NATIONAL COMMITTEE ON HEALTH RESEARCH ETHICS

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Guidelines on Genomics Research

Table of Contents

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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.

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 an individual's genome could potentially lead to the identification of serious findings in the research participants that they and possibly also relatives should be informed of according to general law.

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:
(link to list that is updated continuously in step with development)

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 of biological material from a biobank. (link to the biobank guidelines).

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 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[1] 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.

It must appear from the protocol that in the event of incidental findings, a committee of experts will be set up to assess the implications of the findings and whether they should be fed back to research participants, including the procedure to be followed. The committee could count for example a clinical geneticist, a specialist physician in the field concerned and a molecular biologist. A collaboration could also be established with a department of clinical genetics at a hospital, or a committee could be established by a clinical ethics committee at a hospital.

4.1. 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, 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).

[1] American College of Medical Genetics and Genomics

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 five criteria for feedback of incidental findings, cf. 5.2 below, must be complied with by the collaboration partners.

Please note that any disclosure to a third party is subject to the approval of the Danish Data Protection Agency.

5.0. Informed consent and contact to research participants

Prior to the mapping of the human genome in a project, an informed consent for the genetic examination must be obtained, see, however, section 6.0 about exemption. The procedures for recruitment, contact and information in respect of research participants must be described. Read more about the requirements here (link).

It is of utmost importance that the information provided is understandable since genomics research may be difficult to understand. The National Committee on Health Research Ethics provides a template for good participant information (in Danish). The general rules on information for research participants apply in parallel. You can read more about these rules here (in Danish).

5.1. 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.

5.2. Contact to the research participant about genetic health-related findings

Health-related findings may be covered by the project's purpose, e.g. the finding of mutations of known disease genes studied by the project specifically. Please see 5.1 above about genetic counselling. However, health-related findings could also involve findings that are not covered by the project's purpose, i.e. incidental

findings. Experience from the past five years has shown that important health-related findings rarely occur in research projects. If actively searching for disease-causing mutations in the 59 genes on the ACMG's list, they are found in about 1 %. If measures are taken to avoid these genes, the risk of finding these mutations will obviously be even lower.

Section 15 of the Information Executive Order[2] provides that the investigator must inform the research participant if important information about the health of the research participant is found. Only in the exceptional situations where the research participant has clearly opted out of receiving such findings is the investigator not permitted to inform the research participant. Such an opt-out is only valid if it is an informed opt-out based on current and relevant insight, cf. the standard of good information practice. Before the project begins, it must be ascertained if the research participant wants to opt-out of receiving such findings, see 6.1.

If the investigator identifies a disease-causing change in the genetic sequence (mutation) which is not covered by the purpose of the project, the finding must be presented to the committee of experts, see 4.0 above, which will determine if the following five criteria are present:

- It is likely that a mutation is present,
- there is definite evidence of an association between the mutation and development of the disease,
- the analyses showing the mutation are certain,
- the disease can to a high degree be prevented or treated, and
- the association is of major importance to the research participant.

Research results must generally be validated before they can be used for direct patient counselling. The validity of the analytical methods applied must therefore be taken into account, including the frequency of false-positive findings.

Only genetic variants with a high penetration predisposing to a severe disorder and where this disorder is curable, preventable or treatable should be fed back to research participants. Thus, there is no obligation to feed back risk variants with low or moderate penetration or of uncertain clinical significance. Clinically relevant findings could be findings appearing on the ACMG's list.

An assessment should always be made in the specific case of the burden placed on the research participant concerned relative to the benefits, including e.g. prevention and treatment possibilities. Special attention must be paid to vulnerable research participants.

The committee of experts must submit its assessment to the investigator, and it is the investigator's responsibility to feed back relevant incidental findings to research participants or to delegate this task to an appropriately qualified person/department.

[2] Section 15 of Executive Order no. 1464 of 2 December 2016 on Information and Consent to Participate in Health Research Projects as well as Notification and Monitoring of Health Research Projects (Danish title: Bekendtgørelse om information og samtykke til deltagelse i sundhedsvidenskabelige forskningsprojekter samt om anmeldelse af og tilsyn med sundhedsvidenskabelige forskningsprojekter)

If a research participant has opted out of receiving important health-related findings or has died, it should be assessed whether to contact relatives from the point of view of saving lives and prevent disability. The investigator has overall responsibility for handling incidental findings with diligence and conscientiousness.

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.

6.2 Exemption concerning minors

The National Committee on Health Research Ethics has previously 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.

If a research participants has become of age and an exemption from the consent requirement is sought regarding material collected in a research project permitted previously by the parents, it should be assessed if there is a risk that the now adult research participant will be burdened by this.[3] If the committee in the initial project laid down terms for renewed consent when the child becomes of age, then an exemption from the consent requirement cannot be granted.

7.0 New research projects involving previously generated data

Due to the often sensitive nature of genomics data, the committees require that new analyses of previously generated genomics data must be renotified to the committee. The requirement for renotification also applies if the genomics data are disclosed to a new investigator, including when the intention is to disclose raw data to other researchers via databases (unless the data are disclosed in a completely anonymous form).

The notification must be made to the committee that initially approved the project on extensive mapping of the human genome.

Please also see the guidelines for researchers – special requirements for genome projects

[3] Section 10 of the Committee Act (Consolidation act no. 1083 of 15 September 2017)