DNV·GL

# Consent for clinical genetic testing in Norway

## Considerations to the development of process and content

2020

**Author**
DNV GL, Group Technology and Research (GTR),
Precision Medicine Program

**Contact**
Bobbie N. Ray-Sannerud
Program Director, Precision Medicine Program,
Group Technology and Research (GTR)
E-mail: bobbie.nicole.ray-sannerud@dnvgl.com
Mobile +4741402298

**Acknowledgements**
We would like to acknowledge contributions by Oslo University Hospital (OUS) Legal department and Department of Medical Genetics. We would also like to acknowledge the opinion of the ethical expert Berge Solberg at Norwegian University of Science and Technology (NTNU)

# CONTENTS

# ABBREVIATIONS, DEFINITIONS AND TRANSLATIONS

## DISCLAIMER

The considerations published in this white paper are provided for general information and illustrative purposes only. The following considerations do not represent professional or legal advice of any kind. Obtaining informed consent from patients participating in genetic and genomic testing in the clinical context requires legal and ethical review prior to its development. As a result, readers should seek appropriate legal guidance when developing their consent processes.

## ABBREVIATIONS

| | |
|---|---|
| **ACMG** | American College of Medical Genetics and Genomics |
| **AMG** | Department of Medical Genetics |
| **ANESM** | Agence nationale de l'évaluation et de la qualité des établissements et services sociaux et médico-sociaux |
| **APEC** | Asia Pacific Economic Cooperation |
| **BBMRI-ERIC** | Biobanks and Biomolecular Research Infrastructure -European Research Infrastructure Consortium |
| **CFR** | Code of Federal Regulations |
| **CM/rec** | Compendium Records |
| **DUO** | Data Use Ontology |
| **EPF** | European Patients Forum |
| **ESHG** | European Society of Human Genetics |
| **FISH** | Fluorescence in situ hybridization |
| **GA4GH** | Global Alliance for Genomics and Health |
| **GDPR** | The EU General Data Protection Regulation |
| **GDS** | Genomic Data Sharing (policy) |
| **GPAP** | Genome-Phenome Analysis Platform |
| **HBGRDs** | Human Biobank and Genetic Research Databases |
| **HBM4EU** | Science and Policy for a Healthy Future |
| **HIPAA** | Health Insurance Portability and Accountability Act |
| **IC** | Informed Consent |
| **IVD** | In vitro diagnostics |
| **LDT** | Lab developed test |
| **NGS** | Next generation sequencing |
| **NIH** | National institute of Health |
| **OECD** | Organisation for Economic Co-operation and Development |
| **OUS** | Oslo University Hospital |
| **WES** | Whole exome sequencing |
| **WGS** | Whole genome sequencing |

## DEFINITIONS

| Subject Matter | |
|---|---|
| Clinically actionable variants | Variants where a medical intervention, preventative approach, or early detection is available. |
| Content | Information / substance contained (within) |
| Genetic testing | A type of medical test that identifies changes in chromosomes, genes, proteins, or other similar molecular biomarkers. For example, by one of several methods such as but not limited to WES, WGS, Sanger Sequencing, microarrays, and FISH. |
| Incidental Findings | Findings outside the original purpose of testing are that not sought out but identified. This is a term that has depreciated over the years. |
| Process | A systematic sequence of interdependent actions towards a possible conclusion |
| Reanalysis | The process through which the original data derived from the genetic test and / or sample is reassessed, usually according to new information from the patient or data pipeline |
| Secondary Findings | Findings outside the original purpose of testing that are actively sought out and / or analyzed. |
| Variant | Genetic variation (identified) within a genome |
| Processing (e.g., of genetic data) | Anything that is done to, or with genetic data (including simply collecting, storing or deleting those data). |

| Language | |
|---|---|
| Can | Indicates something that is possible |
| Consideration | A subject or fact that needs to be thought about carefully |
| May | Indicates something that may be permitted |
| Recommendation | A suggestion that something is good or suitable |
| Requirement | Something you must do |
| Shall | Indicates a requirement |
| Should | Indicates a recommendation |

## ENGLISH TRANSLATION OF RELEVANT NORWEGIAN LEGISLATION

| Norwegian title | English title | Date of issue |
|---|---|---|
| Lov om medisinsk bruk av bioteknologi (bioteknologiloven) (opphevet) | The Act Relating to the Application of Biotechnology in Medicine (the Biotechnology Act) (repealed) | 1994 |
| Lov om pasient- og brukerrettigheter (pasient- og brukerrettighetsloven) | The Act Relating to Patients' Rights (the Patients' Rights Act) | 1999 |
| Lov om helsepersonell (helsepersonelloven) | The Act Relating to Health Professionals (the Health Professionals Act) | 1999 |
| Lov om spesialisthelsetjenesten (spesialisthelsetjenesteloven) | The Act Relating to Specialized Health Services (the Specialized Health Services Act) | 1999 |
| Lov om behandling av personopplysninger (personopplysningsloven) | The Act Relating to the Processing of Personal Data (the Personal Data Act) (repealed) | 2000 |
| Lov om humanmedisinsk bruk av bioteknologi (bioteknologiloven) | The Act Relating to the Application of Biotechnology in Human Medicine (the Biotechnology Act) | 2003 |
| Lov om behandlingsbiobanker (behandlingsbiobankoven) | The Act Relating to Biobanks (the Biobank Act) | 2003 |
| Lov om kommunale helse- og omsorgstjenester (helse- og omsorgstjenesteloven) | The Act Relating to Municipal Health and Care Services (the Health and Care Services Act) | 2011 |
| Lov om medisinsk- og helsefaglig forskning (helseforskningsloven) | The Act on Medical and Health Research (the Health Research Act) | 2008 |
| Lov om helseregistre og behandling av helseopplysninger (helseregisterloven) | The Act on Personal Health Data Filing Systems and the Processing of Personal Health Data (the Health Registry Act) | 2014 |
| Lov om behandling av helseopplysninger ved ytelse av helsehjelp (pasientjournalloven) | The Act Relating to Health Records (the Health Records Act) | 2014 |

# EXECUTIVE SUMMARY

With the increased utilization of genomic sequencing in the clinical context in Norway, practical and ethical issues in the development of the content and process of informed consent (IC) are emerging. Challenges exist in bridging the gap between Norwegian law and regulations and clinical practice for establishing an adequate IC process for genetic testing in the clinical context.

The BigMed project, a Norwegian Research Council-funded project, has the aim to address the challenges around the clinical implementation of precision medicine in Norway. An activity within work package 3 and led by DNV GL focused on addressing the challenges in developing IC for clinical genomics. In the scope of this activity, DNV GL performed a literature review, a series of interviews with experts as well as a workshop with Oslo University Hospital (OUS), Department for Medical Genetics (AMG). These activities focused laboratory, clinical, and legal representatives on the legal, ethical, and practical issues related to IC for clinical genetic testing. The emphasis of these activities was on understanding the current and future needs related to:

**a)** the delivery of clear and concise information to support patients and / or guardians in deciding to undergo genetic testing; and
**b)** increasing the further sharing of knowledge generated through clinical pathways for the benefit of current and future patients.

The project findings detail the issues and nuanced considerations associated with various consent challenges around genetic testing in the clinical context. Towards developing a practical strategy for managing these challenges, a set of considerations were developed to serve as a starting point for laboratories and clinics for the development of the content and process of IC in the clinical genomic setting.

# INTRODUCTION

National and international legislation, scientific literature, professional guidelines, and society discussions continue to influence the development of practices of obtaining informed consent (IC) in the clinical context for genetic testing across the globe.

The technological and clinical boundaries of how genetic diseases are diagnosed and managed are being pushed and extended at a rate that makes it challenging for authorities and professional bodies to keep ethical guidelines and regulations up-to-date and relevant. This has spurred urgent and necessary discussion on the scope for IC. Relevant legal and ethical issues include (i) establishing a common interpretation of which elements of genomic data are considered anonymous versus personal as these two categories are regulated differently by national law and General Data Protection Regulation (GDPR); (ii) developing a process and consenting for re-contacting the patient and / or their family members after initial results have been delivered; and (iii) the potential re-use of data. The manner in which the purpose, benefits, and potential risks of genetic testing are communicated with patients will influence the voluntary decision a patient makes about whether to begin or continue with the genetic testing. Therefore, a careful review of patient needs must be considered with reference to medical, legal, ethical, and societal implications in any discussion.

The goal of this work, funded through the BigMed project, aims to provide a starting point of IC development considerations, designed to guide healthcare professionals working within clinical genomics in Norway. The work reviews the ways in which genetic testing in the clinical context affects the IC process by drawing upon a review of the literature surrounding the relevant legal, ethical, policy statements, scientific literature, and best practices; a series of qualitative interviews; and input from a diverse set of experts from laboratory, clinic, and legal departments at a workshop (details in appendix 1). The interviews and workshop were based on several use-cases at the OUS, AMG, the largest medical genetic department in Norway. Representatives were drawn from both the clinical and laboratory units, and for the clinical areas of rare disease, hereditary cancer, heart disease and childhood cancers, as well as the legal department at OUS.

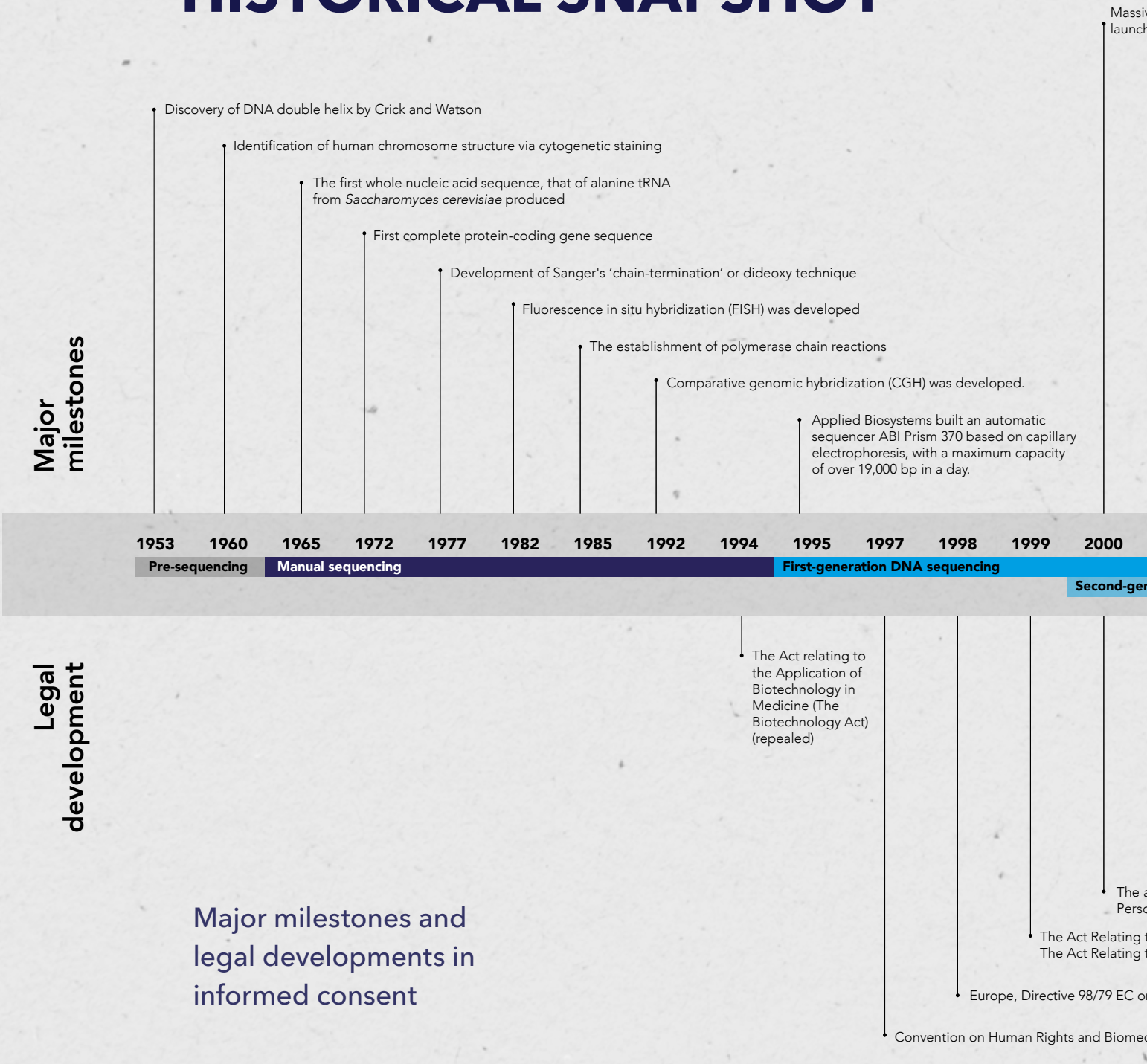
# PURPOSE OF INFORMED CONSENT

The concept of consent in medicine appeared in the 18th century for the first time in the legal case of Slater v Baker & Stapleton, where surgery was performed against the will of the patient, which questioned the paternalistic practice of 'doctor knows best'(1,2).

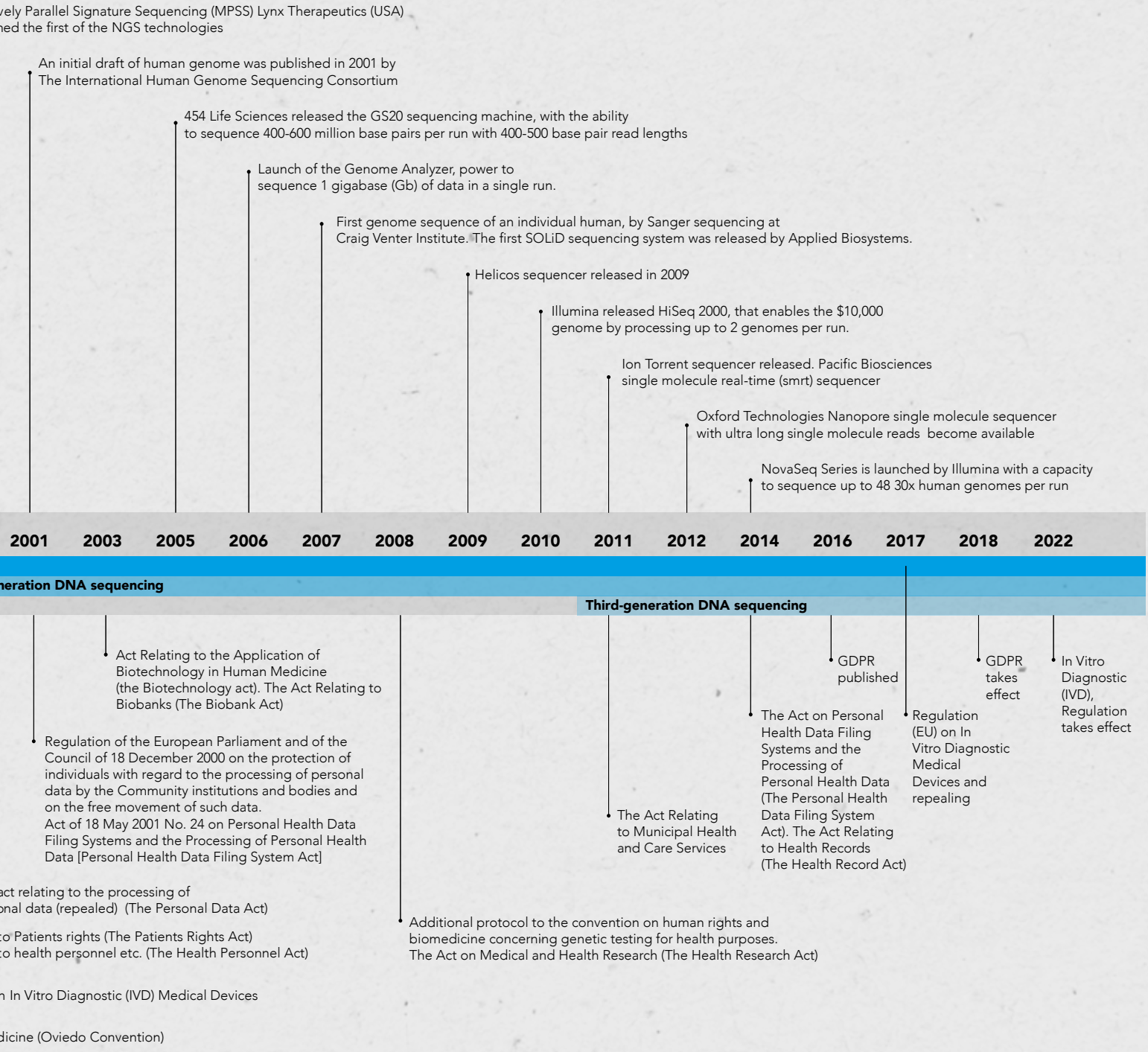
Medical ethics continued to be debated in late 19th and early 20th centuries (3). It was only in 1947 that the Nuremberg code set out the principle of obtaining 'informed consent', after the Nuremberg trial of war crimes relating to human experimentations committed by the Nazi regime during WWII (4,5). Seventeen years later, the World Medical Association adopted in its general assembly the Declaration of Helsinki, which stated the ethical principles for medical research involving human subjects (6). A general principal of the Nuremberg code and the declaration of Helsinki were to secure the autonomy of individuals to ensure that all enrolment in a clinical trial should depend on free-will or 'consent', in addition to the fundamental medical principle: "primum non nocere". To obtain consent based on free will, it is necessary that individuals understand the nature of the treatment. In other words, individuals must be appropriately 'informed' prior to consent, in contrast to the ancient paternalistic medical practice when clinicians used technical jargon only they understood and made decisions on behalf of their patients. Hence, 'informed consent' promotes a more balanced relationship between patients and doctors, and more generally between society and its healthcare system. Today, consent is a fundamental principle enshrined in the healthcare legislation, given either implicitly or in writing in conjunction with healthcare delivery or medical research.

With the recent development of genomic sequencing technologies, new ethical considerations are important in respect of the concept of IC. Genetic sequencing enables personalized care; however, much of its progress depends on sharing patients' genotype and phenotype data. At the same time, genotype and phenotype data is inherently sensitive and sharing such data has called into question the potential to infringe privacy. As a matter of course, the GDPR (7) imposes specific requirements to the processing of sensitive personal information (i.e. genetic data in our case), of which consent is a central element. Moreover, the potential of genetic testing to predict pre-symptomatic disease adds to existing ethical questions related to prenatal diagnostic or communication about a disease risk to family members. All these concerns related to the consent process often require documentation by hospitals.

# GENETIC TESTING IN CLINICAL PRACTICE: A HISTORICAL SNAPSHOT




Major milestones and legal developments in informed consent


vely Parallel Signature Sequencing (MPSS) Lynx Therapeutics (USA)
hed the first of the NGS technologies
An initial draft of human genome was published in 2001 by The International Human Genome Sequencing Consortium
454 Life Sciences released the GS20 sequencing machine, with the ability to sequence 400-600 million base pairs per run with 400-500 base pair read lengths
Launch of the Genome Analyzer, power to sequence 1 gigabase (Gb) of data in a single run.
First genome sequence of an individual human, by Sanger sequencing at Craig Venter Institute. The first SOLiD sequencing system was released by Applied Biosystems.
Helicos sequencer released in 2009
Illumina released HiSeq 2000, that enables the $10,000 genome by processing up to 2 genomes per run.
Ion Torrent sequencer released. Pacific Biosciences single molecule real-time (smrt) sequencer
Oxford Technologies Nanopore single molecule sequencer with ultra long single molecule reads become available
NovaSeq Series is launched by Illumina with a capacity to sequence up to 48 30x human genomes per run
2001
2003
2005
2006
2007
2008
2009
2010
2011
2012
2014
2016
2017
2018
2022
neration DNA sequencing
Third-generation DNA sequencing
Act Relating to the Application of Biotechnology in Human Medicine (the Biotechnology act). The Act Relating to Biobanks (The Biobank Act)
Regulation of the European Parliament and of the Council of 18 December 2000 on the protection of individuals with regard to the processing of personal data by the Community institutions and bodies and on the free movement of such data.
Act of 18 May 2001 No. 24 on Personal Health Data Filing Systems and the Processing of Personal Health Data [Personal Health Data Filing System Act]
act relating to the processing of onal data (repealed) (The Personal Data Act)
o Patients rights (The Patients Rights Act)
o health personnel etc. (The Health Personnel Act)
n In Vitro Diagnostic (IVD) Medical Devices
dicine (Oviedo Convention)
Additional protocol to the convention on human rights and biomedicine concerning genetic testing for health purposes.
The Act on Medical and Health Research (The Health Research Act)
The Act Relating to Municipal Health and Care Services
The Act on Personal Health Data Filing Systems and the Processing of Personal Health Data (The Personal Health Data Filing System Act). The Act Relating to Health Records (The Health Record Act)
GDPR published
Regulation (EU) on In Vitro Diagnostic Medical Devices and repealing
GDPR takes effect
In Vitro Diagnostic (IVD), Regulation takes effect

Genetic and genomic testing is moving at a steady rate into clinical practice and relies on a long history of scientific development, particularly in genetics, molecular biology, and genomics.

A timeline depicting the key events within the rapidly changing landscape of genetic and genomic testing may provide some insight to the challenges associated with IC. As illustrated, technologies are continuously developing, and as they mature, they are being transferred from the research environment to patient care. As a result, government agencies are repeatedly challenged with creating or modifying regulations governing these to ensure the safety and privacy of patients. This results in a series of legislative documents governing different aspects of technologies. Archived documents have been replaced with updated regulations, while others are still valid and operative, making it non-trivial to navigate and comply.
An example of this is the emergence of laws that cover genetic testing for healthcare purposes and the processing of genetic data outside of healthcare purposes. Another example of a complicated set of regulations is the relationship between the GDPR, national health laws and the Oviedo-convention. The GDPR makes up the general framework for the processing of personal data in all EU and EEC countries, while the processing of health and genetic information is subject to special regulations in national law and the Oviedo Convention of the Council of Europe. This means that at some point of the processing, you might move out of the scope of the national laws, and into the scope of the GDPR – but it is not clear where to draw this line. With an accelerated phase of new technologies, development and their transfer to healthcare, regulatory documents must constantly address emerging challenges.

## THE CURRENT LEGAL FRAMEWORK FOR INFORMED CONSENT IN GENETIC AND GENOMIC TESTING IN NORWAY

Under Norwegian health law, consent to ordinary healthcare has traditionally been obtained orally during the doctor's consultation with the patient, or one has assumed an implied consent based on the patient's behavior and the mere fact that the patient consults the health services, cf. the Patient Rights Act § 4-2 subsection one. However, genetic and genomic testing of humans is additionally and specifically regulated in Ch. 5 of the Biotechnology Act. The Oviedo Convention (8) and the Additional Protocol on Genetic Analysis (9) make up the overarching framework, while nationally the Biotechnology Act constitutes the most important regulatory document.

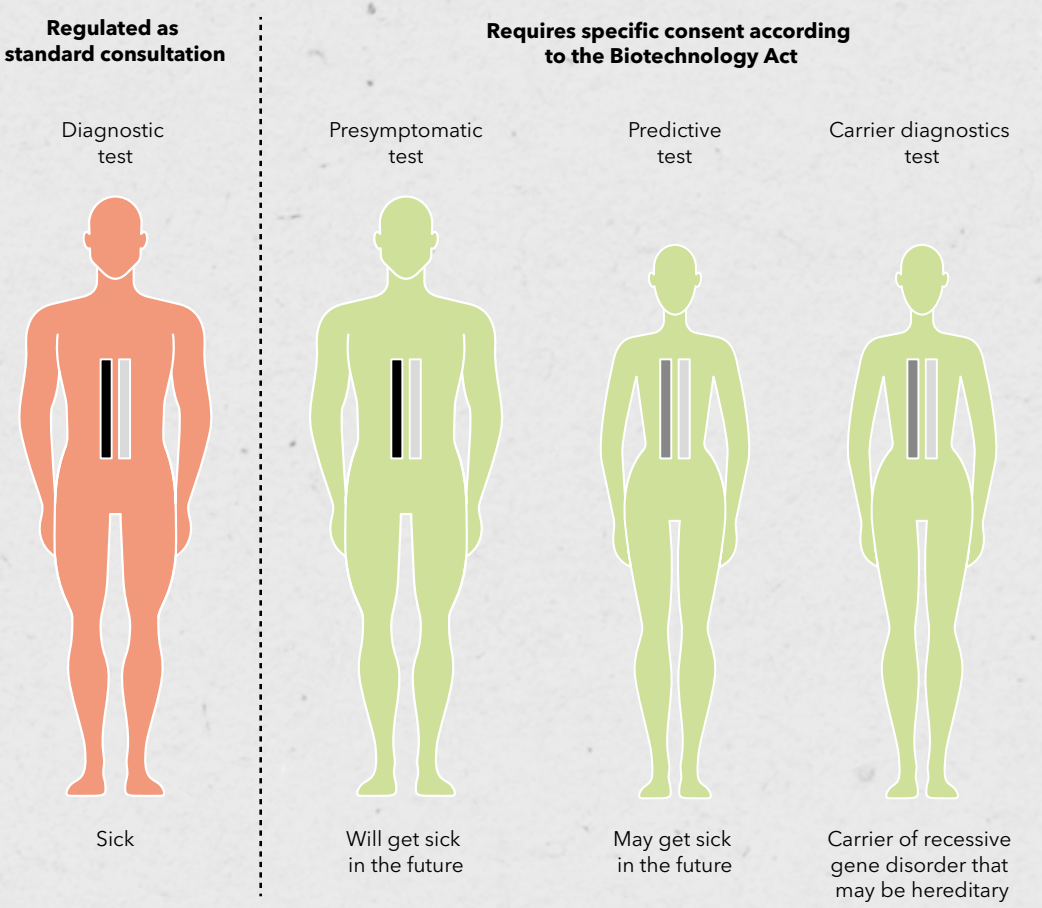



**Figure 2** Illustration of categories requiring written consent or not for genetic and genomic testing according to the current rules set out in the Biotechnology Act § 5-4, cf. § 5-1. Reprinted from Bioteknologirådet, by S. Bratlie, 2017. Retrieved 2020 Jan 10, form http://www.bioteknologiradet.no/temaer/gentesting/. Copyright 2017 by The Norwegian Biotechnology Advisory Board. Reprinted with permission.

The Biotechnology Act draws a line between genetic testing for diagnostic purposes and genetic testing for pre-symptomatic, predictive, and / or carrier purposes (Figure 2), cf. the Biotechnology Act § 5-1. Consent to genetic testing which is purely diagnostic is regulated by the general rules for consent to healthcare in the Patient Rights Act. The consent does not have to be in writing, but it must be informed and voluntary, cf. the Patient Rights Act § 4-1 subsection one. In order to be informed, the patient must have received adequate and sufficient information about the genetic test and its possible consequences, cf. the Patient Rights Act §§ 3-2 and 3-5. The Oviedo Convention further emphasizes that the consent should be free and informed.

For genetic testing for pre-symptomatic, predictive, and / or carrier purposes conversely, written IC and genetic counseling is required, cf. the Biotechnology Act §§ 5-1 and 5-4. This is due to the implication of such findings. However, depending on which genetic test or analysis is conducted, and aligned with rapid technological advances, a diagnostic test may also reveal pre-symptomatic, predictive, and / or carrier conditions. This has caused some confusion as to whether it is the purpose or the findings of the test that determines how it is categorized and thus as to when the special requirements (i.e. written consent and genetic counseling) in the Biotechnology Act apply. On the one hand, the Biotechnology Act has historically been interpreted in a manner where the findings of the test have been decisive of whether the test is categorized as predictive or diagnostic. On the other hand, legal academics have advocated that this interpretation is a fallacy, and that the test shall rather be categorized according to its purpose (10). Legislative changes of the Biotechnology Act which supports the latter are currently under review by the Norwegian Ministry of Health and Care Services (11).

The Biotechnology Act also explicitly states that children under the age of 16 shall not receive genetic testing that can reveal pre-symptomatic, predictive, and / or carrier conditions unless such testing can reveal conditions for which treatment is available that can prevent or reduce damage or adverse effects on the child's health, cf. the Biotechnology Act § 5-7 subsection one. In these cases, the parent or guardian should receive genetic counseling and have provided written consent prior to testing, cf. the Biotechnology Act § 5-4 subsection two.

### CURRENT LEGISLATION FOR THE SUBSEQUENT PROCESSING OF DATA GENERATED FROM GENETIC TESTS

The Biotechnology Act regulates consent for genetic testing, but does not regulate the processing of genetic data, neither for health care purposes, nor research or other kinds of subsequent processing.

The processing of health data in the patient's medical record is based on the legal duty to document the healthcare, cf. the Health Professionals Act § 39 and the Patient Record Act. It is not based on the patient's consent, and the patient has no right to object to the processing. Furthermore, processing of health data by clinicians is a necessary prerequisite for providing sound healthcare, in terms of diagnosis and treatment, to patients. Clinicians must wisely make use of the data gathered in the medical records in order to make the right decisions when it comes to diagnosis and treatment. Nor this processing of patient data is based on the patient's consent.

The question arises as to whether there are types of processing of data that the clinicians would want to carry out, that is not covered in national legislation.

The national health legislation partly allows and partly imposes processing of health data for other purposes than providing healthcare to the specific patient. Health data may be used for quality assurance and research without the patient's consent. There are for instance a number of legal grounds for submitting patient data to national health registers, cf. the Health Registry Act. However, the question arises as to whether there are types of processing of data that the clinicians would want to carry out, that is not covered in national legislation. One example is to make use of advanced IT-tools for sharing genetic information and other health data in order to match the patient with other similar patients around the world. This can be used to generate and explore medical knowledge outside the research setting and can be fundamental for providing healthcare to other patients.

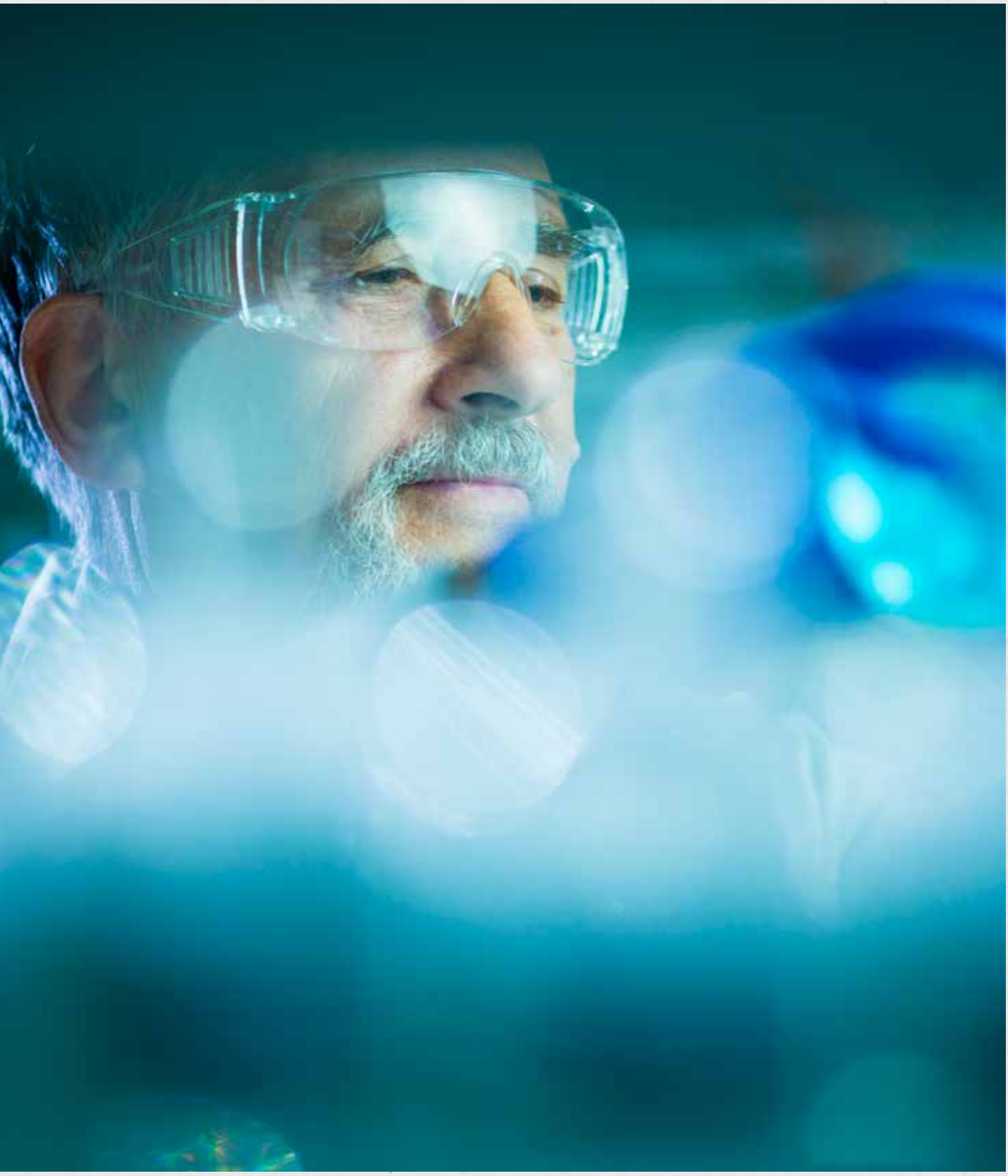
Sharing of this kind might not be regulated by Norwegian health law, as there are no legal grounds that accurately covers the activity. According to the GDPR, the health institution (i.e. the data controller) must make sure that it has a proper legal basis for the processing in question. This raises a number of new questions. What is the scope of the obligation to process health data, in this case genetic data, in order to provide healthcare? Is processing of data in matchmaking tools a part of the ordinary clinical pathway? Can such data sharing be categorized as quality assurance, and thus have its legal basis in the Health Professionals Act? This is when consent as a legal ground for processing becomes relevant.

# INFORMED CONSENT IN THE LANDSCAPE OF SCIENTIFIC AND TECHNOLOGICAL ADVANCES IN GENOMICS

Any discussion surrounding IC in clinical genomics must take into consideration the specific and significant ways in which genomics technologies and diagnostics may differ from older methodologies, and the implications of this on IC.

Modern genetic tests are complex. Assays may test single, pre-defined genetic variants, or may target dozens through thousands of genes. These targets may be specifically described in the indication of testing (i.e. BRAF V600E), but biomarkers may have loose or subjective descriptions (i.e. EGFR fusions), may be contained within larger panels of biomarkers, only some of which may be relevant for the indication (i.e. comprehensive cancer panels), may be composites of many genetic variants (i.e. tumor mutational burden), or may be wholly unknown until after testing and diagnostic work-up (i.e. WGS or WES in rare disease diagnostics).

In many instances genetic tests may have no or only limited negative predictive power, where a negative test result does not exclude an underlying genetic cause for disease. Health personnel and the general public may not be familiar with this mode of testing: historically, and in many cases, a negative result from a laboratory test does in fact indicate the absence of a certain biomarker. NGS-



based diagnostic tests may also have limited positive predictive value, especially for complex variants, and confirmatory methods or reflex testing may be applied systematically or ad hoc, depending on results. Additionally, even if a pathogenic variant is confirmed, it may only have limited penetrance, meaning that the linkage between a genetic finding and pathogenicity may be unclear. The question is then posed if the IC process may be the only tool to convey the nuanced view linking between test results, underlying biology, and disease to not only inform, but manage the expectations of patients in this evolving landscape. If so, is it possible to envision an IC process that thoroughly conveys all the weaknesses in genetic testing and for that matter, other medical tests with similar features?

Clinical insights obtained from the data derived from a genetic test are rapidly changing, based on new understandings and developing technologies. This affects the necessity for continual diagnosis and management of diseases and introduces consent challenges surrounding the reanalysis or reinterpretation of data. Effectively, data from a test which is negative today may be reanalysed in the future, where the availability of new analysis methods, new clinical knowledge, or different treatment algorithms may result in changes to clinical management. While some institutions approach genetic tests as a single and final/definitive laboratory result, the potential for reanalysis means in some cases an ongoing clinician-patient relationship is either explicitly stated or implied. Delivering clarity and managing patient expectations surrounding reanalysis and negative results is one of the key challenges when considering consent policies.

While sharing the results of testing may have little utility outside of a public health context for many assays, data sharing is a central component of many genetic diagnostics and increases the speed with which personalized genomic medicine becomes a reality. The IC process poses an opportunity for patients to consider the trade-offs between privacy and usefulness for themselves and others and make decisions related to how their data can be used. For example, while for certain tests the value of sharing data is low, in a rare disease context, patient matching and consultation with external clinicians is crucial to the diagnostic process. Furthermore, NGS genetic tests often produce additional data outside the original scope of testing, that can have utility for both the patient being diagnosed and for others. Managing data sharing and authorization policies and IC for these potential purposes may challenge existing consent mechanisms and information systems.

To complicate matters further, many types of data may be generated during the course of testing. Genetic data about particular patients, aggregate data from populations of patients, data from quality-control measures, sample metadata, and medical knowledge (i.e. variant classifications) may all be produced by health institutions.

# There are a wide range of potential data uses both within and outside of primary diagnosis that may challenge IC procedures:

1. Technical metrics from the diagnostic may be used both within the hospital and with other organizations to ensure test quality and validity.
2. For difficult cases, sharing data about the primary patient, either for expert consultation or patient-matching initiatives may be essential to diagnose the patient.
3. The diagnostic work-up for some tests requires population variant frequency statistics, which patients can both contribute to but also benefit from.
4. Certain genetic markers may make patients eligible for inclusion into research studies or clinical trials, which can directly impact their treatment plan.
5. Test results, raw NGS data, and other health data about patients may have research value for the discovery of new biomarkers and development of new diagnostics and treatments.
6. To add to the complexity surrounding primary and secondary data use, withdrawal of consent may not be possible once patient data has been shared, and without adequate tracking and metadata annotation, data may be mistakenly used for purposes outside the original scope of consent.
7. Genetic tests may have the possibility of uncovering secondary findings, such as risk factors for developing genetic diseases, or diagnostic findings related to undiagnosed diseases, pregnancy, or cancer. These findings may impact not only the patient, but also the patient's relatives: consanguinity, non-paternity, and carrier status can all be detected with genetic tests. These topics add to the existing practical and ethical questions surrounding patient confidentiality, contacting relatives, and the moral responsibilities and limits of healthcare workers.

# RESULTS

## Three challenges to delivering clinical consent for genetic testing

For Norwegian hospitals conducting genetic testing in the clinical context, the process of obtaining consent has quickly become a focus of attention.

The organization and processes required to offer genetic testing are complex. Treatment teams include new medical specializations and combine counseling, clinician, IT, geneticist, and laboratory roles, and the diagnostic process may be spread over multiple sites within a hospital or indeed multiple health institutions. Defining clear responsibilities, tracking consent and data privileges across IT systems, and ensuring the wishes of the patient are followed when data and diagnoses may travel across laboratories or across the globe, are all key challenges health institutions must address when implementing a responsible consent solution.

With the aim to ensure that the patient or parental guardian can make a voluntary and informed decision about whether to begin or continue with genetic testing, this project gathered information from a literature review, a series of semi-structured qualitative interviews, and input from a diverse set of experts from laboratory, clinic, and legal departments at a Norwegian hospital gathered together at a workshop (specifics to the methodology are detailed in appendix 1) on the current and future needs to the IC process. Findings from this work identified challenges for clinics and laboratories in delivering clear and informative communication to the patient or guardian for making an informed decision. These challenges have been divided into the following three areas:

1. **determining which laws in Norway govern IC;**
2. **building consensus at the local level (healthcare organization) on how to bridge the gap between Norwegian law and clinical practice for establishing an adequate IC process; and**
3. **a need to develop a harmonized practice around the process of delivering and obtaining IC.**

# 1

# Determining which laws in Norway govern IC

| Challenge |
|---|
| Variation in the understanding to which specific laws exist that currently govern IC |
| Variation in the interpretation of when written versus non-written consent is required |
| Variation in the interpretation around the process for children turning the legal age of consent |

| Challenges | Relevant legislation |
|---|---|
| Does the scope of the different legal grounds in national health law cover all necessary requirements for processing of genetic data generated from genetic testing in a clinical context? | Health Professionals Act, Health Registry Act (and corresponding regulations), Patient Records Act, Regulation of Electronic Patient Records, Health Research Act, the Data Protection Act and the GDPR. |
| When written consent and genetic counseling is required for genetic testing | Biotechnology Act and the Patient Rights Act |
| If/when written consent is required for the subsequent processing of the generated data | Health Professionals Act, Health Registry Act (and corresponding regulations), Patient Record Act, Regulation of Electronic Patient Records, Health Research Act, the Data Protection Act and the GDPR. |
| How to ensure that the patients' rights (among others with regards to patient autonomy and the right to information) are adequately safeguarded in relation to genetic testing | The Patient Rights Act (especially Ch. 3 and 4 concerning involvement, informational rights and consent), the Biotechnology Act (Ch. 5), and the Health Research Act (depending on in which context the genetic testing is performed). |
| How to ensure the data subjects' rights when processing genetic data generated from genetic testing | The Data Protection Act and the GDPR |

# 2

# Building consensus at the local level (healthcare organization) on how to bridge the gap between Norwegian law and clinical practice for establishing an adequate IC process

| Challenge |
| --- |
| Currently in Norway, a standardized national approach to an IC process in the clinical genomics context does not exist. As a result, IC processes are developed within individual organizations and clinics, and can be fragmented |
| Variation in practice for the management of incidental / secondary findings |
| Variation in practice for the actions to take around the management of re-contacting patients and an identified specified period post-testing |
| Lack of guidance to how clinicians handle incidental findings that have implications for family members |
| Variation in practice for the actions to take for the management of children (e.g., the transfer of IC when turning of legal age) |
| Variation in practice for the communication to the patient for the management of reanalysis and its triggers (as well as specific acknowledgement as to when new knowledge becomes available) |
| Variation in practice for the communication to the patient for the management of sharing of data internationally and nationally, with specific acknowledgement around the use of databases and consulting (by phone and email) |
| Variation in practice for the actions to take for the management of contacting patients for research such as how patients can be contacted regarding relevant research |
| Variation in practice for the process of notifying at-risk family members who would benefit from changes in clinical management |
| Variation in practice for the determination of clinically actionable variants |
| Lack of consistent approach for the management of expectations for continuous diagnostics (e.g., reanalysis and its triggers, targeted genes versus incidental findings) |

# 3

# A need to develop a harmonized practice around the process and the written content of delivering and obtaining IC

| Challenge |
| --- |
| Lack of standardization and variation of processes for delivering and obtaining IC |
| Variation of approaches in the timing and time duration to deliver IC |
| Variation in the understanding of the "owner" of the IC process and material |
| Variation in practical implementation in response to the withdrawal of consent or rejection of genetic testing |
| Challenge around the process for determining if the patient received the information clearly to make an informed decision |
| Lack of standardization around the information included in the written material used for IC |
| Conflicting information in the literature available around the best practices for which written elements to include in IC |
| Variation of opinions if consent to research should be given on the same or separate form |
| Lack of robust processes to ensure consent is linked to data use throughout hospital processes |
| The complex processes for the collection of IC and management of consented data would benefit from electronic support systems but these are currently lacking |
| A need to include the patient's perspective in the development of the IC process |
| A need to include the healthcare professional delivering IC in the development of the IC process |

# CONCLUSION

It is a practical challenge that the genetic testing laboratories normally do not have a direct relationship with the patients they analyse. Hence they do not know the patient or the relationship between the patient and the clinician who requested the genetic testing; nor what kind of information the patient has received; what the patient expects from the test; whether the patient has taken a stand concerning information about incidental findings; or how the laboratory can use the generated data from each patient. As previously mentioned, the requirements of IC and genetic counseling is regulated in both the Biotechnology Act and the Patient Rights Act and hence a laboratory must simply trust that the requiring clinician has fulfilled his or her duties according to these laws, but even so, the laboratory is still left with several unresolved needs concerning reporting of findings, re-contact, processing of data etc.

**To be able to manage subsequent questions after a genetic test, obtaining written consent can be a tool to provide both the clinician and the laboratory and / or the healthcare organization with information about the patient's wishes, as well as to make sure that the patient has been provided with sufficient information and given an appropriate opportunity to manage the subsequent processing of his or her genetic data.**

However, it should be noted that the challenges related to the subsequent processing of genetic data is to a certain extent not yet resolved under Norwegian health laws and it is still subject to debate how they should be tackled. Written IC represents a needs-driven solution, but it may not be the final one.

The following IC considerations pinpoint several topics that were drawn from findings presented in the interviews and workshop that healthcare organizations should have in mind when developing policies for genetic testing, and policies for the subsequent processing of genetic data generated from such testing. Policies can not only reinforce more consistent practices but can result in delivering clearer informative information to the patient who is deciding to go through with genetic testing or not.

The IC considerations also point to topics for the development of the process and material content of IC. Healthcare organizations should be aware that it might not be acceptable to address all these topics in the same consent form. Consenting to be genetically tested for predictive purposes is for instance specifically regulated by the Biotechnology Act, whilst consenting to health research purposes is regulated in the Health Research Act, therefore requirements for consent for each of them may differ. In addition, the mere processing of genetic data may or may not be covered by

national health laws, depending on the processing in question, cf. point 1.2. If the IC is designed to cover both further data processing (i.e. form the legal basis for processing), participation in research and / or several other topics, the healthcare organization or the relevant data controller should carefully consider how to present such a consent to a patient, cf. GDPR article 7 no. 2.

Additionally, there are different regulations concerning withdrawal of consent depending on what constitutes the legal basis of the processing in question and which laws apply to the processing, cf. amongst others the Patient Rights Act § 4-1 subsection two, the Health Professionals Act Ch. 8, the Health Research Act Ch. 4 and 7 and the GDPR article 7 no. 3. A withdrawal of a consent to healthcare in accordance with the Patient Rights Act § 4-1 subsection two for instance, does not affect the health professional's legal duty to document the healthcare in accordance with the Health Professionals Act §§ 39 and 40.

Moreover, it is questionable whether all of the mentioned topics in these considerations should or can be regulated in a consent due to other specific requirements by law, such as the general duty of offering sound and proper healthcare, cf. amongst others the Health Professionals Act § 4. One should also be aware of, and consider the distinction between, the ethical consent to participation in research and consent as a legal basis for processing of data in accordance with the GDPR. A consent to research may not always also constitute the appropriate legal basis for the data processing. It falls out of the scope of this white paper to discuss these questions further, but the health organizations should be conscious of these questions when drawing up IC policies and seek legal advice in the process.

# Considerations to the development of the clinical consent process and content for genetic testing in Norway

## INTRODUCTION

The rapid uptake of genome sequencing into everyday clinical practice has introduced challenges related to IC. The following considerations draw upon a literature review, a series of semi-structured qualitative interviews, and input from a diverse set of experts from laboratory, clinic, and legal departments gathered together at a workshop from a Norwegian hospital at a workshop. The following considerations are categorized into five sections: 1) legal compliance; 2) local policy development; 3) considerations to the development of the IC process; 4) considerations to the development of the IC written consent; and 5) final considerations.

The considerations are intended as a resource for laboratories and clinics as a starting point for the development or enhancement to their process around IC in the clinical genomic setting. The considerations do not represent legal advice of any kind. Obtaining informed consent from patients participating in genetic testing in the clinical context requires legal and ethical review prior to its development. Therefore, appropriate legal guidance when developing consent processes is recommended. In addition, prospective evaluation is needed to determine whether the considerations enhance the IC process.

# 1. Legal compliance

In terms of legal compliance, a review of national as well as international legislation, particularly in the EU, must be considered as a basis when developing the IC processes and content for genetic testing in a clinical context. To accommodate the pace of technology developments, the law will continue to develop and adapt, therefore, it is important that healthcare management system puts into place a fixed regular review of those developments to ensure that IC processes are compliant.

Currently, for the development of IC, legal compliance should refer to the following two categories and their respective laws:

| Consent to genetic testing | The processing of genetic data for and beyond healthcare purposes |
|---|---|
| Biotechnology Act | Health Research Act |
| Patient Rights Act | Health Professionals Act |
| | Health Registry Act |
| | Patient Record Act |
| | Regulation of Electronic Patient Records |
| | The Norwegian Data Protection Act and the GDPR |

* At the time of writing this paper, a public draft by the Norwegian Directorate of Health for Laboratory Guidelines and Genetic Analysis (No.: Laboratorieveileder for genetiske analyser av fødte) and a public consultation for legislative changes to the Biotechnology Act were under review (11,12). The outcomes of both the upcoming guidelines and potential changes in the Biotechnology Act are recommended for review in terms of their implications for future practices of IC for genetic testing in the clinical context.

# 2. Local policy development

Bridging the gap between the law and clinical practice can require healthcare organizations to develop institutional policies, that are continually reviewed, to provide anticipatory and consistent approaches to cope with the challenges inherent to the rapidly changing landscape of genetic testing. Development of these policies should take into consideration the related national and international current and developing laws. Results from the workshop identified several topics that should be considered:

A. **MANAGEMENT OF INCIDENTAL AND / OR SECONDARY FINDINGS**
- How they will be managed, and process to ensure documentation to the patient's choice in return of such findings.
- Information that addresses situations where return of results may be relevant.
- Defined approaches for cases when incidental findings have implications for family members.

B. **MANAGEMENT OF RECONTACT, POTENTIALLY WITHIN A SPECIFIED PERIOD POST-TESTING**

C. **MANAGEMENT OF OBTAINING IC FROM CHILDREN AND THEIR PARENTAL GUARDIANS**
- With mention of the management of shifting the right for individuals to IC once they turn 16.

D. **MANAGEMENT FOR REANALYSIS AND ITS TRIGGERS**
- With specific acknowledgement to a systematic approach to identification of new knowledge availability.

E. **THE SHARING OF GENETIC DATA, INTERNATIONALLY AND NATIONALLY**
- With specific acknowledgement around the use of databases.
- With specific acknowledgement around consulting other specialists outside of the home institution (by phone and email).

F. **CONTACTING PATIENTS FOR RESEARCH**
- Differentiate between research, clinical trials, and quality registry.

G. **DISCLOSURE AND PROCESS FOR NOTIFYING AT-RISK FAMILY MEMBERS WHO WOULD BENEFIT FROM CHANGES IN CLINICAL MANAGEMENT**

H. **WHICH VARIANTS ARE CLINICALLY ACTIONABLE AT ANY GIVEN TIME**

I. **MANAGEMENT OF IC**

# 3. Considerations to the process of delivering IC

The following set of considerations can serve as a resource for addressing the challenges of how to approach the delivery and management of IC for genetic testing in the clinical context.

### A. ASSIGN RESPONSIBILITY TO WHO OBTAINS CONSENT

- A qualified healthcare professional, preferably a genetic counselor or a specialist.
- Where written consent is required, a defined process is to be followed.
- The responsible healthcare professional should consider the impact the doctor-patient relationship will have on the patient. Patient-doctor relationships are often implicitly paternalistic-authoritarian which may have implications to patient's perceived role in making decisions.

### B. GENETIC COUNSELING OR EQUIVALENT

- Legal requirements in Norway apply only to predictive testing; however, consideration shall be taken for diagnostic testing as well. Assign genetic counseling before, and in some cases, during, and after the testing.
- Efforts are made to ensure the same genetic counselor is involved in all counseling sessions and rotation of new counselors are minimized.

### C. ENSURE DECISION-MAKING CAPACITY

- The patient or guardian is determined to be psychologically and intellectually capable to make a voluntary decision about whether to undergo genetic testing.
- Decision making capacity is typically determined by the healthcare professional obtaining consent.
- To facilitate understanding, consider the use of supplementary tools such as videos, pamphlets, and / or other educational materials that take into consideration variations in cognitive and scientific literacy levels (e.g., genetic / scientific literacy), language, and cultural expectations.
- Institute a language service policy that includes an interpreter fluent in both Norwegian and the patient's spoken language to aid the consent process (with specific training in the language around genetics).

**D. TIME-POINTS AND DURATION**

- The delivery of IC must take place and be obtained prior to testing.
- Timing should take into account the feasibility of receiving and processing information.
- The patient should be provided with relevant information such as to the purpose and the nature of the test, as well as the implications of its results for review prior to the appointment (e.g., as an information packet).
- The concepts around genetic testing can be particularly challenging to convey and may require ample time for understanding.
- IC is achieved through dynamic interactions, adapting to the needs and situation of the patient, and in some cases, through an ongoing process, rather than a one-time informational session.

**E. EXPRESSING A DECISION**

- Following delivery of IC to the patient, the patient must be provided with adequate time to digest that information.
- Once a decision is made, the patient must then clearly communicate their decision.

**F. REFUSAL OR WITHDRAWAL**

- Highlight the participant's right to refuse and / or withdraw consent as well as any limits on this right (e.g., different laws concerning withdrawal of consent apply to different kinds of processing of data, see section 1.3. general comments).
- Provide instructions for how to initiate such a request.
- Offer alternative options if applicable (in lieu of testing).

**G. OWNERSHIP**

- Due to its recent implementation into the clinic, the genetic testing landscape is expected to continue to experience rapid changes, thus requiring a review of the IC process and written material, at minimum, on an annual basis.

# 4. Considerations to the content of the written material for delivering IC

The following set of considerations can serve as a resource for addressing the challenge of how to approach the development of the written IC material for genetic testing in the clinical context.

A. As a basis, the written material should include the simplest language that accurately describes the concepts, as short as possible, and avoid being overly technical. Written material should be available in multiple languages to ensure the material is in a language the patient understands. The consent form should be limited to just a few pages in length.

B. Research-related consent documents can remain separate from the clinical consent form to ensure and maintain clarity. The clinical consent form can contain a question regarding contact for future research. In this case, a statement on the clinical consent form that can be signed off individually may contain, "I consent to being contacted about genomic research in the future. If interested, I will be asked to sign a separate consent form." Consent to research participation in Norway is specifically regulated in Helseforskningsloven.

C. The basic elements of the written material for IC may vary, but a suggested list is provided below.

The way in which this information is communicated should be via a verbal and dynamic interaction with a qualified healthcare professional. The elements are divided into two categories which can be combined, depending on the nature of the test. These categories are: i) genetic testing; most of the elements here should be considered in the written material and ii) processing of data generated from genetic tests; most of the elements here can be considered in the written material as the topics may be regulated by law and thus, not necessarily dependent on the patient's consent.

### I. GENETIC TESTING

**1 ABOUT THE TEST**

A. Scope & purpose of the test: diseases it targets, the name of the genes tested, their reportable range, and the analytical sensitivity and specificity
B. Limitations of the test
C. Description of the test process

D. Benefits and risks of the test
E. Voluntary nature of testing
F. The possibility of refusal (e.g., limitations to this right once a sample has been drawn to which the withdrawal of samples or data is possible or not possible and a description of alternative diagnostic tests if available).
G. Information pertinent to relatives (e.g., practices around informing them or not)

**2 POTENTIAL OUTCOMES**

A. Negative
B. Positive
C. Variant of uncertain significance (implications to parental / family testing)
D. The chance of incidental and / or secondary findings (e.g., Non-paternity, consanguinity, diagnosis unrelated to patient's presentation, prognostic / predictive biomarkers, clinically versus non clinically actionable)
E. Unknown significance
F. No findings

**3 RETURN OF RESULTS**

A. Triggers for recontact with a specified period post-testing
B. Reanalysis (expectation management to how often and the process)
C. Genetic risk to family members & contact (practice around informing them or not)
D. Policy of returning results to relatives
E. Use of confirmatory testing

## II. PROCESSING OF DATA GENERATED FROM GENETIC TESTS

**4 LABORATORY SAMPLE AND DATA STORAGE**

A. Storage and disposal
B. Purpose of storage
C. Type of stored material
D. Ownership / rights of / to the sample
E. Future (secondary) use of data

**5 Privacy and confidentiality**

A. Re-identification risk
B. Submission to internal and external databases
C. National and international data transfer
D. Type of shared data
E. Rights, limitations and risks associated with withdrawal from sharing

**6 Research**

A. Inquire if patient would like to be contacted for research

# 5. Final Considerations

Final considerations for laboratories and clinics in the development of their IC process and written material for genetic testing in the clinical context.

A. The development of IC process should not be viewed as serving primarily a legal objective meant to protect the healthcare organization, but rather having the primary purpose of educating patients about the purpose, risks, and benefits for making a voluntary decision about whether to begin or continue with genetic testing. This is achieved through dynamic interactions, adapting to the needs and situation of the patient, and in some cases, it may be an ongoing process, rather than a one-time informational session.

B. It might not be acceptable to address all these topics in the same consent form. Consenting to be genetically tested for predictive purposes is for instance specifically regulated by the Biotechnology Act, whilst consenting to health research purposes is regulated in the Health Research Act, therefore requirements for consent for each of them may differ. In addition, the mere processing of genetic data may or may not be covered by national health laws, depending on the processing in question, cf. point 1.2. If the IC is designed to cover both further data processing (i.e. form the legal basis for processing), participation in research and / or several other topics, the healthcare organization or the relevant data controller should carefully consider how to present such a consent to a patient, cf. GDPR article 7 no. 2.

C. Input by patient advocacy groups should be considered in the development process, especially for specialized consent forms (e.g. pediatric testing).

D. Genetic counselors play a key role not only in pre-testing counseling, interpretation and delivery of results, but also in the facilitation of decision making in gathering IC. Due to this, genetic counselors should be involved in developing the IC process, especially as it pertains to contributing to material around genomic literacy and education.

E. It is of importance that a process is developed to ensure patient participation in relevant research is developed and managed, where IC allows the option for contacting patients when this becomes available.

F. The consideration of electronic applications to deliver consent, to increase efficiency and effectiveness, that are safe and secure, provide improved patient access to information, time to review and comprehension, having transparent information, and subsequent implementation of consent decisions is recommended

G. International legislation is also relevant when discussing consent and processing of genetic data – Universal Declaration on the Human Genome and Human Rights (UNESCO, 11 November 1997), International Declaration on Human Genetic Data (UNESCO 16 October 2003) and The Universal Declaration of Human Rights (10 December 1948), hereunder and among others the right to private life, the right to science and the right to health and healthcare.

# APPENDICES

## Appendix 1

### METHODS

The considerations formulated from this project draw upon a literature review, a series of semi-structured qualitative interviews, and input from a diverse set of experts from laboratory, clinic, and legal departments at a Norwegian hospital gathered together at a workshop.

### LITERATURE REVIEW

A review of the literature was conducted covering the topic of IC in clinical genomics for a) national and international legislation, particularly in the EU, around the requirements for IC; b) ethical principles around genetic testing and implications for IC; c) best practices in the development of IC forms by a selection of world-leading healthcare organizations; d) policy statements and recommendations by professional societies; and e) scientific publications where IC is specifically addressed in clinical genomics. Table 1 refers to the number of documents reviewed in each of their respective categories.

| TOPICS | NUMBER OF DOCUMENTS REVIEWED | EXAMPLES |
|---|---|---|
| Legal | 42 | GDPR (7), The Biology Act Norway (13), Hearing on Biotechnology Act (2019) (11), Health Research Act (14), and HIPAA (15) |
| Ethical principles | 4 | Helsinki Declaration (16); Declaration of Taipei on ethical considerations regarding health databases and biobanks (2002) (17). |
| Best practices | 6 | The Australian Health Genomics consent form on genetic testing (18), Mayo Clinic in USA (19), and Genomics England (20). |
| Professional guidelines | 10 | GA4GH (21), ACMG, Points to consider for IC for genome/exome sequencing (22); and ESHG, Guidelines for diagnostic next-generation sequencing (2015) and Whole-genome sequencing in health care Recommendations of the European Society of Human Genetics (2013) (23). |
| Scientific publications | 21 | A selection of scientific publications reviewed below. |
| | | |

Table 1: Number of documents reviewed in each of their respective categories

Findings from the literature review suggest that; while national and international legislation provide the legal basis for which healthcare organizations can refer to in their development of their IC processes, challenges exist in bridging the gap between law and clinical practice.

Organizational and national initiatives that have addressed this gap were more closely examined and mapped against the findings from the subsequent interviews and workshops. Amongst these initiatives was the work by Australian Genomics in 2017 in creating a National Clinical Consent Working Group to identify opportunities to standardize consent processes for genomic testing across the country. In 2018, the working group conducted a systematic review of existing consent forms, developing guidelines for the content of consent materials, and drafted a consent form and supporting information.

The work resulted in the development of a National Approach to Clinical Consent for Genetic testing (18) and has gained global recognition, specifically by the Global Alliance for Global Health (GA4GH). Knowledge acquired from this mapping was additionally combined with initiatives and literature that specifically addressed considerations of basic elements to include in the content of the IC process (24,25).

The right not to know; to opt out of the analysis of secondary findings, and published a set of guidelines for healthcare providers delivering medical genetic services. Similar to this is the bioethics commission (2012) publication of a set of guidelines on return of genomic sequencing results and implications for a robust IC process to ensure ethical clinical care (26).

| LEGAL | | |
|---|---|---|
| | DOCUMENT | REFERENCE |
| 1 | The European Parliament and the Council of the European Union. Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (GDPR) | (7) |
| 2 | The Personal Data Protection Act, Singapore (2012) | (27) |
| 3 | Council conclusions on Health in the Digital Society - making progress in data-driven innovation in the field of health (2017/C 440/05) | (28) |
| 4 | Code of Ethics of the World Medical Association. Declaration of Helsinki, 1964 | (16) |
| 5 | Council of Europe - Recommendation CM/Rec(2019)2 of the Committee of Ministers to member States on the protection of health-related data, 2019 | (29) |
| 6 | The Biotechnology Act, 2003 | (13) |
| 7 | The government's report on public hearing on changes to the Biotechnology Act, 2019. | (11) |
| 8 | The Norwegian Data Protection Agency: Privacy concerns of genetics testing, 2013 | (30) |
| 9 | Notes of the Norwegian Directorate of Health's Sector Council meeting, 2019 | (31) |
| 10 | The Health Research Act, 2008 | (14) |
| 11 | Meldinger til Stortinget - Evaluering av bioteknologiloven | (32) |
| 12 | NSHG: Feedback on External hearing for laboratory guidelines for genetic testing of born individuals | (33) |
| 13 | Act relating to treatment biobanks, 2003 | (34) |
| 14 | The EU General Data Protection Regulation Answers to Frequently Asked Questions, 2017 | (35) |
| 15 | The OECD Privacy Framework, 2013 | (36) |
| 16 | ANESM: letter of framing, 2017 | (37) |
| 17 | APEC Privacy Framework, 2005 | (38) |
| 18 | DNA testing of children outside the healthcare system, 2018. | (39) |
| 19 | Master's Thesis: Consent to genetic testing - comparative analysis of current law and practice, 2018 | (40) |
| 20 | How the GDPR changes the rules for scientific research, 2019 | (41) |
| 21 | HIPAA: Privacy Rule, 2003 | (15) |
| 22 | The Patient Rights Act, 1999 | (42) |
| 23 | The Health Personnel Act, 1999 | (43) |
| 24 | Health and Care Services Act, 2011 | (44) |
| 25 | The Specialist Healthcare Act, 2018 | (45) |
| 26 | Public hearing draft on laboratory guidelines for genetic testing of born individuals, 2018 | (12) |

| ETHICAL | | |
|---|---|---|
| | **DOCUMENT** | **REFERENCE** |
| 1 | HBM4EU Legal and Ethics Policy Paper, 2018 | (46) |
| 2 | Beauchamp T, Walters. Contemporary Issues in Bioethics. 1994, Belmont, California: Wadsworth Publishing Company | (47) |
| 3 | Anticipate and Communicate: Ethical Management of Incidental and Secondary Findings, 2013 | (48) |
| 4 | Presidential Commission for the Study of Bioethical Issues. Privacy and progress in Whole Genome Sequencing, 2012. | (26) |
| 5 | Declaration of Taipei on ethical considerations regarding health databases and biobanks, 2017 | (17) |

| BEST PRACTICES | | |
|---|---|---|
| | **DOCUMENT** | **REFERENCE** |
| 1 | Genomics England: Evaluation of the Consent Process and Patient Documentation, 2019 | (20) |
| 2 | Accenture. Informed consent and data in motion, 2016 | (49) |
| 3 | OUH, Consent form for High Throughput Sequencing (HTS), 2019 | (50) |
| 4 | OUH, Consent form for diagnostic genetic testing of a minor, 2019 | (51) |
| 5 | OUH, Consent form for cancer diagnostic genetic testing of deceased relative, 2019 | (52) |
| 6 | OUH, Information sheet to parents about genomic Trio-tests, 2019 | (53) |
| 7 | OUH, Consent form for diagnostic genetic testing, 2019 | (54) |
| 8 | Norwegian Institute of Public Health: Questionnaires and consent forms in the Norwegian Mother, Father and Child Cohort Study (MoBa),2019 | (55) |
| 9 | Telemark Hospital. Declaration of informed consent for deep-sequencing testing, 2015 | (56) |
| 10 | Haukeland University Hospital. Information to parents for Trio Testing, 2019 | (57) |
| 11 | RD Connect: Code of Conduct for user access to the RD-Connect Genome-Phenome Analysis Platform (GPAP) for health-related information, 2018 | (58) |
| 12 | National Institutes of Health: Genomic Data Sharing Policy (GDS), 2014 | (59) |
| 13 | Electronic Code of Federal Regulations. Protection of Human Subjects, 2018 | (60) |
| 14 | Data Use Ontology approved as a GA4GH technical standard | (61) |
| 15 | Australian Genomics Health Alliance. A National Approach to Clinical Consent for Genetic and Genomic Testing | (18) |
| 16 | Mayo Foundation for Medical Education and Research. Informed Consent for Genetic Testing, 2019 | (19) |

| PROFESSIONAL GUIDELINES | | |
|---|---|---|
| | DOCUMENT | REFERENCE |
| 1 | European Patients Forum. The new EU Regulation on the protection of personal data: what does it mean for patients? A guide for patients and patients' organisations, 2016 | (62) |
| 2 | Global Alliance for Genomics and Health: Consent Policy, 2015 | (21) |
| 3 | ACMG Board of Directors. Points to consider for informed consent for genome/exome sequencing. Genet Med, 2013 | (22) |
| 4 | "Matching" consent to purpose: The example of the Matchmaker Exchange, 2017 | (63) |
| 5 | Patient re-contact after revision of genomic test results: points to consider—a statement of the American College of Medical Genetics and Genomics, 2019 | (64) |
| 6 | Guidelines for Human Biobanks and Genetic Research Databases (HBGRDs), 2010 | (65) |
| 7 | The Norwegian Directorate of Health. Public hearing draft on laboratory guidelines for genetic testing of born individuals, 2018 | (12) |
| 7 | The Norwegian Directorate of Health. Genetic testing. Regulation, approved entities and reporting | (66) |
| 8 | The Norwegian Ministry of Health and Care Services. A new system for easier and more secure access to health data, 2017 | (67) |
| 9 | The Norwegian Directorate of Health. Summary of The Norwegian Strategy for Personalised Medicine in Healthcare, 2016 | (68) |
| 10 | Whole-genome sequencing in healthcare Recommendations of the European Society of Human Genetics, 2013 | (23) |

| SCIENTIFIC PUBLICATIONS | | |
|---|---|---|
| | DOCUMENT | REFERENCE |
| 1 | GDPR Application in Research Setting | (69) |
| 2 | Consenting Patients to Genome Sequencing | (70) |
| 3 | Re-identifiability of genomic data and the GDPR | (71) |
| 4 | A randomized controlled study of a consent intervention for participating in an NIH genome sequencing study. | (72) |
| 5 | Applying bioethical principles to human biomonitoring | (73) |
| 6 | Healthcare professionals' and patients' perspectives on consent to clinical genetic testing: moving towards a more relational approach | (74) |
| 7 | IC for whole-genome sequencing studies in the clinical setting. Proposed recommendations on essential content and process | (75) |
| 8 | Response to Knoppers et al. | (76) |
| 9 | Variation among Consent Forms for Clinical Whole Exome Sequencing | (77) |
| 10 | Genome sequencing in research requires a new approach to consent | (78) |
| 11 | IC in Genomics and Genetic Research | (79) |
| 12 | Yes, there's still a consent problem | (80) |
| 13 | Re-contacting patients in clinical genetics services: recommendations of the European Society of Human Genetics | (81) |

| | | |
|---|---|---|
| 14 | Recommendations for the integration of genomics into clinical practice | (82) |
| 15 | Models of consent to return of incidental findings in genomic research | (83) |
| 16 | Guidelines for diagnostic next-generation sequencing | (25) |
| 17 | Beyond Consent: Building Trusting Relationships with Diverse Populations in Precision Medicine Research | (84) |
| 18 | Consent issues in genetic research: Views of research participants | (85) |
| 19 | The GDPR and the research exemption: considerations on the necessary safe-guards for research biobanks | (86) |
| 20 | Rules for processing genetic data for research purposes in view of the new EU GDPR | (87) |
| 21 | IC: Issues and challenges | (88) |
| 22 | Readability of IC forms for whole-exome and whole-genome sequencing | (89) |
| 23 | Model consent clauses for rare disease research | (24) |
| 24 | Ethical implications of the use of whole genome methods in medical research | (90) |
| 25 | Stakeholder views on secondary findings in whole-genome and whole-exome sequencing: a systematic review of quantitative and qualitative studies | (91) |

## INTERVIEWS

A series of six semi-structured qualitative interviews was carried out with representatives from different clinical and laboratory sections at OUS AMG to gain an insight into the workflows and challenges related to consent. To gain an understanding as complete as possible of the needs arising from these, the representatives were drawn from both the clinical and laboratory units, and for the clinical areas of rare disease, hereditary cancer, cardiac and cardiovascular genetics and childhood cancers, as well as the legal department at OUS. These interviews were between 30 and 60 minutes in duration and insights gathered were processed to extract the main findings and themes relevant for the consent workshop (see following section).

## WORKSHOP

Using OUS AMG as a case to explore consent needs within genomic medicine, a workshop was facilitated by DNV GL. Twenty participants from different clinical functions and genetic labs within OUS AMG, together with the BigMed legal working group from OUS legal department, came together to map and link current and future consent needs across the clinical, laboratory, and legal space. Without considerations to the current legal framework, the participants were prompted to explore potential consent needs related to use of clinical genetic data to the benefit of the primary patient, as reference data and as basis for both academic and industry research (Figure 3).

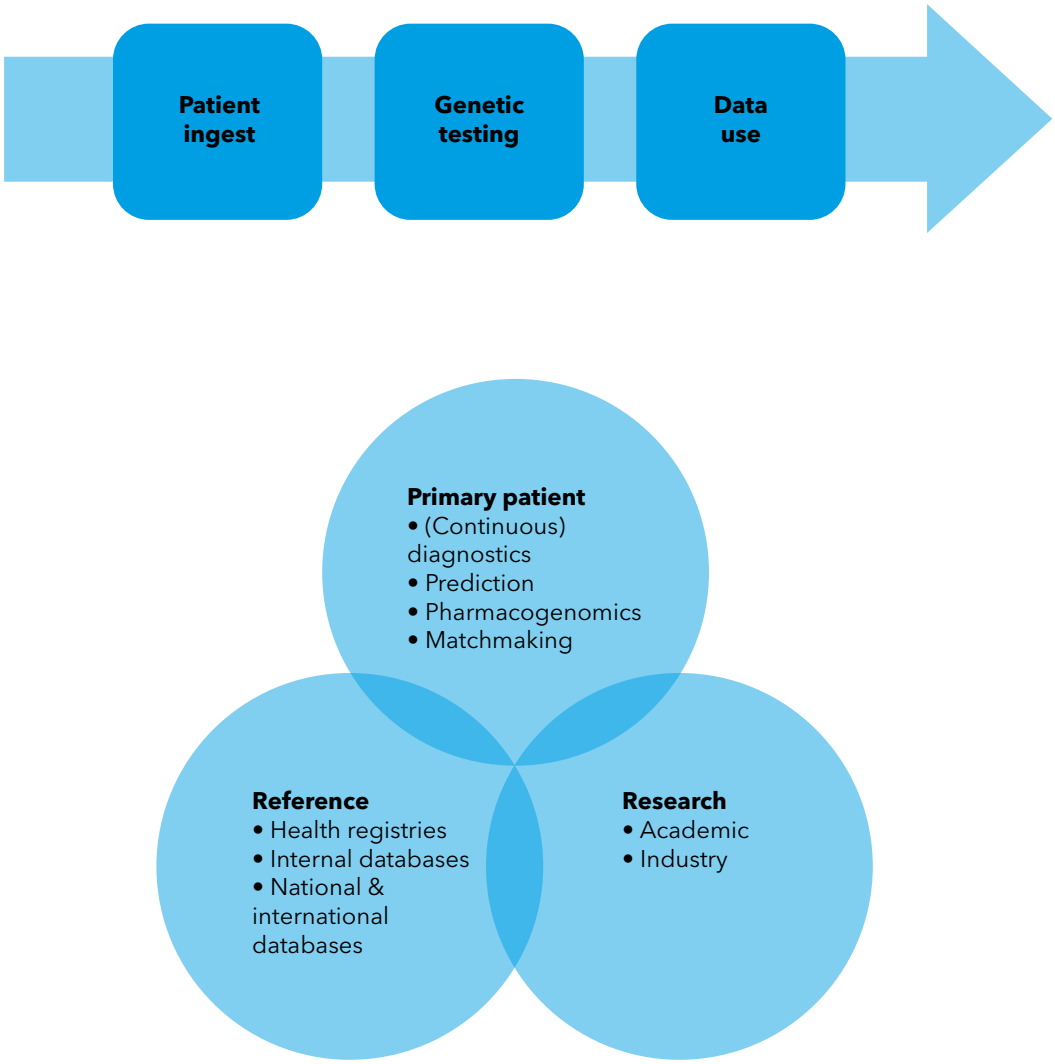



Figure 3. Scope: current and future needs

Building on insights from the literature review and interviews conducted, the workshop participants were split into cross-disciplinary groups and asked to deep dive into, and detail consent needs related to the four groups of challenging themes illustrated in Figure 4. Findings were discussed in plenary, allowing all participants to provide complementary information, and prioritized according to criticality and complexity in handling.

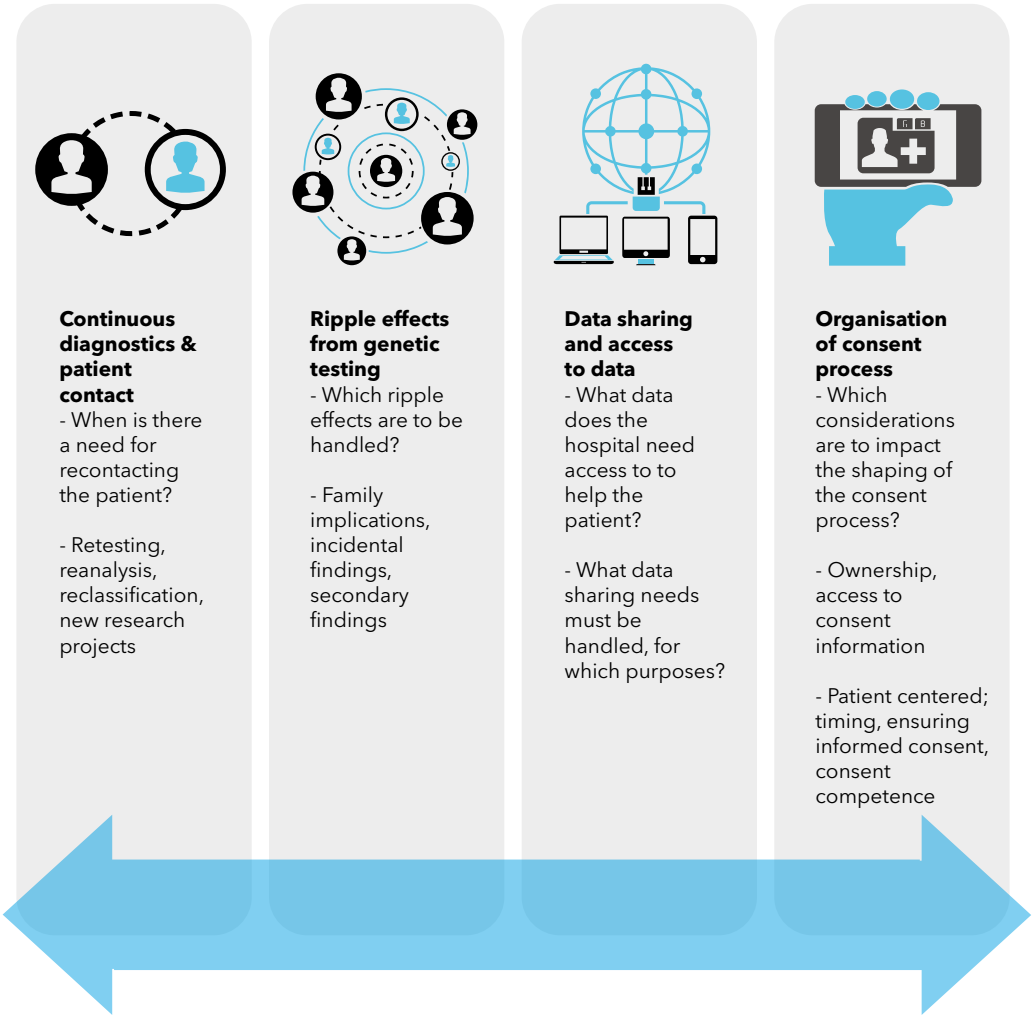



Figure 4. Challenging themes in consent for genetic medicine

# Appendix 2

## RESULTS FROM THE WORKSHOP

**WORKSHOP PARTICIPANTS THEN ORGANIZED FINDINGS INTO THE FOLLOWING CATEGORIES:**

a) Critical / difficult: Needs perceived as very critical and difficult to manage
b) Critical / easy: Needs perceived as very critical but easy to manage
c) Less critical / difficult: Needs perceived as less critical and easy to manage
d) Less critical / easy: Needs perceived as very critical but easy to manage

| CONTINUOUS DIAGNOSTICS AND PATIENT CONTACT | | |
|---|---|---|
| | **TOPIC** | **SPECIFIC NEEDS AND CONSIDERATIONS** |
| Critical, difficult | Continuous diagnostics | Continuous diagnosis introduces new ethical questions and needs for managing consent as both the knowledge base and potential for ripple effects will change over time. Inclusion of continuous diagnostic elements in consent creates patient expectations. There is a need to clarify patient rights and the hospitals' obligations and opportunities related to continuous diagnostics. |
| Critical, difficult | Reanalysis | Triggers for reanalysis should be identified and communicated to the patient as part of securing IC. There is a need for clear policy on the relationship between changes in the test design (e.g. changes in gene panels), analysis process or changes in knowledge base (e.g. VUSes monitoring and changes) and opportunity / obligation to perform reanalysis of a patient, including any limitations as to how far back in time the hospital should investigate. |
| Critical, easy | Actionable findings | Need for clear policy for, and communication of, actionable and non-actionable findings. A common practice is to return only actionable results to treating physician and patients. There is a need for curation and harmonization of what is considered actionable. |
| Critical, easy | Re-contacting | Need for clear policy for, and communication of, potential re-contacting with changes in knowledge base and reanalysis. Need to clarify potential period for re-contacting (e.g. a certain number of years). |
| Critical, easy | The right to know and the right not to know | Consentees must be thoroughly informed about the right to know and the right not to know, and implications of such choices over time. |
| Critical, easy | Participation in research | Consent should include option to re-contact patient in cases where relevant research projects are initiated. |

| RIPPLE EFFECTS FROM GENETIC TESTING | | |
|---|---|---|
| | **TOPIC** | **SPECIFIC NEEDS AND CONSIDERATIONS** |
| Critical, difficult | Primary versus incidental findings for primary patient | Need for clear policy for, and communication of, management of incidental findings with implications for primary patient. Treatment implications, pharmacogenomic implications, implications for prenatal decision making. |
| Critical, difficult | Incidental findings with consequences for family members | The hospital should have a clear policy for, and communication of, incidental findings with consequences for family members (e.g. false paternity), which is out of scope for the consent for the primary patient. |
| Critical, difficult | Potential pharmaco-genetic implications of data | Potential pharmacogenetic implications should be explained to the patient as part of securing IC. |

| DATA SHARING AND ACCESS TO DATA | | |
|---|---|---|
| | **TOPIC** | **SPECIFIC NEEDS AND CONSIDERATIONS** |
| Critical, difficult | Genotype and phenotype data | Need access to and sharing of genotype and phenotype data. |
| Critical, easy | Variant interpretation data | Need for national and international sharing of variant interpretation data. |
| Critical, easy | Quality assured data | Need access to and sharing of quality assured, curated data. |
| Critical, easy | International data sharing | Access to and sharing to international data sharing resources such as ClinVar, Matchmaker Exchange. |
| Critical, easy | National data sharing | Access to and sharing to aggregated data repositories at national level. |
| Critical, easy | Internal data sharing | Internal quality register. Need for long-term hospital internal data storage after test purpose has been completed, for secondary use of data. |
| Critical, easy | Research | Need to make data available for research. |
| Critical, easy | Continuous diagnostics | Access to data for reanalysis (not available today). |
| Critical, easy | IC | Information to the patient about data sharing purposes and risks in an understandable language. |

| NEEDS RELATED TO ORGANIZATION OF THE IC PROCESS | | |
|---|---|---|
| | **TOPIC** | **SPECIFIC NEEDS AND CONSIDERATIONS** |
| Critical, difficult | Consent management | Roles and responsibilities, accountability<br>Linking of consent to consented data to ensure correct data use<br>Consent withdrawal management, including management of connected data. |
| Critical, difficult | The act of being informed | Need to ensure that the patient is sufficiently informed to understand implications and potential consequences of consent. |
| Critical, difficult | Changes in consent scope and patient preference | Need for system that is adaptable to changes in patient preferences, laws, and the changing genomic landscape.<br>Identify the process for re-contacting of patients. |
| Critical, difficult | Consent for underaged / not consent competent patients | Management of changes in parental rights.<br>Management of consent and transfer of patient information to primary patient when underaged patients become consent competent. |
| Critical, difficult | Timing of consent | Avoid overwhelming the patient in critical situations.<br>Avoid creating perceived pressure for the patient to consent to data use beyond primary test. |

# Appendix 3

## ADDITIONAL FINDINGS

During the discussions, the participants often touched upon specific needs for clarification and guidance on legal requirements. Suggestions to solutions for consent management also naturally came up during the discussions. Both categories of input were collected and are summarized in figures 5 and 6.

| REFLECTIONS RELATED TO LEGAL BASIS FOR CONSENT AND CONSENT AS LEGAL RATIONALE IN PRECISION MEDICINE | NEEDS FOR LEGAL CLARIFICATION / GUIDANCE ON SPECIFIC TOPICS |
|---|---|
| • There is a need to balance privacy considerations and responsible healthcare services.<br>• Today, there is a data processing pathway parallel to and beyond the patient pathway. Consent must cover both.<br>• Consent is a legal mechanism for data sharing, but it is not possible to consent to sharing that challenges the principle of responsible healthcare services and where different risk willingness would lead to different access to healthcare services.<br>• Ethical consideration: should willingness to share data be connected to the receiving of healthcare services?<br>• Informed consent is one approach, but other strategies should also be considered to enable data sharing for precision medicine to avoid consent fatigue and overwhelming administrative burden. An alternative route is changes in the regulatory framework.<br>• Consent is a tool to protect the patient and patient's privacy, not a system for the hospital to protect themselves from possible subsequent criticism or penalties. | • Clarification is needed on the anonymous / personal nature of different categories of genetic and attached data, as sharing of anonymous data is unproblematic. Guidance on anonymisation process and sharing of anonymous data is available from the Norwegian Directorate of Health.<br>• For consent withdrawal, clarification is needed on which data is to be withdrawn from which repositories.<br>• Clarification is needed on data storage; how long can / will different categories of data be stored. |

Figure 5. Reflections on consent as legal rationale for data management in precision medicine, and specific needs for legal clarifications.

| SUGGESTED REQUIREMENTS FOR CONSENT MANAGEMENT SOLUTION | OTHER ASPECTS TO BE CONSIDERED |
|---|---|
| • Consent solutions should be digital living data and support<br>• Traceability<br>• Searches to control and manage what the patient has consented to<br>• Connect consent and consented data (logistics management)<br>• Consent withdrawal linked to withdrawal of consented data<br>• Dynamic management of consent over time<br>• Manage changes in consent<br>• For time-limited consent, alerts should be pushed to consent manager and / or patient and / or referring clinician | • Should there be one common consent solution for OUS AMG?<br>• Could the patient, after receiving information, go home and contemplate what they would like to consent to?<br>• Disconnect need to provide information to the patient and the hospital's need to secure consent for secondary / other use of data.<br>• Need consent to allow sharing of personal data with external experts for diagnostic purposes<br>• Should the patient be involved in developing consent? |

Figure 6. Suggested requirements for consent management solution, and other aspects to be considered

# REFERENCES


1. Shokrollahi K. Request for treatment: The evolution of consent. Ann R Coll Surg Engl. 2010;
2. Slater v Baker and Stapleton, 94 ER 860. 1797.
3. Vollmann J, Winau R. Informed consent in human experimentation before the Nuremberg code. British Medical Journal. 1996.
4. Germany (Territory under Allied occupation 1945-1955 : U S Zone). Trials of war criminals before the Nuernberg Military Tribunals under Control Council law no. 10, Nuremberg, October 1946-April, 1949. Washington, D.C.: U.S. G.P.O.; 1949.
5. Shuster E. Fifty years later: the significance of the nuremberg code. N Engl J Med. 1997;
6. World Medical Association. Declaration of Helsinki. Recommendations guiding doctors in clinical research. Adopted by the World Medical Association in 1964. 1964;
7. The European Parliament and the Council of the European Union. Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (GDPR). Official Journal of the European Union 2016.
8. Council of Europe. Convention for the protection of human rights and dignity of the human being with regard to the application of biology and medicine: Convention on human rights and biomedicine. Oviedo; 1997.
9. Council of Europe. Additional Protocol to the Convention on Human Rights and Biomedicine, concerning genetic testing for health purposes. Eur J Health Law. 2008;
10. Befring AK. Persontilpasset medisin: rettslige perspektiver. Oslo: Gyldendal; 2019.
11. The Norwegian Ministry of Health and Care Services. The government's report on public hearing on changes to the Biotechnology Act. 2019.
12. The Norwegian Directorate of Health. Public hearing draft on laboratory guidelines for genetic testing of born individuals. 2018.
13. The Norwegian Ministry of Health and Care Services. Act of 5 December 2003 No. 100 relating to the application of biotechnology in human medicine, etc. [The Biotechnology Act]. 2003.
14. The Norwegian Ministry of Health and Care Services. Act of 20 June 2008 No. 44 on medical and health research [Health Research Act]. 2008.
15. Office for Civil Rights. Summary of the HIPAA Privacy Rule: HIPAA Compliance Assistance. 2003;
16. World Medical Association. Code of Ethics of the World Medical Association. Declaration of Helsinki. Br Med J. 1964;
17. World Medical Association. Annexe 2. WMA Declaration of Taipei on ethical considerations regarding health databases and biobanks. J Int bioéthique d'éthique des Sci. 2017;
18. Australian Genomics Health Alliance. A National Approach to Clinical Consent for Genetic and Genomic Testing [Internet]. 2019 [cited 2019 Oct 28]. Available from: https://www.australiangenomics.org.au/resources/for-professionals/national-clinical-consent/
19. Mayo Foundation for Medical Education and Research. Informed Consent for Genetic Testing. 2019.
20. Evaluation of Consent Process and Patient Documentation | Genomics England [Internet]. [cited 2019 Oct 22]. Available from: https://www.genomicsengland.co.uk/consent-evaluation/
21. Global Alliance for Genomics and Health. Global Alliance for Genomics and Health: Consent Policy. 2015.

22. ACMG Board of Directors. Points to consider for informed consent for genome/exome sequencing. Genet Med. 2013;
23. van El CG, Cornel MC, Borry P, Hastings RJ, Fellmann F, Hodgson S V, et al. Whole-genome sequencing in health care. Recommendations of the European Society of Human Genetics. Eur J Hum Genet. 2013;
24. Nguyen MT, Goldblatt J, Isasi R, Jagut M, Jonker AH, Kaufmann P, et al. Model consent clauses for rare disease research. BMC Med Ethics. 2019;
25. Matthijs G, Souche E, Alders M, Corveleyn A, Eck S, Feenstra I, et al. Guidelines for diagnostic next-generation sequencing. Eur J Hum Genet. 2016;24(1):2–5.
26. Presidential Commission for the Study of Bioethical Issues. Privacy and progress in Whole Genome Sequencing. 2012.
27. Personal Data Protection Act 2012 - Singapore Statutes Online [Internet]. [cited 2019 Oct 21]. Available from: https://sso.agc.gov.sg/Act/PDPA2012#P1IX-P22-
28. Council of the European Union. Council conclusions on Health in the Digital Society — making progress in data-driven innovation in the field of health. Off J Eur Union. 2017;
29. Recommendation CM/Rec(2019)2 of the Committee of Ministers to member States on the protection of health-related data. 2019.
30. The Norwegian Data Protection Agency. Privacy concerns of genetics testing. 2013.
31. The Norwegian Directorate of Health. Notes of the Norwegian Directorate of Health's Sector Council meeting. 2019.
32. The Norwegian Ministry of Health and Care Services. Evaluation of the Biotechnology Act. Report to the Norwegian Parlament. 2016.
33. The Norwegian Society of Human Genetics. Responce to the public hearing on guidelines for genetic testing of born induviduals. 2018.
34. The Norwegian Ministry of Health and Care Services. Act of 21 February 2003 No. 12 relating to treatment biobanks. 2003.
35. BBMRI-ERIC Common Service ELSI. The EU General Data Protection Regulation Answers to Frequently Asked Questions Updated Version 2.0. 2017.
36. Organization for Economic Cooperation and Development. The OECD privacy framework. 2013.
37. ANESM. Lettre de cadrage: Droits des personnes et démarche de protection des données personnelles. 2017.
38. Asia Pacific Economic Cooperation. APEC Privacy Framework (2005). Apec. 2005.
39. The Norwegian Biotechnology Advisory Board. DNA testing of children outside the health care system. 2018.
40. Anthonisen FS. Consent to genetic testing - comparative analysis of current law and practice. University of Oslo; 2016.
41. European Parliamentary Research Service. How the General Data Protection Regulation changes the rules for scientific research. 2019.
42. The Norwegian Ministry of Health and Care Services. Act of 02 July 1999 No. 63 relating to patients' rights. 1999.
43. The Norwegian Ministry of Health and Care Services. Act of 2 July 1999 No. 64 relating to Health Personnel etc. [The Health Personnel Act]. 1999.
44. The Norwegian Ministry of Health and Care Services. Act of 24 June 2011 No. 30 relating to municipal Health and care services, etc. [Health and Care Services Act]. 2011.
45. The Norwegian Ministry of Health and Care Services. Act of 2 July 1999 No. 61 on Specialized Health Services. 1999.
46. Knudsen LE, Faber BA. HBM4EU Legal and Ethics Policy Paper. 2018.
47. Beauchamp TL, Walters L. Contemporary issues in bioethics. 4th.ed. Belmont: Wadsworth; 1994.
48. Presidential Commission for the Study of Bioethical Issues. Anticipate and communicate: Ethical management of incidental and secondary findings in the clinical, research, and direct-to-consumer contexts. 2013.
49. Accenture. Informed consent and data in motion. 2016.
50. Oslo University Hospital. Consent Form for High Throughput Sequencing. 2019.
51. Oslo University Hospital. Consent Form for diagnostic genetic testing of a minor. 2019.
52. Oslo University Hospital. Consent Form for cancer diagnostic genetic testing

of deceased relative. 2019.
53. Oslo University Hospital. Information sheet to parents about genomic Trio-tests. 2019.
54. Oslo University Hospital. Consent Form for diagnostic genetic testing. 2019.
55. Norwegian Institute of Public Health. Questionnaires and consent forms in the Norwegian Mother, Father and Child Cohort Study (MoBa) [Internet]. 2019 [cited 2019 Oct 22]. Available from: https://www.fhi.no/en/studies/moba/for-forskere-artikler/questionnaires-from-moba/
56. Telemark Hospital. Declaration of informed consent for deep-sequencing testing. 2015.
57. Haukeland University Hospital. Information to parents for Trio Testing. 2019.
58. RD-Connect. Code of Conduct for user access to the RD-Connect Genome-Phenome Analysis Platform for health related information. 2018.
59. National Institutes of Health. National Institutes of Health Genomic Data Sharing Policy. 2014.
60. Electronic Code of Federal Regulations. Protection of Human Subjects [Internet]. 2018 [cited 2019 Oct 21]. Available from: https://www.ecfr.gov/cgi-bin/-retrieveECFR?gp=&SID=83cd09e1c0f5c6937cd9d7513160fc3f&pitd=20180719&n=pt45.1.46&r=PART&ty=HTML
61. Data Use Ontology approved as a GA4GH technical standard [Internet]. [cited 2019 Oct 22]. Available from: https://www.ga4gh.org/news/data-use-ontology-approved-as-a-ga4gh-technical-standard/
62. European Patients Forum. The new EU Regulation on the protection of personal data: what does it mean for patients? A guide for patients and patients' organisations [Internet]. 2016 [cited 2019 Oct 21]. Available from: https://www.eu-patient.eu/globalassets/policy/data-protection/data-protection-guide-for-patients-organisations.pdf
63. Dyke SOM, Knoppers BM, Hamosh A, Firth H V., Hurles M, Brudno M, et al. "Matching" consent to purpose: The example of the Matchmaker Exchange. Hum Mutat. 2017;
64. David KL, Best RG, Brenman LM, Bush L, Deignan JL, Flannery D, et al. Patient re-contact after revision of genomic test results: points to consider—a statement of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2019;
65. Organization for Economic Cooperation and Development. OECD guidelines on human biobanks and genetic research databases. Eur J Health Law. 2010;
66. The Norwegian Directorate of Health. Genetic testing. Regulation, approved entities and reporting. [Internet]. 2019 [cited 2019 Oct 23]. Available from: https://www.helsedirektoratet.no/tema/bioteknologi/genetiske-undersokelser
67. The Norwegian Ministry of Health and Care Services. A new system for easier and more secure access to health data. 2017 Jun.
68. The Norwegian Directorate of Health. Summary of The Norwegian Strategy for Personalised Medicine in Healthcare. 2016;
69. Johns Hopkins Medicine. Preparing for the EU GDPR in research settings. 2018.
70. Niemiec E, Howard HC. Consenting Patients to Genome Sequencing. Clin Genome Seq. 2019 Jan 1;31–55.
71. Shabani M, Marelli L. Re- identifiability of genomic data and the GDPR . EMBO Rep. 2019;
72. Turbitt E, Chrysostomou PP, Peay HL, Heidlebaugh AR, Nelson LM, Biesecker BB. A randomized controlled study of a consent intervention for participating in an NIH genome sequencing study. Eur J Hum Genet. 2018;
73. Harrison M. Applying bioethical principles to human biomonitoring. In: Environmental Health: A Global Access Science Source. 2008.
74. Samuel GN, Dheensa S, Farsides B, Fenwick A, Lucassen A. Healthcare professionals' and patients' perspectives on consent to clinical genetic testing: Moving towards a more relational approach. BMC Med Ethics. 2017;
75. Ayuso C, Millán JM, Mancheño M, Dal-Ré R. Informed consent for whole-genome sequencing studies in the clinical setting. Proposed recommendations on essential content and process. Eur J Hum Genet. 2013;
76. David KL, Best RG, Brenman LM, Bush L, Deignan J, Flannery D, et al. Response to Knoppers et al. Genet Med. 2019;21(10):2403.
77. Fowler SA, Saunders CJ, Hoffman MA. Variation among Consent Forms for Clinical Whole

Exome Sequencing. J Genet Couns. 2018;
78. Budin-Ljøsne I, Bentzen HB, Solbakk JH, Myklebost O. Genomsekvensering i forskning krever ny tilnærming til samtykke. Vol. 135, Tidsskrift for den Norske Laegeforening. Norwegian Medical Association; 2015. p. 2031–2.
79. McGuire AL, Beskow LM. Informed Consent in Genomics and Genetic Research. Annu Rev Genomics Hum Genet. 2010;
80. Caulfield T, Murdoch B. Genes, cells, and biobanks: Yes, there's still a consent problem. PLoS Biol. 2017;
81. Carrieri D, Howard HC, Benjamin C, Clarke AJ, Dheensa S, Doheny S, et al. Recontacting patients in clinical genetics services: recommendations of the European Society of Human Genetics. Eur J Hum Genet. 2019;
82. Bowdin S, Gilbert A, Bedoukian E, Carew C, Adam MP, Belmont J, et al. Recommendations for the integration of genomics into clinical practice. Genetics in Medicine. 2016.
83. Appelbaum PS, Parens E, Waldman CR, Klitzman R, Fyer A, Martinez J, et al. Models of consent to return of incidental findings in genomic research. Hastings Cent Rep. 2014;
84. Kraft SA, Cho MK, Gillespie K, Halley M, Varsava N, Ormond KE, et al. Beyond Consent: Building Trusting Relationships With Diverse Populations in Precision Medicine Research. Am J Bioeth. 2018;
85. Goodman D, Johnson CO, Wenzel L, Bowen D, Condit C, Edwards KL. Consent issues in genetic research: Views of research participants. Public Health Genomics. 2016;
86. Staunton C, Slokenberga S, Mascalzoni D. The GDPR and the research exemption: considerations on the necessary safeguards for research biobanks. Eur J Hum Genet. 2019;
87. Shabani M, Borry P. Rules for processing genetic data for research purposes in view of the new EU General Data Protection Regulation /706/689/179 /706/689 review-article. European Journal of Human Genetics. 2018.
88. Nijhawan L, Janodia M, Muddukrishna B, Bhat K, Bairy K, Udupa N, et al. Informed consent: Issues and challenges. Journal of Advanced Pharmaceutical Technology and Research. 2013.
89. Niemiec E, Vears DF, Borry P, Howard HC. Readability of informed consent forms for whole-exome and whole-genome sequencing. J Community Genet. 2018;
90. Kaye J, Boddington P, De Vries J, Hawkins N, Melham K. Ethical implications of the use of whole genome methods in medical research. European Journal of Human Genetics. 2010.
91. Mackley MP, Fletcher B, Parker M, Watkins H, Ormondroyd E. Stakeholder views on secondary findings in whole-genome and whole-exome sequencing: A systematic review of quantitative and qualitative studies. Genetics in Medicine. 2017.

SAFER, SMARTER, GREENER

**DNV GL AS**
NO-1322 Høvik, Norway
Tel: +47 67 57 99 00
www.dnvgl.com

**Bobbie N. Ray-Sannerud**
Program Director,
Precision Medicine Program,
Group Technology and
Research (GTR)

bobbie.nicole.ray-sannerud@
dnvgl.com
Mobile +4741402298

**DNV GL**
DNV GL is a global quality assurance and risk management company. Driven by our purpose of safeguarding life, property and the environment, we enable our customers to advance the safety and sustainability of their business. We provide classification, technical assurance, software and independent expert advisory services to the maritime, oil & gas, power and renewables industries. We also provide certification, supply chain and data management services to customers across a wide range of industries. Operating in more than 100 countries, our experts are dedicated to helping customers make the world safer, smarter and greener.

**Group Technology & Research**
At Group Technology & Research our focus is on new knowledge and technology areas that have a long term impact on the industries we serve. Our White Papers highlight findings from our research programmes, and are intended to advance knowledge and to help prepare our customers, their stakeholders and our own organization for the future. Find out more at www.dnvgl.com/research

 **Design:** etngrafisk.no **Images:** page 1, 8, 17, 19: Shutterstock, page 26: Getty Images.