Commission for Incidental Findings

Policy document on 'Disclosing incidental findings in a diagnostic setting' by the division Genome Diagnostics of the Department of Human Genetics, Radboudumc

Background

Incidental findings

When comparing the genetic material (genome) of any two individuals only 0.1% will differ. Most of these DNA differences at DNA level, also referred to as genetic variants, will have NO impact on the health status of the individual. A small number of these differences WILL HAVE an impact, and may cause disease. A genetic test can be used to identify such a disease-causing variant (pathogenic mutation) in an individual presenting with a genetic disorder. Sometimes a genetic test identified a disease causing mutation that is irrelevant to the clinical question for which the test is performed, but is in fact predisposing to another disease. Such variant is called an ***incidental finding***. In most circumstances, the incidental finding has a direct effect on the health of the individuals in whom it is identified. It is however, also possible that it discloses carrier status for a disease, which has NO imminent health risk for the individuals it is encountered in, but IS of medical relevance for the health of (unborn) children of the individual. Genetic variants that have NO health consequences for the individual himself, his blood relatives or his progeny (such as variants related to ethnicity or level of sporting excellence are, by definition, NOT an incidental finding, and will as such, not be reported.

In English literature, different nomenclature is used to denote incidental findings, including 'unsought for findings', 'accidental findings', 'co-incidental findings' and 'unsolicited findings'. There is, however, a difference between incidental findings and 'secondary findings'. *Secondary findings* are disease causing variants which, with informed consent of the patient, are actively looked for when analyzing the genetic test results, but which are not of direct relevance for the clinical question. This scenario is also denoted as opportunistic screening. Opportunistic screening *will not be* performed when a genetic test is performed at the Radboudumc. The commission will only consider disclosure of incidental findings to individuals that were identified by chance.

Classification of genetic variants

Genetic variants identified in a genetic test are classified according to a (worldwide) standardized methodology because for each individual DNA difference it is not known whether it causes disease:

Class 1: variant is CLEARLY NOT pathogenic, and there is no increased disease risk

Class 2: variant is UNLIKELY TO BE PATHOGENIC, and unlikely to increase disease risk

Class 3: variant of UNKNOWN SIGNIFICANCE (also referred to as VUS or VOUS): it is unknown whether this variant causes disease

Class 4: variant is LIKELY TO BE PATHOGENIC: there is likely to be an increased risk of disease

Class 5: Variant is CLEARLY PATHOGENIC: there is an increased risk of disease

Policy

The policy of the Department of Human Genetics of the Radboudumc, as written below, is applicable to incidental findings, as there is NO active search for disease causing variants in genes that have no relation to the disease for which the patient is referred to by the treating physician. This policy is based on guidelines published by Vears *et al.* (Eur J Hum Genet . 2018 26:36-43, 2018).

General remarks

A genetic variant for which there is insufficient proof of pathogenicity, is by definition not considered to be an incidental finding (Class 1, Class 2 and Class 3 variants).

Incidental findings will only be reported during an ongoing clinical consultation. In the event that a variant is reclassified based on novel knowledge gained, it is considered good clinical practice to recontact the patient and send a revised report for variants disclosed as incidental findings that were wrongly deemed (likely) pathogenic.

Variants with a potential health risk for the patient (or his blood relatives)

In principle, incidental findings that, at time of discovery, cause a disease which course CANNOT be changed by medical intervention, will NOT be reported.

Mentally competent individuals aged 12 and above will be informed on incidental findings relevant for their own health (or for that of their blood relatives) when medical intervention is possible.

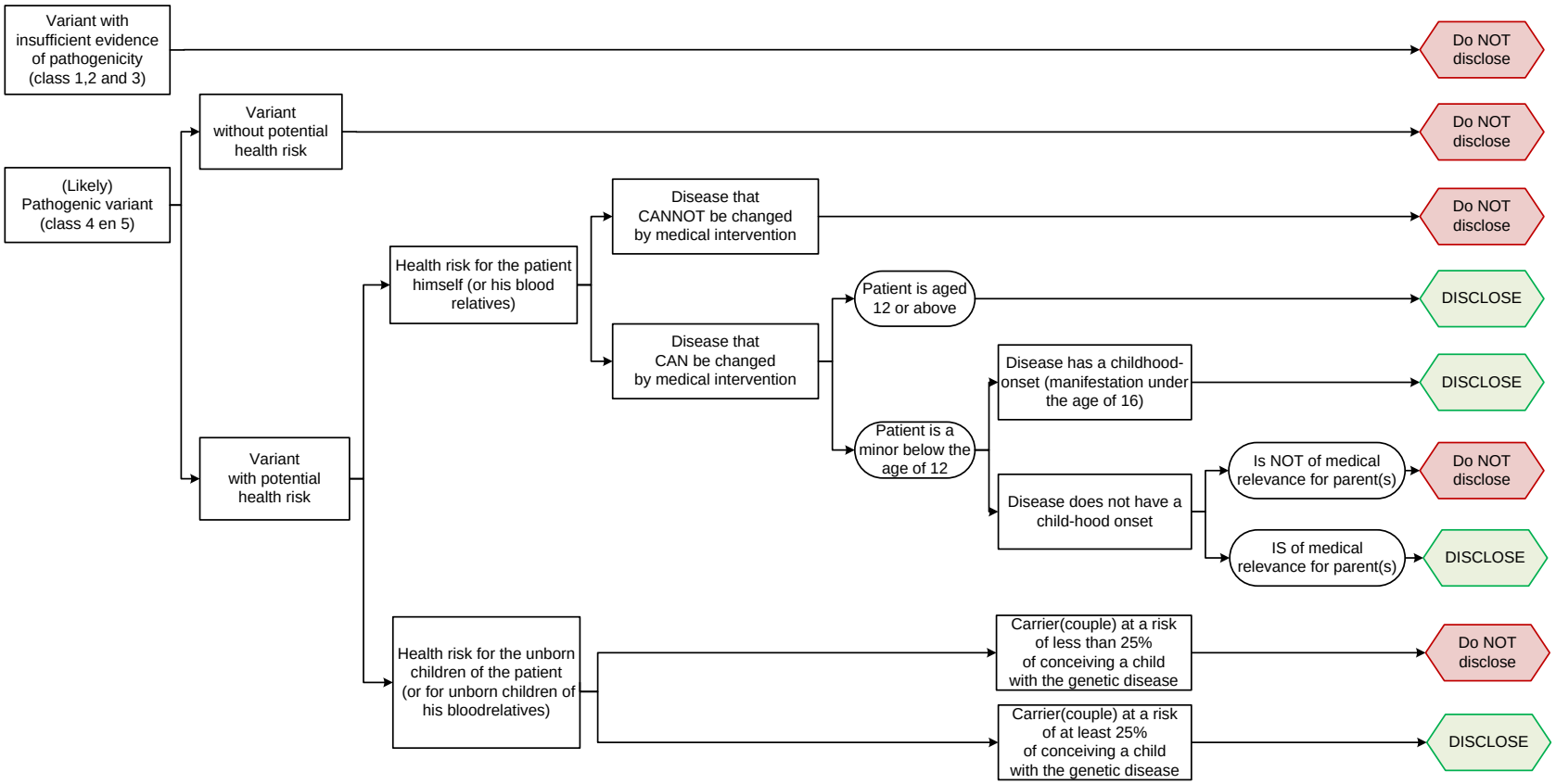
For minors below the age of 12, incidental findings related to a childhood-onset disease (manifestation under the age of 16) for which medical intervention is possible will ALWAYS be disclosed.

For minors below the age of 12, incidental findings increasing the risk of adult-onset diseases WILL NOT be disclosed. Nonetheless, incidental findings of potential medical relevance to one of the parents WILL BE disclosed if options to medically intervene are available.

Variants with a potential health risk for the patient's unborn progeny (or for the unborn progeny of his blood relatives)

Incidental findings related to genetic carrier status, will - in principle - NOT be disclosed as they, by definition, are NOT of medical relevance to the patient himself. Nonetheless, carrier status exposing the carrier, or couple, at a risk of at least 25% of conceiving a child with a genetic disorder WILL BE disclosed.

Figure 1: *Flowchart on the disclosure of incidental finding by the Department of Human Genetics of the Radboudumc*



Commission for Incidental Findings

In the event the genetic laboratory identifies an incidental finding (Class 4 and Class 5 variants in disease genes not relevant for the clinical consultation), it will be evaluated in the Commission for Incidental Findings. The Commission is made up of a laboratory specialist clinical genetics, a clinical geneticist, a molecular biologist, a medical social worker, an ethicist, and a legal representative. The task of the Commission for Incidental Findings is to categorize the incidental finding according to the policy document (flow chart in figure 1). In addition, the Commission for Incidental Findings has to weigh various factors to decide whether or not it is in the best interests of the patient to disclose the incidental finding. These factors include, but are not limited to:

- The penetrance of the genetic disorder, being the risk that someone with this genetic variant will indeed develop the disease.
- The severity of the disorder.
- The psycho-social impact on the patient instilled by the knowledge that he has an increased risk to develop the disease.
- The age of onset for clinical manifestation of the disorder.
- The treatment opportunities for the disorder
- Physical exertion of the screening program(s) the patient may face
- The time needed to diagnose the genetic disorder without prior knowledge of the incidental finding

The commission maintains the right to deviate from her policy when confronted with exceptional circumstances or compelling arguments to the contrary.

The substantiation of this policy is presented in appendix 1.

Commission for Incidental Findings

Policy on "Disclosing Incidental Findings"

Substantiation

Prelude

The document you are about to read provides the substantiation underlying the policy to disclose incidental findings in genetic diagnostic testing. To facilitate legibility of this substantiation, the document is written in the singular form, which includes the following:

- Throughout this document, when referring to 'parents', it should be read as 'parents and/or legal guardians'
- All references to the masculine gender should be taken to include the feminine. For example, 'his parents' refers to 'his and/or her parents'.

Introduction

The Commission for Incidental Findings has defined policy guidelines providing the fundamental tenets for evaluating whether or not incidental findings identified in a clinical diagnostic setting should be disclosed to the referring physician, or his replacement. These policy guidelines are included as an appendix.

This document substantiates these guidelines. The primary scope is the (open) norm that health care professionals have the duty to conduct themselves as good carers (Medical Treatment Contracts Act, hereafter WGB, 7:453). The following applies to act in compliance with the duty to practice the average standard of care:

1. The health care professional is guided in his professional practice by the promotion of health and well-being in humans
2. The health care professional does not willingly expose his patients to treatments with (potential) injury or damage, unless the expected health benefits outweigh the potential risks associated with this treatment.
3. The health care professional provides the necessary treatment and/or advice for the disease for which the patients sought medical attention. That is, the health care professional will not actively look for other potential health care problems outside the scope of the clinical consultation. However, he will act upon health care problems that he encounters in conformity with the clinical consultation for which the patient sought medication attention.
4. A patient's autonomy is the fundament on which the health care professional must base medical interventions. In light of this autonomy, the patient is entitled to clear and concise information on his health situation and the proposed course of care he can expect, to empower him to make an informed decision on whether or not he wants incidental findings to be disclosed to him.

5. In principle, the parents of minors will not be informed on incidental findings, in order to preserve the child's anticipatory autonomy ('right to an open future').
6. The health care professional does not have a duty of care to independently disclose incidental findings to blood relatives of the patients who sought medical attention.

<u>Policy rule 1</u>: Only incidental findings will be considered for disclosure.

There is no benefit to the patient's health to disclose information on genetic variants which (clearly) do not cause disease (Class 1 or 2), or which are unknown to cause disease (Class 3, VUS). Especially for the latter, it can be anticipated that disclosure of such information may lead to anxiety and uncertainty (i.e. do harm).

<u>Policy rule 2:</u> Incidental findings will only be disclosed during an ongoing medical treatment agreement.

Disclosure of incidental findings after closure of a medical treatment agreement would imply that the health care professional acts beyond the scope of the clinical question the patient sought medical attention for and that he actively looks for other (potential) health concerns.

<u>Policy rule 3:</u> Patients will be re-contacted and informed if already disclosed incidental findings are, with progressive insights, no longer considered to be an incidental finding.

By informing the health care professional (or his replacement) who had a medical treatment agreement with the patient of the fact that an already disclosed incidental finding, is with progressive insight, no longer considered to be of clinical relevance (i.e. no longer an incidental finding), further (potential) harm, in terms of unnecessary uncertainty, anxiety, detrimental social and societal impact, as well as futile medical intervention, can be avoided.

<u>Policy rule 4:</u> Incidental findings will only be disclosed to patients if, at the time of discovery and disclosure, medical interventions to prevent and/or treat the disorder are available.

Disclosure of incidental findings related to a disease for which no medical intervention(s) exist will not be of benefit to the patient's health. In fact, disclosure of such information may possibly do harm by causing psychological, sociological or societal problems. Some patients may however still wish to be informed on these findings as knowledge will empower them to make better informed life decisions. Nonetheless, it is beyond the health care professional's responsibility to assist in making better informed specific life decisions that are not embedded in the clinical consultation for which the patient sought medical attention.

<u>Policy rule 5:</u> For patients under the age of 12, incidental findings will only be disclosed if they increase the risk on a childhood or adolescent onset disorder, and if medical intervention is available.

If the incidental finding causes a disease that manifests during early childhood or adolescence, the health care professional must disclose the incidental finding, because of his duty to act to the benefit of the patient's health and well-being, thus revoking the parental wish not to know. Incidental findings that cause an adult onset disorder are however not disclosed out of respect of the child's autonomy and his right to an open future. When competent, the child should be given the opportunity to choose whether or not incidental findings should be disclosed to him.

<u>Policy rule 6:</u> If an incidental finding is identified in a minor, which causes an adult-onset disorder, parents will be informed, if this knowledge benefits the health and well-being of the parents.
This policy rule limits the child's autonomy and right to an open future. This limitation is however justified as it may be expected that the child would consent to disclose information that would be to the benefit of the health and well-being of his parents given the child's exceptional relationship to them.

<u>Policy rule 7:</u> Incidental findings related to carrier status of genetic disorders will not be disclosed to (parents of) patients unless the patient or his blood relatives have a 25% chance at least, to conceive a child with the genetic disorder for which carrier status was identified.

Disclosure of incidental findings related to carrier status does NOT benefit the health or well-being of the patient himself. It however IS of potential medical relevance to his unborn progeny, or to the unborn progeny of his blood relatives. Knowledge on carrier status allow the patient or his blood relatives to make well-informed reproductive choices, which benefit the health and well-being of the unborn progeny.