Information form
'Genetic diagnostic testing by exome or genome sequencing'

CENTRE FOR MEDICAL GENETICS, GHENT UNIVERSITY HOSPITAL

BACKGROUND

The genetic (hereditary) material or DNA is a long chain (sequence) of four building blocks (nucleotides) that we designate with a letter (A, T, G or C). Some parts of the DNA contain the information or code our cells need to produce proteins. Proteins are important building blocks of our body and are essential in many normal (body) processes. The parts of coding DNA are called "genes". We have an estimated 20000 genes. Each gene contains coding parts (exons) and non-coding parts (introns). The exons of all genes are called the exome. This comprises only 1-2% of the total DNA of humans (genome). To detect a change in the DNA sequence (variant), one must read out/sequence the DNA.

GENETIC ANALYSIS

A targeted genetic test is performed to look for the disease-causing or so-called pathogenic variant(s) that may provide an explanation for a particular disease. A genetic test is not designated to detect all possible variants. Moreover many DNA variants don't have an impact on one's health; these variants are part of the normal (benign) genetic variation within the population.

In function of the disease the decision will be made to analyse only one gene or a group of genes previously shown to play a role in the development of this disorder.

- **Analysis of one gene**: analysis of one specific gene is done because the clinical picture of the disorder is very clear and the genetic cause will most likely be found in this gene. An example is a patient with cystic fibrosis where the cystic fibrosis gene will be analysed.
- **Gene panel analysis**: analysis of a group of genes or a gene panel is performed. These genes are all linked to a similar condition. In a person with skeletal abnormalities, it may be better to examine multiple genes because the clinical picture is not specific enough to prioritise one particular skeletal disorder as the diagnosis.

In case gene panel analysis could not detect the cause of the condition or when little is known about the cause of the condition, more in-depth DNA testing can be performed.

- Analysis of the **Mendeliome**: the DNA sequence of all genes currently linked to a known condition is defined
- Analysis of the **exome**: the DNA sequence of all genes including those whose function is still unknown is defined
- Analysis of the **genome**: the DNA sequence of the complete DNA, as well exons as introns, is defined.

SAMPLE COLLECTION

Genetic testing is done on DNA isolated from blood. DNA can also be isolated from other body tissues, such as skin cells or muscle tissue.

INTERPRETATION OF THE RESULT OF THE GENETIC TEST

If a variant is found that may be the cause of the specific condition, it is called a pathogenic or disease-causing variant. However, interpretation of the results is not always straightforward. It is sometimes unclear whether a particular variant is pathogenic rather dan benign. Therefore, it may be appropriate to perform further **family studies** and also examine the DNA of relatives (parents, brothers, sisters, grandparents, etc.). The purpose of family testing is to find out whether everyone in the family with the same condition also carries the same DNA variant(s) and whether relatives who do not have the condition do not carry the variant(s). First of all, this family research is appropriate in the parents. Therefore, (extensive) genetic testing is often started on DNA from the child as well as from both parents ('trio analysis').

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Sometimes genetic testing does not offer an explanation for the condition in question. A normal result does not exclude the presence of a genetic disorder. Our knowledge about the causes of genetic diseases is continuously increasing; so it is possible that in the **future** more will be known about this specific disorder.

INCIDENTAL FINDINGS

In exome and genome sequencing, there is always a real chance of discovering a pathogenic variant that does not underlie the disease condition for which the genetic test was initiated, but that may cause an increased probability to another well-defined condition now or in the future. This is called an **incidental finding**. In case a gene panel is analysed, the chance of discovering an incidental finding is obviously lower than when the Mendelioma or the entire exome or genome is analysed.

The incidental findings can be divided into three categories:

- **Situation A: Conditions leading to a severe disease at young age ('early-onset') and for which specific follow-up, prevention and/or treatment is possible.**
  This refers only to pathogenic variants found during the genetic analysis in young patients or in a prenatal context. An example is a metabolic disease for which a specific diet from birth onwards is indicated.
  ➔ Such incidental findings are always reported.

- **Situation B: Conditions leading to a severe disease later in life ('late-onset') and for which specific follow-up, prevention and/or treatment is possible.**
  These include cardiovascular diseases (such as a risk of cardiac arrhythmia) or an increased risk of cancer, such as a pathogenic variant in the gene BRCA1 that implies a significantly increased risk of breast and ovarian cancer.
  ➔ Such incidental findings are always reported.

- **Situation C: Conditions leading to a severe disease but for which, until now, with the current knowledge, no targeted clinical follow-up, prevention and/or medical treatment is available**.
  Such findings will only be reported if considered helpful for health and well-being regarding follow-up recommendations and/or reproductive options by a committee of experts of the Centre for Medical Genetics Ghent.
  ➔ Each person has the possibility to choose whether or not he/she wishes to be informed of such incidental findings.
  ➔ This option is not applicable in a prenatal context or in minors: variants of situation C (in case of 'late-onset') are not reported in these cases.

The result of the genetic testing is always discussed during a consultation with a clinical geneticist.

PSEUDONYMISATION

Genetic data are among the sensitive information within privacy laws. Therefore, the stored data are linked to a number specifically linked to one person. This pseudonymisation allows us to analyse genetic data without knowing to which person they belong. Only healthcare providers with a treatment relationship (i.e. a clinical treatment relationship or persons involved in diagnostic analysis) can retrieve the identity of the person.

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Informed consent 'Genetic diagnostic testing by exome or genome sequencing'

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	INFORMATION PATIENT	LEGAL REPRESENTATIVE
First name and surname:		
Date of birth:		

Exome or genome sequencing regarding the following condition or question:

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I understand the following information regarding genetic testing in myself/the person I represent:

1. To identify the cause of the condition mentioned above, a large number of genes will be investigated.
2. The body material shall be used solely for medical purposes and all data obtained from this research shall be protected by medical confidentiality. The DNA data will be stored in a secure database.
3. Since genetic research is often done in collaboration with other genetic centres, DNA samples or genetic data can be exchanged with these centres, within the context of the condition or quality control.
4. When performing a genetic test, there is always an existing but rare chance of detecting an incidental finding:
   - DNA variants causing a severe condition for which targeted follow-up, prevention and/or medical treatment is available will be reported.
   - For severe conditions for which, until now, with the current knowledge, no targeted follow-up, prevention and/or medical treatment is available, I decide whether they will be reported. Note: this option is not applicable in the prenatal context or in minors.
     ☐ YES: I wish to be informed of such incidental findings.
     ☐ NO: I do not wish to be informed of such incidental findings.
5. Pseudonymised genetic data can be used as internal control and can also be shared with other physicians/research groups.
6. A normal result does not exclude a genetic cause. In the future, I will have the opportunity to inquire whether there are already new insights that may influence the results of this analysis.
7. For any further questions, I can contact a physician from the Department Medical Genetics of the Ghent University Hospital (09/332 36 03).

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8. If no cause for the condition is found, the obtained data may be further analysed in a research setting to try to find the cause after all. If this yields clinically relevant information, I will be invited to discuss these results.
   ☐ YES: I agree to further analyse the data in a research context.
   ☐ NO: I do not agree to further analyse the data in a research context.
9. The results of this additional research may be used pseudonymised in scientific studies.
   ☐ YES: I agree to process these results in a pseudonymised way in scientific studies.
   ☐ NO: I do not agree to process these results in a pseudonymised way in scientific studies.
10. At any time, I can decide to stop participating in this study. At that point, no new data will be generated.
11. I understand that my and/or my child's DNA sample, DNA sequences or clinical data can be exchanged with other genetic centres in the context of targeted research in my family members.

I decide, based on the information obtained and of my own free will, to have this genetic test performed:
☐ on myself ☐ on my child/the person I represent

Name: ……..... Date: …… Signature: ……..

Name physician: .....Date: ……..... Signature: ……..……

Drawn up in duplicate, one of which is intended for the patient and one for his representative if applicable.

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