NATIONAL COMMITTEE ON HEALTH RESEARCH ETHICS

Holbergsgade 6
1057 Copenhagen K
Denmark

T: +45 72 26 93 70
M: kontakt@nvk.dk
W: www.nvk.dk

Guidelines on Genomics Research and Research in Sensitive Bioinformatics Data

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1.0. Preamble

The purpose of these revised guidelines is to ensure that genomics research takes place according to the provisions of the Committee Act in relation to research participants' autonomy, safety and well-being, which come before scientific interests to acquire new knowledge, cf. section 1 of the Committee Act[1].

Genome analyses provide data about the personal genetic constitution of individuals, including constitutional (hereditary) and acquired (somatic) changes that form the basis of health and diseases throughout life. Extensive mapping of the human genome could lead to the identification of severe findings in research participants. The participants may be informed of these findings according to the rules of the Executive Order on the Return of Findings[2]. If the research participant's relatives are at risk, it is recommended to encourage the research participant to contact these relatives so they can be evaluated and treated.

The requirements for information and consent call for special considerations in these projects. The general rule is that informed consent or consent by proxy must be obtained for the mapping of an individual's genome.

2.0. The concept of extensive mapping of the human genome

In overall terms, extensive mapping of the human genome is understood as:
Analyses that provide detailed information on large portions of the human genome of individuals whereby large volumes of information are typically generated.

You can read more about the methods that fall under the concept here:
https://en.nvk.dk/rules-and-guidelines/guidelines-on-genomics-research/list-of-methods

3.0. Notification of genomics research to the competent authority

The notification of research, including genomics research, into biological material is described in the Guidelines on the use of biological material in health research projects (the biobank guidelines) of the National Committee on Health Research Ethics. The biobank guidelines describe, inter alia, how biological material is to be handled if a project collects, stores and/or uses biological material, including if biological material (and data) is transferred to EU countries and countries outside the EU (third countries).

The project must be notified to the regional committee in the region of the investigator's main place of work. However, the notification must be submitted to the National Committee on Health Research Ethics if the biological material has already been collected from the research participants, and the project seeks exemption from the requirement to obtain renewed consent for extensive mapping

[1] Consolidated Act no. 1338 of 1 September 2020 on Research Ethics Review of Health Research Projects and Health Data Research Projects (Danish title: *Lovbekendtgørelse nr 1338 af 1. september 2020 af lov om videnskabsetisk behandling af sundhedsvidenskabelige forskningsprojekter og sundhedsdatavidenskabelige forskningsprojekter*)

[2] Executive Order no. 829 of 8 June 2020 on the Return of Important Health-Related Findings in Notifiable Health Research Projects and Health Data Research Projects as well as Certain Register Research Projects (Danish title: *Bekendtgørelse nr. nr 829 af 8. juni 2020 om tilbagemelding om væsentlige helbredsmæssige fund fra anmeldelsespligtige sundhedsvidenskabelige og sundhedsdatavidenskabelige forskningsprojekter samt visse registerforskningsprojekter*).

of biological material from a biobank.[3] If the research involves research on existing genomics data generated by extensive genetic analyses, notification must also be made to the National Committee on Health Research Ethics. See section 7.

4.0. Requirements for research projects involving extensive mapping

Analysis of the human genome using NGS involves many steps in the actual sequencing process, i.e. the generation of DNA sequences as a copy of research participants' DNA or RNA for the bioinformatic processing of data (alignment, variant calling and variant annotation). To achieve utmost transparency, it is important that the trial protocol contains sufficient information to facilitate the assessment of the project, which is undertaken by the research ethics committee system.

The protocol should contain information about:

- Which region of the genome the project will be studying (gene panels, exomes, the whole genome, the epigenome, RNA).
- Which types of sequences the project intends to study (rare or common variants, structural variants, etc.).
- Which sequencing platform or high-density arrays the project intends to use.
- Which bioinformatic tools the project intends to use, e.g., variant calling, annotation and validation.
- Which sequencing depth the project intends to use.
- How the project intends to store raw data, where and for how long.
- An assessment of the estimated frequency of important health-related incidental findings along with reasons.

Since the purpose of the project is to acquire new knowledge in a special area of interest, the project can focus on specific areas so as to preferably generate bioinformatic data from specific regions of the genome. In this connection, the project can disregard data from other regions, e.g. regions of the genome where certain variants are known to significantly affect the health of the research participant. This can be achieved for example if certain regions are not subjected to bioinformatic processing. This could be done by, e.g. disregarding the clinically relevant genes on the ACMG's list[4] by not "calling" variants or by filtering out all called variants of the genes on the list before further analysis. It must appear from the project description that the selection is performed in such a way that data related to unwanted information are not generated or registered.

Genomics research can be exploratory with a lesser degree of very accurate hypotheses or endpoints. In certain cases, the research is more hypothesis-generating. However, the Committee Act requires research projects to be *concrete*. The committee will focus on whether the project has a defined purpose or methodological scope with an underlying research question. The scientific purpose of the analyses must be described. It must be indicated what the project is searching for, and the methodological choices must be justified to enable the

[3] https://en.nvk.dk/rules-and-guidelines/guidelines-on-the-use-of-biological-material-in-health-research-projects

[4] American College of Medical Genetics and Genomics: https://www.acmg.net/

committee to assess the scientific standard, including the project's research-ethical justification.

A validation phase is likely to strengthen the project's scientific basis. This phase could be integrated in the same project if it is the same investigator and it has been concretised and justified which research participants, which material and which methods are to be used in the specific validation. Otherwise, the validation must be submitted as a new notification.

4.1. Committee of experts for assessment of incidental findings

Genomics research which is carried out according to the methods described in the National Committee on Health Research Ethics' list of "Methods within extensive mapping of the human genome"[5] is characterised by a likelihood of identifying important health-related incidental findings.

Important health-related incidental findings are findings identified in a health research project or health data research project that are unrelated to the project's purpose, revealing that the research participant or health data research participant (see section 7) unexpectedly suffers from or with certainty or a high degree of probability is predisposed to a life-threatening or clearly serious disease that can be treated, prevented or alleviated.

In research projects involving a high risk of making important health-related incidental findings, the investigator or the health data investigator must describe their reasoned considerations about the likelihood of making important health-related incidental findings. See section 4(3) of the Executive Order on the Return of Findings.

The project must also describe the composition of the committee of experts that must be established if important health-related incidental findings are identified as well as procedures for how members to the committee of experts are appointed. See sections 5 and 6 of the Executive Order on the Return of Findings. The protocol could also describe the collaboration with a clinical genetics department in relation to the return of important health-related incidental findings.

The committee of experts must consist of a healthcare professional authorised in the studied disease area and must additionally consist of members possessing the necessary expertise to assess if the criteria for returning findings are met, cf. section 5 of the Executive Order on the Return of Findings. Read more about these criteria under 5.2 below.

4.2. Collaboration with external partners on genomics data

In genomics research, the investigator may use an external laboratory or an external company to undertake the genetic, including bioinformatic, analyses. In this case, the project must state the nature of the tests and the analytical methods and the laboratory/company used for analysis of the tests. It should be stated that a written data processor agreement on this specific purpose will be entered into, according to which the laboratory or the company is not allowed to use the entrusted information for other purposes than the task performed on behalf of the data controller. For assistance in the preparation of a data processor agreement,

[5] https://en.nvk.dk/rules-and-guidelines/guidelines-on-genomics-research/list-of-methods

please see the website of the Danish Data Protection Agency (the standards of the Danish Data Protection Agency pursuant to the new data protection regulation, which enters into force on 25 May 2018; in Danish only).

If, additionally or supplementary, the investigator establishes an effective research collaboration with other researchers on the analysis or use of genomics data either in Denmark or inside or outside the EU, the purpose and framework must be specified in the protocol. The following must appear clearly from the protocol:

- Which data will be disclosed to specific collaboration partners?
- That the extensive sequencing will be used solely for research within the authorised project's purposes.
- If the project intends to make raw data available to other researchers, e.g. as required by journals, or if sequencing data are not destroyed but stored after completion of the project, this is assumed to take place in compliance with the Act on Processing of Personal Data.
- That the four criteria for return of important health-related incidental findings, cf. 5.2 below, must be complied with by the collaboration partner.

Please note that certain situations require the approval of the Danish Data Protection Agency before information can be disclosed to a third party, cf. section 10(3) of the Danish Data Protection Act. See the Danish Data Protection Agency's Executive Order no. 1509 of 18 December 2019 on Disclosure of Personal Data Covered by Section 10(1) and (2) of the Data Protection Act as well as the guidance notes for Executive Order no. 1509 of 18 December 2019 on Disclosure of Personal Data Covered by Section 10(1) and (2) of the Data Protection Act.

4.3. Research with minors

Section 19 of the Committee Act lays down conditions that must be met for minors to be included in research. Reference is also made to [6]section 18 of the Executive Order on Notification regarding the minor's voluntary participation.

A distinction should be made between the inclusion of healthy children and children suspected to suffer from a genetic disorder. Both extensive mapping and targeted genetic analyses could put a strain on minors, especially healthy minors, if in childhood or adolescence they risk being confronted with incidental findings of a serious health-related nature that might not present until adulthood. This particularly applies to the type of genetic studies that neither serve treatment nor preventive purposes for the children involved. The right of these children to have an open future ought therefore to be taken into account in the protocol of this type of research projects.

5.0. Informed consent and contact to research participants

The written information to research participants must state that it concerns a request for their participation in a health research project, and the information must be presented in a way enabling the research participant to decide if they want to participate in the health research project. It is of utmost importance that the

[6] Executive Order no. 825 of 4 June on Notifiable Health Research Projects and Health Data Research Projects (Danish title: *Bekendtgørelse nr 825 af 4. juni 2020 om anmeldelsespligtige sundhedsvidenskabelige og sundhedsdatavidenskabelige forskningsprojekter*)

information provided is comprehensible since genomics research could be difficult to understand.

The information must instruct the participant that they could be informed of important health-related incidental findings if the conditions of the Executive Order on the Return of Findings are met, unless the research participant has opted out of being told of any such findings. It must describe that these conditions imply, among other things, that a preceding assessment of the finding's clinical relevance and certainty has been carried out and that the finding concerns a life-threatening or clearly serious disease or predisposition to a disease that may to a significant degree be prevented, alleviated or treated and is of considerable importance to the research participant and their vital interests.

Reference is made to the researcher check lists, which also describe the special requirements for the information in genomics research.

The National Committee on Health Research Ethics has made available a proposed standard text reflecting good practice for information provided to research participants in projects involving genomics research. The text can be inserted in participant information involving only genomics research or in participant information in which genomics research forms a part, as a supplement to, for example, clinical trials of medicines.[7]

A new optional standard consent form has also been provided for use in projects involving extensive mapping of the human genome.[8] The text should be adapted to projects involving incompetent or deceased persons. The text is supplemented by a declaration for the very rare cases in which research participants declare not to be informed of life-saving findings and the research participant continues in the project. The declaration concerns the right not to know, cf. section 15(3) of the Executive Order on the Return of Findings.

In projects in which the identification of individual important health-related incidental findings is more unlikely, the research participant can be informed that it is so. This could be the case in exploratory analyses of biomarkers in aggregated data, such as in clinical trials of medicines. However, these studies are not exempt from the obligation to establish a committee of experts. When research participants are informed of an insignificant risk of health findings, it is convenient to add that no return of information does not necessarily mean that the research participant is healthy. The general rules on information for research participants apply in parallel.

5.1. Information and inclusion of minors

Children cannot themselves give their consent to the collection of blood samples for use in genomics research. A consent by proxy from the parents must be obtained. Section 18(3) of the Executive Order on Notification contains provisions on information to research participants and requires the voluntary participation of children in research. Children must be consulted, and the information must be

[7] See appendix 2 (in Danish only):
https://www.nvk.dk/~/media/NVK/Dokumenter/Deltagerinformation_god_genominformation.docx

[8] (in Danish only)
https://www.nvk.dk/~/media/NVK/Forsker/Forskertjeklister/forskertjekliste_samtykkeerklaeringer.docx

adapted to the child's age. The consultation requirements become stricter in step with the child's age and mental ability to understand the research.

5.2. Genetic counselling

The research participants must be offered qualified genetic counselling if the research project results in the finding of a genetic variant of health importance to the research participant.

Especially in projects studying mutations in highly penetrant genes (e.g. in monogenetic diseases) must qualified genetic counselling be offered before the consent to participate in a research project is obtained.

Genetic counselling is to be offered by a medical specialist experienced in the relevant disease group(s) or by other appropriately trained and supervised personnel groups. The investigator may thus delegate the task of informing the research participant of potential health findings to a qualified professional.

5.3. Return of important health-related incidental findings

The investigator or health data investigator may return important health-related incidental findings to the research participant or the health data research participant if there is certainty or a high degree of probability that the person concerned is predisposed to a life-threatening or clearly serious disease and the return of the information is necessary to protect the vital interests of the research participant or health data research participant.

The committee of experts must assess:

1) if the disease or disposition to disease can be significantly prevented, treated or alleviated

2) if the disease or disposition to disease is of major importance to the research participant or health data research participant

3) the clinical validity of the finding, and

4) if the method used to identify the finding is reliable.

The assessment of whether a finding should be returned is carried out jointly with the committee of experts or the clinical genetics department of a hospital. However, it is the investigator or health data investigator who ultimately decides if a finding should be returned to the participant.

Please note that it is only persons subject to a statutory obligation of confidentiality who may inform research participants or (health data) research participants. In case the investigator or health data investigator is not subject to a statutory obligation of confidentiality, the information must be communicated via a healthcare professional subject to a confidentiality requirement, cf. section 3(2) of the Executive Order on the Return of Findings.

The investigator or health data investigator must ensure compliance with the provisions of the General Data Protection Regulation when personal data are

disclosed to the committee of experts, the clinical genetics department or any involved healthcare professionals.

However, no return of information must take place if the research participant has requested not to know. Please see the preprinted declaration forms on the "Right not to know" from the National Committee on Health Research Ethics. Such an opt-out should be an informed opt-out based on current and relevant insight, cf. the standard of good information practice.

Incidental findings are validated before any finding is returned to the research participant. The validity of the analytical methods applied should therefore be taken into account, including the frequency of false-positive findings.

The rules on the return of findings concern genetic variants with a high penetration predisposing to a severe disorder and where this disorder is curable, preventable or treatable. Thus, the rules on the return of findings do not apply to risk variants with low or moderate penetration or of uncertain clinical significance. Clinically relevant findings could be findings appearing on the ACMG's list.

6.0. Exemption from renewed consent from research participants when the biological material comes from a biobank

Below is described the practice followed in cases of exemption from the consent requirement in situations when the biological material has been collected by a previously authorised health research project (research biobank) or from patients in the course of treatment (clinical biobank), including exemption in projects involving minor participants.

6.1. Exemption concerning research participants with capacity

An exemption from renewed consent can be granted if the project does not involve health risks and does not otherwise impose strains on the research participant, or if it is impossible or requires disproportionate efforts to obtain consent.

When assessing whether to exempt a project from the consent requirement, the National Committee on Health Research Ethics emphasises inter alia:

- That the purpose of the new project is related to the previous project/clinical area for which the material was initially sampled/collected.
- That the research participants were initially informed about the research with genetic material (genes) if an earlier research project exists.
- Whether a large share of the research participants have died.
- Whether the project will be searching for highly penetrant variants of significance to serious diseases, with derived consequences of the risk of incidental findings.
- That the applicant will be following the National Committee on Health Research Ethics' genomics guidelines concerning incidental findings and will use a committee of experts to assess such findings.
- The time when consent was obtained. Particular attention should be paid to the information received and the consent given many years ago.
- That the investigator/person responsible for the biobank will check if the research participants have opted out of research in the Tissue Application Register.

In health research projects where the consent requirement has been exempted as well as in health data research projects, the investigator or health data investigator is responsible for ensuring that any return of important health-related incidental findings to the research participant or health data research participant takes place with due consideration to the individual's right not to receive said information. See section 9 of the Executive Order on the Return of Findings.

6.2. Exemption concerning minors

Any research involving minors must generally only take place when an informed consent of the parents has been obtained. However, if a project applies for exemption from the consent requirement, the National Committee on Health Research Ethics will pay particular attention to ensuring that exemption from the consent of the parents does not put any strain on the minor. In this respect, it is important to bear in mind that genomics research could have particular implications for the entire family, which makes it important to consider the consequences of involving/not involving the parents.

The National Committee on Health Research Ethics has denied exemption from the consent requirement in a research biobank because of the potential strain put on children, especially the healthy children, as they might later on be confronted with findings of a serious health-related nature that might not be of importance before adulthood. In the specific project, the genetic studies neither served treatment nor preventive purposes in relation to the children.

However, the National Committee on Health Research Ethics has granted exemption from the consent requirement for research in material from a clinical biobank involving material from seriously ill children many of whom had died, and where the research project concerned the disease the children suffered from.

Some of the major research projects that were carried out more than 18 years, still hold material of research participants who have now come of age. If an exemption from the consent requirement is sought in relation to material of a study that the parents previously consented to, it must be assessed if there is a potential risk that the now adult research participant could be burdened by this.[9] If the committee in the initial project laid down terms for renewed consent at the time when the child becomes of age, then an exemption from the consent requirement cannot be granted. But even if such a term does not exist, the National Committee on Health Research Ethics will be reluctant to grant exemption and will propose that the research participants who are now of age give their own consent to genomics research.

Use of material from the PKU biobank

The PKU biobank, which is an important research resource, has a special status. If the material from this biobank is to be subjected to genomics research with an exemption from the consent requirement, including targeted sequencing, attention is drawn to the fact that the PKU tests were initially sampled for specific treatment or research-related purposes often materially differing from the purpose of the new research projects in which exemption from the consent requirement is later applied for. The PKU test is sampled shortly after the child's birth and at a time

[9] Section 10 of the Committee Act.

when it is not very likely that the parents would have been able to make predictions about later research-related applications concerning studies of hereditary dispositions.

The National Committee on Health Research Ethics has denied granting such exemptions since the parents have not been sufficiently informed of the genomics research, which is even more true for the children who have now come of age and whose biological material is the subject matter. Several individuals in the collection will now be adults. The same considerations can be made for targeted analyses. Both the information given to the parents and the consent that was obtained have also changed over the years since the PKU biobank was first established.

7. Health data research projects with genomics data or data from diagnostic imaging

As of 15 June 2020, the Committee Act introduced a requirement for notification and processing of research projects with sensitive bioinformatics data, cf. section 14. The requirement concerns existing genomics data from extensive mapping of the human genome or from diagnostic imaging and without the use of biological material. The research projects must be notified to the National Committee on Health Research Ethics.

Health data research projects therefore constitute research in sensitive bioinformatics data being

- Genomics data from a previous health research project with extensive mapping
- Genomics data from patient treatment with extensive mapping
- Data from diagnostic imaging from a previous health research project
- Data from diagnostic imaging from patient treatment

These projects are termed health data research projects, and the investigator is termed health data investigator. Likewise, the individuals whose data are being processed are termed health data research participants.

In defining the scope of the research in regard to quality assurance, it is of relevance if the knowledge being generated is generalizable, i.e., if the study intends to provide broad general knowledge benefiting several treatment facilities or if the knowledge acquired is to be gathered in one single place for internal use. It will therefore be relevant if the results are for internal use or for external use. If, for example, the investigators consider to publish the results, then it is most likely research.

7.1. The purpose of the rules

The rules primarily serve to strengthen the general public's safety and trust in research as well as improve the framework for health research. The rules aim to safeguard the rights, integrity and privacy of the health data research participants.

The focus will be on ensuring that data have been lawfully obtained and on assessing the benefits to society, i.e., the therapeutic aim of the research. The focus will also be on ensuring a high scientific research standard while making sure to

keep the research participants from harm by safeguarding their integrity and right to privacy.

What matters is that incidental health findings including the bioinformatics data are handled in an ethically defensible way, see sections 4-6, but not section 5 on information to research participants. Thus, the committee only considers the research and will not impose conditions in relation to obtaining informed consent.

When notifying a project to the committee, the health data investigator must submit the documents appearing from the researcher check lists for health data research projects. See here.

7.2. The scope of research using patient records

Particular attention should be paid to data extracted from patient records, checking when the project should be notified to the region as a request for access to research in patient records and when the project is a health data research project to be notified to the National Committee on Health Research Ethics. In the case of research in patient record data derived from extensive mapping of the human genome in the clinic, this is always a health data research project, and the application for access to conduct research in these data are to be submitted to the National Committee on Health Research Ethics, not to the region.

In the case of data from diagnostic imaging, diagnostic imaging means treatment of patients by means of and/or assisted by imaging techniques – X-ray, CT scan, MRI scan, PET scan and ultrasound scan – alone or in combination. The specialisation is "Diagnostic radiology", but also covers many micro-invasive treatments and sampling whereby an ultrasound scan, an X-ray, or a CT scan or the like assists in the treatment of patients. Diagnostic imaging can, however, also be used in other specialist fields than radiology, e.g. nuclear medicine and oncology. These projects specifically study the images, meaning that it is the image as a medium that is the research project's primary focus and specific domain. In addition – and secondarily – other data from patient records or data from health registers may be included.

The underlying purpose of the notification duty has been to factor in the increased risk of making incidental findings when the image medium specifically and in itself is subjected to renewed research.

Thus, health data research projects are those specifically requiring that a special response mechanism be put in place to handle identified incidental findings since the image medium in itself is the centrepiece of the research, whereas the "classic" projects with requests for access to numerous health data from the patient record, such as address, age, diagnoses, laboratory or blood test results, prescriptions, discharge summaries, X-rays, anaesthetic records, etc., in which the X-ray is considered more of an "add on", are not to be subjected to the new procedure that applies to the complex health data research projects. These projects must be notified to the region, thereby applying for access to carry out research on patient records.

Please also see the guidelines for researchers – *special requirements for genome projects* (in Danish only)[10]

[10] https://www.nvk.dk/~/media/NVK/Forsker/Forskertjeklister/IV_forskertjekliste_saerkrav_forskning_i_genomer.docx