Dutch national consensus-based guideline for the disclosure of incidental findings during clinical genetic diagnostic testing

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Background

Incidental findings

When comparing the genetic material (genome) of any two individuals only 0.1% will differ. Most of these 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 (=pathogenic) variant(s) in an individual.

Classification of genetic variants

The pathogenicity of DNA variants identified is evaluated and classified according to a (worldwide) standardized methodology (1,2):

- Class 1: variant is CLEARLY NOT pathogenic, and there is no increased risk of disease
- Class 2: variant is UNLIKELY TO BE PATHOGENIC, and unlikely to have an increased risk of disease
- Class 3: variant of UNKNOWN CLINICAL SIGNIFICANCE (in literature 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

Incidental findings

The primary aim of clinical genetic diagnostic testing is to identify the genetic cause of the disease observed in the patient. Depending on the clinical question for which the patient seeks medical advice, different types of genetic diagnostic tests can be performed. These tests include assays targeting a *single* gene, *multiple* genes (e.g., gene panel analysis) or *all* genes at once (exome or genome). The more genes included in the analytical process, the higher the risk of uncovering an accidental finding. Such accidental findings are irrelevant to the clinical question for which the patient sought medical attention and prompted the referring clinician to perform the test. Variants uncovered by chance are called ***incidental findings*** (3). In English literature, also different nomenclature is used to denote incidental findings: 'unsought for findings', 'accidental findings', 'co-incidental findings' and 'unsolicited findings'.

There are two levels in which incidental findings can be distinguished: at the level of the health risk of the patient and at the level of the type of disorder. At the level of the patient's health risk, the following categories exist:

- Incidental finding with a direct effect on the health status of the individual in whom it has been identified, and/or on that of his blood relatives (mostly involving dominant disorders, but for example, also the presence of two (likely) pathogenic compound heterozygous variants in the same gene known to cause in a recessive disorder).
- Incidental findings that only have an increased health risk for the (unborn)children of the patient, or of his blood relatives (this mostly relates to the identification of carrier status of one (likely) pathogenic variant in a gene that is known to be involved in a recessive disorder).

At the level of the type of disorder to which (likely) pathogenic variant(s) in the gene predispose(s), two categories can also be distinguished:

- Disorders for which medical interventions exist (i.e. for which preventative measures, screening programs and/or treatment options are available).
- Disorders for which no medical interventions exist. There may however, be reproductive choices for the patient and/or his blood relatives. (Knowledge regarding) these disorders may also influence life decisions of the patient and/or his blood relatives (including their personal relationships, financial considerations or career choices).

<u>Scope of the directive</u>

- The guideline present in this document (currently) only apply to variants identified during **exome and genome** sequencing in a **postnatal setting.**
- The guideline presented in this document only apply to **likely pathogenic (class 4) and pathogenic (class 5) variants** in genes with established disease-gene relationships (based on the advice by Berg et al. (4)). This, for instance, excludes variants in genes related to ethnicity or level of sporting excellence, as well as variants for which there is insufficient proof of variant pathogenicity (class 1, class 2 and class 3 variant).

- The guideline presented in this document only applies to **variants uncovered as incidental findings**, which were not actively looked for while processing and interpreting the genetic data. This, therefore, **excludes variants uncovered as secondary findings**, which for instance can be uncovered by an active search for pathogenic variants in genes reported on the ACMG list (5). Additionally, this also excludes germline mutations actively sought for to facilitate personalized treatment options.

Duties and responsibilities

- Laboratory Specialist Clinical Genetics (LSCG): the person who performs the genetic analysis and reports a potential incidental finding to the Commission.
- Referring clinician: the person who performs the pre-test counselling, requests the genetic diagnostic test, and reports the results, as well as a potential incidental finding, to the patient. The referring clinician has, as the main treating physician of the patient in charge of the clinical genetic consultation, the ultimate responsibility on the decision to disclose, or not to disclose, an incidental finding to the patient, where he uses the Commissions advice to support his decision.
- Commission: a multidisciplinary team of experts who discuss and evaluate the incidental finding to formulate an advice for the referring clinician regarding the (non-)disclosure of the variant. At minimum, a clinical geneticist and clinical genetic laboratory specialist, both not involved in the direct care of the patient, serve on the Commission. It is, however, a preferred course of action to also consult with the referring clinician, as well as the laboratory specialist clinical genetics who uncovered the incidental finding, to contribute to this discussion.

Notes for further reading

The policy guideline presented here is based on a European guideline (6). However, the commission maintains the right to deviate from her policy when confronted with exceptional circumstances or compelling arguments to the contrary. In the event of a deviation from the guideline, the arguments must be documented in the patient's health care records.

To facilitate legibility, the document is written in the singular form, for which following applies:

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

Of note, when referring to potential consequences for the parents (for instance when referring to reproductive choices or carrier status), this only refers to the biological parents of the patient.

Policy rules

Policy rule 1: Incidental findings will, in principle, only be disclosed to patients during an ongoing medical treatment agreement for exome or genome sequencing.

- In the event that a variant is reclassified based on novel knowledge gained:
    - It is considered good clinical practice to inform the referring clinician and recontact the patient if a previously (likely) pathogenic variant (class 4 or 5), disclosed as incidental finding, is reclassified to a class 3, class 2 or class 1 variant.
    - If the laboratory initially classified a variant as class 1, 2 or 3, and thus did not consider it to be an incidental finding, now reclassifies the variant to be a (likely) pathogenic variant (class 4 or 5), the incidental finding is observed after closure of the medical treatment agreement. The variant should be discussed in the commission, and the referring clinician must be informed. The commission may still advise to disclose the variant to the patient. Note, the laboratory has no duty to actively search for additional, previously examined, patients who could also have this variant.

Policy rule 2: Incidental findings predisposing to a disease for which medical interventions exist, will ALWAYS be disclosed, unless the patient signed 'opt-out'.*

**The right of a patient NOT to be informed on an incidental finding must be respected, provided that during pre-test counselling, the patient willingly signed 'opt-out'. For minors aged 12 to 16 years, the minor and (both) parents must jointly support the decision to 'opt-out'.*

This refers to diseases that may affect the patient himself (regardless of the mode of inheritance of the disease) and for which - according to the state of scientific knowledge and clinical best practice guidelines - preventative measure, screening or treatment options exist at the moment the incidental finding is uncovered.

- 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 this category of incidental findings, opt-out DOES NOT exist.
- For minors below the age of 12, incidental findings increasing the risk of *adult-onset* diseases for which medial intervention exist, require careful consideration to come to a decision to disclosure or not to disclose (arguments in favour for and against disclosure are provided in the substantiation of this policy). Important considerations include the child's right to an open future, his future right to autonomy, and the (potential) increased risk in the parents and blood relatives to manifest the disease. A procedure to opt-out for this category of incidental findings DOES exist.

Policy rule 3: Incidental findings predisposing to diseases WITHOUT opportunities for medical intervention will NOT be disclosed, unless the patient signed an 'opt-in'.**

***The right of a patient to be informed on this type of incidental findings must be respected, provided that during pre-test counselling, the patient willingly signed to 'opt-in'. In principle, minors below the age of 16 years are not offered to 'opt-in'.*

This refers to diseases that may affect the patient himself (regardless of the mode of inheritance of the disease) and for which - according to the state of scientific knowledge and clinical best practice guidelines – NO preventative measure, screening or treatment options exist at the moment the incidental finding is uncovered.

- Whereas no immediate health benefits for the patient himself are expected for a disease for which no medical interventions exist, knowledge thereof does allow him to make informed

decisions related to reproductive choices (prenatal genetic testing and/or pre-implementation genetic diagnosis) or influence other life decisions (personal relationships, financial planning or career wise). It is the duty of the clinical geneticist to inform the patient of these considerations during the pre-test counselling when addressing the opportunity to 'opt-in' for disclosure of this category of incidental findings.

- It must be made clear to the patient that his choice to 'opt-in' applies to both early-onset, as well as late onset diseases.

Policy rule 4: Incidental findings related to carrier status of a genetic disease will NOT be reported, unless it becomes apparent from the test performed, that the patient or his blood relatives have a chance of at least 25% to have offspring manifesting the genetic disease.***

*****The right of a patient NOT to be informed on carrier status must be respected, provided that during pre-test counselling, the patient willingly signed to 'opt-out'.*

- Incidental findings related to carrier status of genetic diseases where the patient or his blood relatives have less than 25% to have an affected child with this disease will not be disclosed (also, there are no options for 'opt-in'). For couples with a desire to have children, preconception carrier testing is a better alternative to answer their clinical question related to the increased risk to have children with a (severe) recessive disease.
- Incidental findings related to carrier status are thus only disclosed for X-linked disorders in females and autosomal recessive disorders when both parents carry a (likely) pathogenic variant in the same gene (in practice, this is often the same variant, with the child being heterozygous (e.g. not affected) and both parents being heterozygous). If carrier status for a recessive disease is only identified in one of the parents, there is no duty to determine carrier status (e.g. actively search for the presence of a (likely) pathogenic variant in the same gene) of the other parent.

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6. Vears D.F., Sénécal K., Clarke A.J., Jackson L., *et al.* Points to consider for laboratories reporting results from diagnostic genomic sequencing. European journal of human genetics, 26:36–43 (2018).

Appendix

Appendix 1 | Substantiation of the Dutch national consensus-based guideline for the disclosure of incidental findings during clinical genetic diagnostic testing

Appendix 2 | Flowchart for the disclosure of incidental findings during clinical genetic diagnostic testing