfunnsmedisin (University of Bergen, Faculty of Medicine, Department of Global Public Health and Primary Care)	Conducting research and education in a wide range of disciplines: physiotherapy, genetic counselling, epidemiology, social medicine, statistics, nursing, social pharmacy, ethics and general medicine.	<a href="http://www.uib.no/igs">http://www.uib.no/igs</a>
Universitetet i Bergen, Det Medisinske Fakultet, Klinisk institutt 2 – K2 (University of Bergen, Faculty of Medicine, Department of Clinical Science)	Aims to conduct research, guidance and teaching to achieve the Faculty's vision 'new knowledge for better health'.	<a href="http://www.uib.no/klin2">http://www.uib.no/klin2</a>
Universitetet i Oslo, Det Matematisk-naturvitenskapelige Fakultet, Forskningsgruppen for Logikk og Intelligente Data - LOGID (University of Oslo, The Faculty of Mathematics and Natural Sciences, Research Group for Logic and Intelligent Data – LOGID)	The work is based on well-established methods from logic, which is extended and enhanced to tackle tomorrow's challenges in fields like Semantic Web and Big Data.	<a href="https://www.mn.uio.no/ifi/forskning/grupper/logid/">https://www.mn.uio.no/ifi/forskning/grupper/logid/</a>

Entity	Precision medicine related activity/ focus in Norway	Link to website
Universitetet i Oslo, Det Medisinske Fakultet, Institutt for Helse og Samfunn, Avdeling for Helseledelse og Helseøkonomi - HELED (University of Oslo, Faculty of Medicine, Institute of Health and Society, Department of Health Management and Health Economics - HELED)	Conducting research and teaching in the fields of health economics, health policy, health systems, quality of care, and health management involving economists, political scientists, and physicians.	<a href="http://www.med.uio.no/helsam/english/about/organisation/departments/heled/index.html">http://www.med.uio.no/helsam/english/about/organisation/departments/heled/index.html</a>
Universitetet i Oslo, Det Medisinske Fakultet, Institutt for Helse og Samfunn, Senter for Medisinsk Etikkk - SME (University of Oslo, Faculty of Medicine, Institute of Health and Society, Centre for Medical Ethics - CME)	Conducting research within the different subject areas of medical ethics and teaches and supervises medical and odontology students in medical ethics.	<a href="http://www.med.uio.no/helsam/english/about/organisation/divisions/laboratory-medical-ethics/index.html">http://www.med.uio.no/helsam/english/about/organisation/divisions/laboratory-medical-ethics/index.html</a>
Universitetet i Oslo, Det Medisinske Fakultet, Institutt for Klinisk Medisin (University of Oslo, Faculty of Medicine, Institute of Clinical Medicine, Department of Medical Genetics - DMG)	The largest medical genetic department in Norway studying hereditary diseases and performing research on genetic causes of disease.	<a href="http://www.med.uio.no/klinmed/english/about/organisation/divisions/laboratory-medicine/medical-genetics/index.html">http://www.med.uio.no/klinmed/english/about/organisation/divisions/laboratory-medicine/medical-genetics/index.html</a>
Universitetet i Oslo, Det Medisinske Fakultet, Institutt for Klinisk Medisin, Geriatrik Avdeling  (University of Oslo, Faculty of Medicine, Institute of Clinical Medicine, Department of Medical Genetics, Department of Geriatric Medicine)	Focused on prioritised areas of research including dementia, delirium, stroke, and cancer in the elderly population.	<a href="http://www.med.uio.no/klinmed/om/organisasjon/klinikker/medisinsk-klinikk/geriatrik/index.html">http://www.med.uio.no/klinmed/om/organisasjon/klinikker/medisinsk-klinikk/geriatrik/index.html</a>
Universitetet i Oslo, Det Medisinske Fakultet, Institutt for Klinisk Medisin, Akuttklinikken – AKU  (University of Oslo, Faculty of Medicine, Institute of Clinical Medicine, Division of Critical Care – AKU)	Treating patients at all clinics as well as conducting research focused on clinical areas such as prehospital critical care medicine, traumatology, intensive care medicine, anaesthesia activities and pain management.	<a href="http://www.med.uio.no/klinmed/om/organisasjon/klinikker/akuttklinikken/index.html">http://www.med.uio.no/klinmed/om/organisasjon/klinikker/akuttklinikken/index.html</a>
Universitetet i Oslo, Det Medisinske Fakultet, Institutt for Klinisk Medisin, Kardiologisk Avdeling  (University of Oslo, Faculty of Medicine, Institute of Clinical Medicine, Department of Cardiology)	Expertise in research, investigation and treatment of acute and chronic coronary diseases, heart failure, heart disease, heart rhythm disorders, adults with congenital heart failure and cardiac transplant.	<a href="http://www.med.uio.no/klinmed/om/organisasjon/klinikker/hjerte-lunge-kar/kardiologisk-avdeling/index.html">http://www.med.uio.no/klinmed/om/organisasjon/klinikker/hjerte-lunge-kar/kardiologisk-avdeling/index.html</a>
Universitetet i Oslo, Det Medisinske Fakultet, Institutt for Klinisk Medisin, Kreftklinikken – KRE  (University of Oslo, Faculty of Medicine, Institute of Clinical Medicine, Division of Cancer Medicine - KRE)	Conducting extensive national and international and offering highly specialised, multidisciplinary medical and surgical treatment of cancer.	<a href="http://www.med.uio.no/klinmed/om/organisasjon/klinikker/kreftklinikken/index.html">http://www.med.uio.no/klinmed/om/organisasjon/klinikker/kreftklinikken/index.html</a>
Universitetet i Oslo, Det Medisinske Fakultet, Institutt for Klinisk Medisin, Avdeling for Gastro- og Barnekirurgi - AGK  (University of Oslo, Faculty of Medicine, Institute of Clinical Medicine, Department of Gastrointestinal and Children Surgery - AGK)	Treating patients suffering from digestion disorders such as digestive organs, oesophagus, stomach, gut and rectum, and associated internal organs such as liver, bile and pancreas.	<a href="http://www.med.uio.no/klinmed/om/organisasjon/klinikker/kirurgi-inflammasjon-transplantasjon/avdeling-for-gastro-og-barnekirurgi/index.html">http://www.med.uio.no/klinmed/om/organisasjon/klinikker/kirurgi-inflammasjon-transplantasjon/avdeling-for-gastro-og-barnekirurgi/index.html</a>
Universitetet i Oslo, Det Medisinske Fakultet, Institutt for Klinisk Medisin, Institutt for eksperimentell medisinsk forskning  (University of Oslo, Faculty of Medicine, Institute of Clinical Medicine, Institute for Experimental Medical Research)	Research primarily in the area of heart disease, especially heart failure.	<a href="http://www.med.uio.no/klinmed/om/organisasjon/klinikker/hjerte-lunge-kar/eksperimentell-medisinsk-forskning/index.html">http://www.med.uio.no/klinmed/om/organisasjon/klinikker/hjerte-lunge-kar/eksperimentell-medisinsk-forskning/index.html</a>

Entity	Precision medicine related activity/ focus in Norway	Link to website
Universitetet i Oslo, Det Medisinske Fakultet, Institutt for Medisinske Basalfag, Avdeling for Biostatistikk (University of Oslo, Faculty of Medicine, Institute of Basic Medical Sciences, Department of Biostatistics)	Research on statistical methods relevant to medical issues (e.g. measurement uncertainty, survival analysis, causal interference) and on statistical genomics, system biology and epidemiology.	<a href="http://www.med.uio.no/imb/english/about/organisation/departments/biostatistics/index.html">http://www.med.uio.no/imb/english/about/organisation/departments/biostatistics/index.html</a>
Universitetet i Oslo, Det Medisinske Fakultet, Klinikk for Helsestjenesteforskning og Psykiatri - AHUSKHP, og Forskningsenteret ved Akershus Universitetssykehus. (University of Oslo, Faculty of Medicine, Institute of Clinical Medicine, Division of Health Services Research and psychiatry, and the Research Centre at Akershus University Hospital)	Conducting research in teamwork, communications, quality of service and healthcare economics. Healthcare research is focused on quality of care and clinical epidemiology, organisation and user perspectives, and operations analysis.	<a href="http://www.med.uio.no/klinmed/om/organisasjon/klinikker/helsestjenesteforskning-psykiatri/index.html">http://www.med.uio.no/klinmed/om/organisasjon/klinikker/helsestjenesteforskning-psykiatri/index.html</a>
Universitetet i Oslo, Det Medisinske Fakultet, Klinikk for Laboratoriemedisin – KLM (University of Oslo, Faculty of Medicine, Institute of Clinical Medicine, Division of Laboratory Medicine - KLM)	Conducting research and education in the fields of medical biochemistry, pharmacology, medical genetics, microbiology, immunology, pathology and technology supported intervention.	<a href="http://www.med.uio.no/klinmed/english/about/organisation/divisions/laboratory-medicine/index.html">http://www.med.uio.no/klinmed/english/about/organisation/divisions/laboratory-medicine/index.html</a>
Universitetet i Oslo, Det Medisinske Fakultet, Norsk senter for Forskning på Mentale Lidelser – NORMENT (University of Oslo, Faculty of Medicine, Norwegian Centre for Mental Disorders Research - NORMENT)	Research aims to understand the variation in cognitive function in people with psychosis in such a way that it contributes to more accurate diagnoses, improved prognostic counselling and personalised treatment.	<a href="http://www.med.uio.no/norment/english/research/subjects/genetics-of-psychiatric-disorders/">http://www.med.uio.no/norment/english/research/subjects/genetics-of-psychiatric-disorders/</a>
Universitetet i Oslo, Det Medisinske Fakultet, Senter for Kreftbiomedisin (University of Oslo, Faculty of Medicine, Centre for Cancer Biomedicine - CCB)	Unifying basic and translational research for the benefit of cancer patients by multidisciplinary approach focused on disease understanding and development of affordable tools for early detection and tailored treatment.	<a href="http://www.med.uio.no/ccb/">http://www.med.uio.no/ccb/</a>

## CLINICAL DEPARTMENTS AND GROUPS

Entity	Precision medicine related activity/ focus in Norway	Link to website
Akershus Universitetssykehus, Genteknologisk Seksjon, Tverrfaglig Laboratoriemedisin og Medisinsk Biokjemi	This interdisciplinary laboratory medicine and medical biochemistry has manufacturing and working methods ranging from the fully automated sample handling system to manually performed analysis and microscopy.	<a href="https://www.ahus.no/avdelinger/diagnostikk-og-teknologi/tverrfaglig-laboratoriemedisin-og-medisinsk-biokjemi">https://www.ahus.no/avdelinger/diagnostikk-og-teknologi/tverrfaglig-laboratoriemedisin-og-medisinsk-biokjemi</a>
Den Norske Legeforening	Legeforeningen works with health policy, professional development, research, education and working conditions as a framework for medical practice.	<a href="http://legeforeningen.no">http://legeforeningen.no</a>
Folkehelseinstituttet (Norwegian Institute of Public Health)	To gather, summarise and disseminate knowledge about public health and healthcare by conducting activities related to preparedness, counselling, and health analysis, research and services.	<a href="https://www.fhi.no/">https://www.fhi.no/</a>
Genomics Core Facility, Oslo University Hospital and Helse Sør-Ost	Providing state-of-the-art laboratory technology, competence and high-throughput genomic services to study genome structure, dynamics and function using high-throughput sequencing and microarray technologies.	<a href="https://oslo.genomics.no">oslo.genomics.no</a>

Entity	Precision medicine related activity/ focus in Norway	Link to website
Helse Bergen, Haukeland Universitetssjukehus, Regionalt Kompetansesenter for Arveleg Kreft - RKAK (Helse Bergen, Haukeland University Hospital, Bergen - The Regional Competence Center for Hereditary Cancer)	The center investigates risk of the development of cancer disease without proven genetic defects and conduct DNA tests for patients with breast/ovarian cancer to map the cancers in Norway.	<a href="https://helse-bergen.no/avdelinger/laboratorieklinikken/medisinsk-genetikk-og-molekylermedisin/regionalt-kompetansesenter-for-arveleg-kreft-rkak">https://helse-bergen.no/avdelinger/laboratorieklinikken/medisinsk-genetikk-og-molekylermedisin/regionalt-kompetansesenter-for-arveleg-kreft-rkak</a>
Helse Bergen, Haukeland Universitetssjukehus, Seksjon for Forsking og Innovasjon - FoU (Helse Bergen, Haukeland University Hospital, Bergen, Research and Innovation)	Facilitating in improving the quality and quantity of clinical research for health and healthcare services and responsible for research strategies and framework for research and innovation in the healthcare sector.	<a href="https://helse-bergen.no/seksjon-avdeling/Sider/Forsking-og-innovasjon.aspx">https://helse-bergen.no/seksjon-avdeling/Sider/Forsking-og-innovasjon.aspx</a>
Helse Bergen, Haukeland Universitetssjukehus, Senter for Genterapi (Helse Bergen, Haukeland University Hospital, Department of Oncology)	Identifying the genetic and molecular mechanisms that influence the risk of various types of cancer, as well as the mechanisms that have impact on treatment results of cancer patients.	<a href="https://helse-bergen.no/avdelinger/genterapi">https://helse-bergen.no/avdelinger/genterapi</a>
Helse Bergen, Haukeland Universitetssjukehus, Senter for Medisinsk Genetikk og Molekylærmedisin – MGM (Haukeland University Hospital, Centre for Medical Genetics and Molecular Medicine)	Focused on tests, guidance, and diagnostics of patients and their relatives with possible genetic diseases.	<a href="https://helse-bergen.no/avdelinger/laboratorieklinikken/medisinsk-genetikk-og-molekylermedisin">https://helse-bergen.no/avdelinger/laboratorieklinikken/medisinsk-genetikk-og-molekylermedisin</a>
Helse Vest RHF	Through patient-oriented clinical research, Helse Vest contributes to high quality health tests, adapting patients' needs.	<a href="https://helse-vest.no/">https://helse-vest.no/</a>
Nasjonalt Kreftsatsing	Facilitator for research projects in cancer genome aimed to making cancer treatment better and more personalised by providing clinical guidance, developing protocols, promoting personalised treatment and building competence.	<a href="http://kreftsatsing.no/">http://kreftsatsing.no/</a>
Norsk Forening for Medisinsk Genetikk (Norwegian Society for Medical Genetics)	Group within The Norwegian Medical Association (Den Norske Legeforening), which holds the position both as a professional association and as a trade union for Norwegian physicians.	<a href="http://legeforeningen.no/Fagmed/Norsk-forening-for-medisinsk-genetikk/">http://legeforeningen.no/Fagmed/Norsk-forening-for-medisinsk-genetikk/</a>
Norsk Kreftgenomikkonsortium (Norwegian Cancer Genomics Consortium)	Platform to establish the required general technology, methodology and interpretation procedures for utilising the mutation profile of the tumour to guide the adaptation of cancer treatment to an individual patient.	<a href="http://kreftgenomikk.no/">http://kreftgenomikk.no/</a>
Norsk Selskap for Humangenetikk (Norwegian Society for Human Genetics)	Connecting professional communities in human genetics in Norway and abroad, providing human genetics knowledge to Norwegian health services and authorities, patient organisations and public, promoting interest in human genetics research.	<a href="http://www.nshg.no/">http://www.nshg.no/</a>
Oslo Universitetssykehus, Avdeling for Medisinsk Biokjemi (Oslo University Hospital, Department of Medical Biochemistry)	Conducting research in the field of medical biochemistry and responsible for reestablishment of analysis, medical assessment and interpretation of analytical results.	<a href="https://oslo-universitetssykehus.no/avdelinger/klinikk-for-laboratoriemedisin/avdeling-for-medisinsk-biokjemi">https://oslo-universitetssykehus.no/avdelinger/klinikk-for-laboratoriemedisin/avdeling-for-medisinsk-biokjemi</a>
Oslo Universitetssykehus, Avdeling for Medisinsk Biokjemi, Hormonlaboratoriet (Oslo University Hospital, Department of Medical Biochemistry, The Hormone Laboratory)	This Norway's largest endocrinological institution and special laboratory for hormone measurement has an active role in teaching and counselling in endocrinology, internal medicine, gynaecology, paediatrics and also for general practitioners.	<a href="https://oslo-universitetssykehus.no/avdelinger/klinikk-for-laboratoriemedisin/avdeling-for-medisinsk-biokjemi/hormonlaboratoriet">https://oslo-universitetssykehus.no/avdelinger/klinikk-for-laboratoriemedisin/avdeling-for-medisinsk-biokjemi/hormonlaboratoriet</a>
Oslo Universitetssykehus, Avdeling for Medisinsk Genetikk (Oslo University Hospital, Department of Medical Genetics)	The Department for Medical Genetics at OUS is the largest medical genetics department in Norway.	<a href="https://oslo-universitetssykehus.no/avdelinger/klinikk-for-laboratoriemedisin/avdeling-for-medisinsk-genetikk/seksjon-for-laboratoriediagnostikk#les-mer-om-seksjon-for-laboratoriediagnostikk">https://oslo-universitetssykehus.no/avdelinger/klinikk-for-laboratoriemedisin/avdeling-for-medisinsk-genetikk/seksjon-for-laboratoriediagnostikk#les-mer-om-seksjon-for-laboratoriediagnostikk</a>
Oslo universitetssykehus, Avdeling for Patologi, Enhet for Molekylærpatologi (Oslo University Hospital, Department of Pathology, Unit for Molecular Pathology)	Providing diagnoses on tissue and cell samples from inpatient and outpatient patients to determine whether a patient has cancer and as a basis for tailoring treatment and follow-up care.	<a href="https://oslo-universitetssykehus.no/avdelinger/klinikk-for-laboratoriemedisin/avdeling-for-patologi/enhet-for-molekylerpatologi">https://oslo-universitetssykehus.no/avdelinger/klinikk-for-laboratoriemedisin/avdeling-for-patologi/enhet-for-molekylerpatologi</a>

Entity	Precision medicine related activity/ focus in Norway	Link to website
Oslo universitetssykehus, Barne- og Ungdomsklinikken, Avdeling for Nyfødtscreening (Oslo University Hospital, Children's Division, Norwegian National Unit for Newborn Screening)	Serving nationally for screening all newborns for severe congenital diseases and following-up of patients with phenylketonuria.	<a href="https://oslo-universitetssykehus.no/avdelinger/barne-og-ungdomsklinikken/nyfodtscreeningen">https://oslo-universitetssykehus.no/avdelinger/barne-og-ungdomsklinikken/nyfodtscreeningen</a>
Oslo Universitetssykehus, Nasjonal Kompetansetjeneste for Sjeldne Diagnoser (Oslo University Hospital, Norwegian National Advisory Unit on Rare Disorders)	The Advisory Unit supports patients diagnosed with rare diseases and their relatives by providing comprehensive, holistic and personalised care.	<a href="http://www.sjeldnediagnoser.no/">http://www.sjeldnediagnoser.no/</a>
Oslo Universitetssykehus, Stab Forskning, Innovasjon og Utdanning, Seksjon for Forskning, Forskningsavdelingen	Promoting research-based health services to strengthen clinical activities characterised by high quality research, organisation and working conditions, and close collaboration with business and other institutions nationally and internationally.	<a href="https://oslo-universitetssykehus.no/avdelinger/direktorens-stab/stab-forskning-innovasjon-og-utdanning/seksjon-for-forskning#les-mer-om-forskningsavdelingen">https://oslo-universitetssykehus.no/avdelinger/direktorens-stab/stab-forskning-innovasjon-og-utdanning/seksjon-for-forskning#les-mer-om-forskningsavdelingen</a>
Sørlandet Sykehus, Seksjon for Teknologi og e-helse, og Universitetet i Agder, Senter for Kunstig Intelligens Senter for e-helse- og Omsorgsteknologi og Institutt for Informasjonssystem  Sørlandet Hospital HF, The Department of Technology and e-Health, and University of Agder, Centre for Artificial Intelligence Research, Centre for e-Health and Care Technology, and Department of Information Systems	Developing artificial intelligence to structure large amount of data, and utilising new algorithms to conceptually search for specific clinical information (including allergies, critical information, etc.) in patients' EMRs to support clinical decision making.	<a href="https://www.uia.no">https://www.uia.no</a> <a href="https://cair.uia.no/">https://cair.uia.no/</a>
St. Olavs Hospital Universitetssykehuset i Trondheim, Avdeling for Medisinsk Genetikk (St. Olavs Hospital, Department of Medical Genetics and Pathology)	Aims to investigate, diagnose and follow up rare genetic diseases and syndromes based on new sequencing technology, enabling testing of all the genetic variants of a human in one sample.	<a href="https://stolav.no/avdelinger/medisinsk-klinikk">https://stolav.no/avdelinger/medisinsk-klinikk</a>
Sykehuset i Telemark, Seksjon for Medisinsk Genetikk (Telemark Hospital, Section of Medical Genetics)	Clinical and laboratory assessment of patients/families within a broad spectrum of genetic disorders. Particular expertise in rare disorders presenting in childhood and in adult neurology. Early adopters of NGS-technology.	<a href="https://www.sthf.no/avdelinger/medisinsk-serviceklinikk/laboratoriemedisin-avdeling/medisinsk-genetikk-seksjon#les-mer-om-medisinsk-genetikk--seksjon">https://www.sthf.no/avdelinger/medisinsk-serviceklinikk/laboratoriemedisin-avdeling/medisinsk-genetikk-seksjon#les-mer-om-medisinsk-genetikk--seksjon</a>
The Norwegian High-Throughput Sequencing Centre - NSC, Oslo Universitetssykehus og Universitetet i Oslo	National technology core facility offering sequencing services.	<a href="http://www.sequencing.uio.no/">http://www.sequencing.uio.no/</a>
Universtetssykehuset Nord-Norge, Medisinsk Genetisk Avdeling	The group conducts several research projects that include mapping the genetic cause of disease as well as studying how specific genetic variants can lead to disease.	<a href="https://unn.no/avdelinger/barne-og-ungdomsklinikken/medisinsk-genetisk-avdeling-tromso#les-mer-om-medisinsk-genetisk-avdeling-tromso">https://unn.no/avdelinger/barne-og-ungdomsklinikken/medisinsk-genetisk-avdeling-tromso#les-mer-om-medisinsk-genetisk-avdeling-tromso</a>
Oslo University Hospital, Institute for Cancer Genetics and Informatics	Focused on using computer science as a method for significant cancer diagnostic activities and aims to develop new diagnostic and prognostic markers for personalised cancer treatment.	<a href="https://oslo-universitetssykehus.no/avdelinger/kreftklinikken/institutt-for-kreftgenetikk-og-informatikk#les-mer-om-institutt-for-kreftgenetikk-og-informatikk">https://oslo-universitetssykehus.no/avdelinger/kreftklinikken/institutt-for-kreftgenetikk-og-informatikk#les-mer-om-institutt-for-kreftgenetikk-og-informatikk</a>

## INDUSTRY

Entity	Precision medicine related activity/ focus in Norway	Link to website
Abbvie	Scientists in Abbvie are advancing a pipeline of specialty medicines with a focus on cancer, immune-mediated conditions, neurodegenerative diseases and more.	<a href="http://www.abbvie.no/">http://www.abbvie.no/</a>
Amgen	Conducting high-quality research by utilising science and knowledge of biotechnology to develop medicines and targeted treatment methods that can improve health or save lives for severely sick patients.	<a href="http://www.amgen.no">http://www.amgen.no</a>
APIM therapeutics	By exploiting a novel therapeutic target, the company's vision is to develop novel single agent and combinatorial cancer treatments with the potential to address serious unmet patient needs.	<a href="http://www.apimtherapeutics.com/">http://www.apimtherapeutics.com/</a>
Arctic Pharma	Committed to developing innovative anti-cancer drugs by exploiting the "sweet tooth" of cancer cells and their peculiar metabolic features.	<a href="http://www.arcticpharma.com">http://www.arcticpharma.com</a>
Astellas	Improving life by providing innovative medicines in areas of health where there is urgent need for better treatments such as transplant recipients, cancer patients, and patients with life-threatening infections.	<a href="https://www.astellas.no/">https://www.astellas.no/</a>
Astrazeneca	Biopharmaceutical company focused on developing ideas for innovative, effective medicines that make important advances in key therapeutic areas such as cancer, cardiovascular disease, diabetes, mental disorders, respiratory tract and inflammation.	<a href="https://www.astrazeneca.no/">https://www.astrazeneca.no/</a>
Balter Medical	Developing and commercialising applications of the Optical Transfer Theory, a mathematical modelling technique applied to digital photographic images of skin lesions to assist in the diagnosis of melanoma	<a href="http://www.baltermedical.com/">http://www.baltermedical.com/</a>
BerGenBio	A clinical-stage biopharmaceutical company focused on developing a pipeline of first-in-class selective AXL kinase inhibitors to treat multiple aggressive cancers.	<a href="http://www.bergenbio.com">http://www.bergenbio.com</a>
Biogen	Biogen develops, markets and manufactures treatment options for people living with severe neurological, autoimmune and rare diseases.	<a href="https://www.biogen.no/">https://www.biogen.no/</a>
Bionor	Biopharmaceutical company with first mover potential to advance a possible functional HIV cure and has successfully completed a clinical trial using the shock and kill approach.	<a href="http://www.bionorpharma.com/">http://www.bionorpharma.com/</a>
Bristol-Myers Squibb	A global biopharmaceutical company whose mission is to discover, develop and deliver innovative medicines that help patients prevail over serious diseases.	<a href="https://www.bmsnorge.no/">https://www.bmsnorge.no/</a>
Celgene	Sharing data of their global clinical studies for interested parties such as researchers, clinicians and patients, which can facilitate and support precision medicine.	<a href="http://www.celgene.no">http://www.celgene.no</a>
Clever Health	Treating prostate cancer patients by building a profile unique to the patient using blood test results measured on the patient's own reference level, not against a population-based measurement, for follow-up care.	<a href="https://www.cleverhealth.no/">https://www.cleverhealth.no/</a>
Curida	Producer of pharmaceuticals for other pharmaceutical companies mainly for liquid pharmaceuticals as well as to preserve important expertise in Norway and invest in the entire value chain of medical innovations.	<a href="http://curida.no">http://curida.no</a>
GE Healthcare	Offers a wide range of products and services to improve productivity and safety in the healthcare industry and enable healthcare professionals to diagnose better and treat patients.	<a href="http://www3.gehealthcare.no/hb-no">http://www3.gehealthcare.no/hb-no</a>

Entity	Precision medicine related activity/ focus in Norway	Link to website
iNANOD	A nanotechnology based anticancer drug developing company to increase efficacy of cancer drugs and to reduce unintended side-effects for cancer patients and maximise their longevity.	<a href="http://www.inanod.com/">http://www.inanod.com/</a>
Institute for Energy Technology (IFE)	IFE's Isotope Laboratories have an extensive activity in the field of nuclear medicine and development of new radiopharmaceuticals.	<a href="https://www.ife.no">https://www.ife.no</a>
Inven2	Inven2 is the next generation innovation company, established to safeguard and further develop Norwegian innovation by building bridges between high-quality research and the industry.	<a href="http://www.inven2.com/no">http://www.inven2.com/no</a>
IRW Consulting	Nordic Contract Research Organisation (CRO) experienced in conducting clinical trials, Non-Interventional Studies (NIS) and medical device studies, covering all the stages of clinical development.	<a href="http://irwcro.com/">http://irwcro.com/</a>
Janssen	Investing in the best and most available research expertise to lay the groundwork for new ways of treating diseases to continue to play an important role in solving medical needs.	<a href="http://www.janssen.com/norway/">http://www.janssen.com/norway/</a>
Larix	Clinical Research Organisation that assists in all aspects of clinical trials, to pharmaceutical, biotechnology and medical device companies.	<a href="http://www.larix.dk/">http://www.larix.dk/</a>
LINK Medical	A European full-service contract research organisation (CRO) providing project management and product development services for the pharmaceutical and medical device industry, focussing on people and values.	<a href="http://linkmedical.no/">http://linkmedical.no/</a>
Lytix Biopharma	Through the 'release and reshape' effect of LTX-315, the company's clinical-stage product, tumours are sensitised to other types of therapies opening up for a variety of combination treatments.	<a href="http://www.lytixbiopharma.com">http://www.lytixbiopharma.com</a>
Merck Life Sciences	Delivering products and services for life science research in academic and pharmaceutical environments with the focus on genomic, proteomic and cellular analysis.	<a href="http://www.merckmillipore.com/">http://www.merckmillipore.com/</a>
MSD Norge	Research is focused on studying several therapeutic areas, including cardiovascular disease, diabetes, vaccines, neurology and a variety of cancerous diseases conducted at major hospitals and in private practice.	<a href="http://www.msdstudier.no/">http://www.msdstudier.no/</a>
Nacamed	Producing nanoparticles of silicon material for targeted drug delivery of chemotherapy, radiation therapy and diagnostics to kill cancer cells.	<a href="http://www.nacamed.com/">http://www.nacamed.com/</a>
Nextera	Offering a highly versatile and innovative platform that finds its application in a broad array of fields leaning on protein engineering and evolution such as life sciences and drug discovery.	<a href="http://www.nextera.no/">http://www.nextera.no/</a>
Nordic Nanovector	Biopharmaceutical company dedicated to extending and improving the lives of patients with haematological cancers through the development and commercialisation of innovative targeted therapeutics.	<a href="http://www.nordicnanovector.com/">http://www.nordicnanovector.com/</a>
Norgenotech	Creates a platform and tools for diagnostics of individual levels of DNA damage, oxidation and repair capacity, fundamental health indicators relevant to cancer and other diseases and personalised medicine.	<a href="http://www.norgenotech.no/">http://www.norgenotech.no/</a>
Novartis Norge	Creating value for patients and healthcare by positively influencing people's lives by discovering, developing and marketing new products to cure disease and improve quality of life.	<a href="https://www.novartis.no/">https://www.novartis.no/</a>

Entity	Precision medicine related activity/ focus in Norway	Link to website
Onco Invent	Designing better cancer treatments by applying known physical and chemical principles of selected novel materials in new ways to maximise their medical benefit while minimising potential safety concerns.	<a href="http://www.oncoinvent.com/">http://www.oncoinvent.com/</a>
Oncolmmunity	Oncolmmunity is a bioinformatics company offering proprietary machine-learning-based software to address the key knowledge gaps in the prediction of bone fide immunogenic neoantigens for personalised cancer immunotherapy.	<a href="http://www.oncoimmunity.com">http://www.oncoimmunity.com</a>
Oslo Cancer Cluster	A hub for (inter)national networks to support the right treatment to the right cancer patient at the right time. Initiator of National Cancer Genomic Consortium focused on personalised cancer treatment.	<a href="http://oslocancercluster.no/">http://oslocancercluster.no/</a>
PCI Biotech	Biopharmaceutical company focusing on development and commercialisation of novel therapies for the treatment of cancer through its innovative photochemical internalisation (PCI) technology platform.	<a href="http://pcibiotech.no">http://pcibiotech.no</a>
Pfizer, Oncology Business Unit	Initiated a national platform for genetic cancer diagnostics to help ensure that patients receive fast and accurate diagnoses and access to treatments.	<a href="https://www.pfizer.no/">https://www.pfizer.no/</a>
Phoenix solutions	A biotech company developing a technology platform for targeted drug delivery – Acoustic Cluster Therapy (ACT®). ACT® is a unique approach to ultrasound (US) mediated, targeted drug delivery.	<a href="https://www.phoenixsolutions.no/">https://www.phoenixsolutions.no/</a>
Photocure	World leader in photodynamic technology and a pharmaceutical company focused on developing and commercialising solutions in several disease areas such as bladder cancer, HPV and precancerous lesions of the cervix.	<a href="https://www.photocure.com/">https://www.photocure.com/</a>
Preteck	A research-based company that develops and commercialises medical products for clinical diagnosis, and to provide important health-related information.	<a href="https://www.preteck.no/">https://www.preteck.no/</a>
Radforsk	An early-stage evergreen fund dedicated to oncology that works hands-on with selected start-up companies in the immune-oncology sector and possesses first-hand knowledge of the sector.	<a href="http://radforsk.no/">http://radforsk.no/</a>
Roche Norge	Research-based biotechnology company with a strategy for personalised care aimed at having available drugs and diagnostics that enable visible improvements in human health and quality of life and patient survival.	<a href="http://www.roche.no/">http://www.roche.no/</a>
Sintef	Focused on development of microbial production processes, establishment of numerous methods, technologies, assays and laboratories, and development of nanoparticles tailored for drug delivery, biosensors, and new solutions for therapy and diagnostics.	<a href="http://www.sintef.no/">http://www.sintef.no/</a>
Takeda	Delivering leading innovation in gastroenterology and oncology and developing medicines using specialised medicines and new knowledge to create personalised treatment for patient groups who do not receive high-quality treatment today.	<a href="http://www.takeda.no/">http://www.takeda.no/</a>
Targovax	Clinical-stage immuno-oncology company dedicated to the development of highly targeted immunotherapies for cancer patients by developing treatment approaches that harness the patient's own immune system to fight the cancer.	<a href="http://www.targovax.com">http://www.targovax.com</a>
Telenor	Telenor is Norway's sole provider of telecommunications solutions to all Norwegian hospitals, and a market leader in digital welfare technology for municipalities. In addition, Telenor offers technology and solutions to digitalise the healthcare sector and enable mobile workflow.	<a href="https://www.telenor.no">https://www.telenor.no</a>

Entity	Precision medicine related activity/ focus in Norway	Link to website
Teva	As the world's biggest generic company, Teva translates more medicine and helps treat more patients than any other drug company, and thus also significantly reduces public spending.	<a href="http://www.tevapharm.no">www.tevapharm.no</a>
Tieto	Delivering "Lifecare" services to enable seamless care and better system efficiency through enhanced coordination of care and improved communication between the patient and all health and social care providers and caregivers.	<a href="https://www.tieto.no">https://www.tieto.no</a>
Ultimovacs	A pharmaceutical company developing novel immunotherapy against cancer. Our leading product is UV1, a therapeutic cancer vaccine (TCV) directed against human telomerase (hTERT).	<a href="http://ultimovacs.com/">http://ultimovacs.com/</a>
Vaccibody	Vaccibody AS is a biopharmaceutical company dedicated to the discovery and development of novel immunotherapies, prophylactic and therapeutic vaccines which target cancer and infectious diseases, for human and veterinary use.	<a href="http://www.vaccibody.com/">http://www.vaccibody.com/</a>
Zelluna Immunotherapy	Revolutionising cancer therapy by developing TCR-based therapies with the potential to treat a wide range of cancer types and patients.	<a href="http://www.zelluna.com">http://www.zelluna.com</a>

## OTHERS

Entity	Precision medicine related activity/ focus in Norway	Link to website
Bioteknologirådet (The Norwegian Biotechnology Advisory Board)	The Norwegian Biotechnology Advisory Board provides advice, creates debate and informs about the ethical use of biotechnology on humans, animals, plants and microorganisms.	<a href="http://www.bioteknologiradet.no/">http://www.bioteknologiradet.no/</a>
Den nasjonale forskningsetiske komité for medisin og helsefag (The National Committee for Medical and Health Research Ethics)	Set up in 1990 by the Norwegian Ministry of Education and Research, the organisation evaluates ethical questions concerning medical research.	<a href="https://www.etikkom.no">https://www.etikkom.no</a>
Funksjonshemmedes fellesorganisasjon (The Norwegian Federation of Organisations of Disabled People)	The main goal is to work for better living conditions and the fulfilment of human rights for people with disabilities and chronic diseases.	<a href="http://www.ffo.no/">http://www.ffo.no/</a>
Helse Nord, Senter for klinisk dokumentasjon og evaluering	Contributing to quality improvement of patient care through gathering knowledge on quality and health services.	<a href="https://helse-nord.no/skde">https://helse-nord.no/skde</a>
Mental Helse	Working with raising awareness, health promotion, and prevention of mental health problems by involving patients' and their relatives' and experts' knowledge and experiences.	<a href="http://www.mentalhelse.no">http://www.mentalhelse.no</a>
Nasjonalt kompetansesenter for migrasjons- og minoritetshelse (The Norwegian Centre for Migration and Minority Health)	Aiming to be the nexus for migrant and ethnic minority health, through research and policy development, education, training, capacity building and dissemination of research and information nationally and internationally.	<a href="http://www.nakmi.no/">http://www.nakmi.no/</a>
NordForsk	NordForsk is an organisation under the Nordic Council of Ministers that provides funding for and facilitates Nordic cooperation on research and research infrastructure.	<a href="https://www.nordforsk.org">https://www.nordforsk.org</a>
Nordic Health Research and Innovation Networks	Arena for exchange of knowledge and transfer of competency between Nordic countries, resolving common issues, developing common rules and practices, and strengthening the interaction between the hospitals and the industry.	<a href="https://nordicnetworks.org/">https://nordicnetworks.org/</a>
Sirius	Expertise in EU project Optique, a platform to connect end users and data sources and utilise data to solve scalable data access relevant for precision medicine activities.	<a href="http://sirius-labs.no/">http://sirius-labs.no/</a>

