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

Background

Unsolicited 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, 3):

- 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

CNVs can be classified according to these classes as well (3). Recurrent CNVs that show reduced penetrance (that have a relatively high prevalence) and most balanced structural variants, might fall outside these categories. Their classification will be delineated further in another working group.

Unsolicited 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 unsolicited finding. Such unsolicited findings are irrelevant to the clinical question for which the patient sought medical attention and prompted the referring clinician to perform the test (4). In English literature, different nomenclature is used to denote unsolicited findings: 'unsought for findings', 'accidental findings', 'co-incidental findings' and 'incidental findings'. When additional findings are actively sought, they are referred to as 'secondary findings'.

There are two levels at which unsolicited 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:

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

At the level of the type of disorder to which (likely) pathogenic variant(s) in a 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).

Scope of the directive

- The guideline present in this document apply to constitutional variants identified in a **postnatal setting.**
- The guideline presented in this document only apply to **likely pathogenic (class 4) and pathogenic (class 5) variants** (5)). The guideline does not apply to variants that are not deemed (likely) pathogenic (class 1, class 2 and class 3 variants). If there is any uncertainty regarding the classification of the variant, the clinical laboratory geneticist can discuss the finding in a multidisciplinary committee. The guideline only applies to variants in genes with established disease-gene relationships (based on the advice by Berg et al. (5).
- The guideline applies to genes/loci in imprinted regions or with reduced penetrance.
- The guideline presented in this document only applies to **variants that are not deemed causal for (a part of) the phenotypic presentation the genetic test was requested for..**
- This guideline **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 (6). 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 unsolicited finding to the committee.
- Referring clinician: the person who performs the pre-test counselling, requests the genetic diagnostic test, and reports the results, as well as a potential unsolicited 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 committee's advice to support his decision.

- Committee: a multidisciplinary team of experts who discuss and evaluate the unsolicited finding to formulate an advice for the referring clinician regarding the (non-)disclosure of the variant. At a minimum, a clinical geneticist and clinical laboratory geneticist, both not involved in the direct care of the patient, serve on the committee. 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 (7). However, the committee maintains the right to deviate from the 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: Unsolicited 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 unsolicited 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 unsolicited finding, now reclassifies the variant to be a (likely) pathogenic variant (class 4 or 5), the laboratory has no duty to actively search for additional, previously examined, patients who could also have this variant. There is no duty to recontact, because the decision to not disclose the finding has been made based on guidelines that were into place at that moment in time.

Policy rule 2: Unsolicited 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 unsolicited finding is uncovered.

- For minors below the age of 12, unsolicited 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, unsolicited 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; Appendix 1). 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 unsolicited findings DOES exist.

Policy rule 3: Unsolicited findings predisposing to diseases WITHOUT opportunities for medical intervention will NOT be disclosed.

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 unsolicited 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).

Unsolicited findings that have no opportunities for medical intervention are to be discussed in a multidisciplinary committee on unsolicited findings in order to decide on a case by case basis, taking the specific context of the patient into account.

Policy rule 4: Unsolicited 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'.*

- Unsolicited 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. 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.

- Unsolicited 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.
- Balanced chromosomal translocations/inversions/structural variants often do not have direct clinical implications for the health of the individual. The same accounts for mosaicism and premutations. Carrier status might imply however, a risk of 25% or more on affected offspring of this individual.

Literatuur

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Appendices

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

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

The 'Dutch Society of Clinical Genetics' (VKGN) and the 'Dutch Society of Clinical Genetic Laboratory Specialists' (VKGL) have issued a joint mandate for the development of a national guideline for the disclosure of unsolicited findings in the context of clinical genetic diagnostic testing. For this very purpose, a task force was established composed of clinical geneticists and clinical genetic laboratory specialists of all Dutch clinical genetic centres. This task force has formulated policy guidelines. This document provides the substantiation of these guidelines, reflecting the points of consideration taken into account during their formation.

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

1. The health care professional is guided in his professional practice by the promotion of health and well-being in humans (duty of care). This duty also includes informing a patient of (the potential risks of) uncovering a disease unrelated to the clinical question the patient sought medical attention for, but which could (unintentionally) be uncovered during the diagnostic process thereof.
2. The health care professional has a duty to independently inform 'others', such as blood relatives, of the patient, even in the absence of a clinical question from these blood relatives themselves. This responsibility includes the independent notification of 'others' of serious health care problems in the near future, for which medical interventions exist. The national guideline on 'the duty to inform family members in the event of genetic disease' foresees in actions to be taken, should an incidental finding be reported to a patient.
3. The health care professional does not willingly expose his patients to treatments with (potential) injury or damage (i.e., the medical ethical principle 'to do no harm'), unless the expected health benefits outweigh the potential risks.
4. The health care professional provides the necessary treatment and/or advice for the disease for which the patients sought medical attention. The health care professional will not actively look for other (potential) health care problems outside the scope of the clinical consultation. He will however, act upon (potential) health care problems that he encounters in conformity with the clinical consultation for which the patient sought medication attention (i.e., the medical ethical principle of 'duty to inform').
5. Respecting patient's autonomy is an important principle in healthcare. 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.

Scope of the directive

This policy guideline applies to unsolicited findings identified during genetic testing regardless of the technique used

The former version of this policy (version 1.0) only applied to Single Nucleotide Variants (SNVs) identified when performing whole exome – or genome sequencing. The current version applies to all genetic testing techniques used in the diagnostic setting. For NIPT different guidelines apply.

Guidelines for the disclosure of incidental finding in the clinical genetic care pathway already exist. As NIPD is currently performed as research-based screening, it is within reason that the disclosure policy is different than substantiated here. However, for genomic microarray-based analysis, differences in disclosure policies are difficult to explain, as copy number variants (CNV) can also be identified from exome and genome sequencing. The guideline 'Counselling of genome-wide detection of chromosomal aberrations (CNV) using array or NGS-based diagnostics' can be found here. In the event, exome or genome sequencing identifies an unsolicited finding, it is advised to consult this guideline.

Counselling on genetic diagnostic testing is not always performed by a clinical geneticist. Should an unsolicited finding be uncovered under these circumstances, the policy guidelines, as provided here apply, assuming default options for disclosure.

This policy applies to unsolicited findings uncovered in the postnatal germline setting

Whereas the uptake of genetic testing in prenatal care is increasing, with thus similar risks on uncovering an unsolicited finding, other considerations (than those applicable in a postnatal setting) may apply. Hence, a complementary guideline dedicated to disclosure of unsolicited findings in the prenatal setting will follow.

Only genetic variants with sufficient evidence of pathogenicity can be considered as an incidental finding

Health care professionals have a 'duty to care' and a 'duty to inform', but equally a commitment to prevent needless concerns and anxiety ('do no harm'). There is no benefit to the patient's health to disclose information on genetic variants which do not cause disease (class 1 or 2 variants), or which are uncertain to cause disease (class 3 variant). Especially for the latter, it can be anticipated that disclosure of such information may lead to anxiety and uncertainty (i.e., 'do harm'). In exceptional cases, a class 3 variant can be disclosed, for example if a diagnostically validated functional assay exists that can establish the pathogenic nature of the variant. It might be that an additional patient sample needs to be obtained for this test (e.g. urine or plasma).

Only variants that are outside the scope of the indication for which the genetic test is performed can be considered as an incidental finding

- The active search for pathogenic variants that are not relevant in the context of the clinical question (e.g. those outside of the scope the patient sought medical attention for) does not result in unsolicited findings, but are considered to be secondary findings. The active search for secondary findings is also referred to as opportunistic screening (1). In the Netherlands, opportunistic screening is not being offered.
- If, for the benefit of finding the best therapeutic strategy, genetic data are explicitly used to actively search for relevant variants to determine this strategy (e.g. PARP-inhibitors in the presence of BRCA mutation), this will also be counselled during pre-test counselling. In this scenario, the identified variants are not considered unsolicited findings.

Only variants that have consequences for the health of the patient, blood relatives and/or offspring are considered to be unsolicited findings.

- SNVs, numerical chromosome anomalies (for example turner syndrome; Klinefelter syndrome), balanced translocations/inversions/structural variants and chromosomal anomalies that indicate presence of malignancy, can be considered to be unsolicited findings.. Mosaic chromosomal anomalies fall in the scope of unsolicited findings as well.
- Consanguinity is not considered an unsolicited finding. It is considered good clinical care to discuss the finding of consanguinity in another multidisciplinary meeting.

Duties and responsibilities

- The final decision to report the finding to the patient is the responsibility of the healthcare professional requesting the genetic test.

- It is advised to discuss and evaluate the finding reported by the clinical genetic laboratory specialist in a multidisciplinary meeting, preferably in the presence of the referring clinician. The Committee can formulate a recommendation for the referring clinician on the (non-)disclosure of the unsolicited finding to the patient.
- The clinician has the ultimate responsibility for the patient to disclose or withhold the disclosure of unsolicited findings, and uses the recommendation of the committee for support of this decision. It is hence a necessity to inform the clinician about the finding, even though the patient indicated not wanting to be informed about unsolicited findings.

Policy rules

Policy rule 1: Unsolicited findings will, in principle,only be disclosed during an ongoing medical treatment agreement.

Disclosure of unsolicited 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 without an ongoing medical treatment agreement. Unexpected recontacting of a patient could be experienced as a (unwanted) breach of privacy. A timely disclosure of unsolicitedfindings is therefore preferred.

Under certain circumstances, it can however occur that an unsolicited finding is uncovered after closure of the medical treatment agreement. In these scenarios, the referring clinician can deviate from the policy guidelines and decide to disclose the unsolicitedl finding despite the absence of a medical treatment agreement. An example of such a scenario is the reclassification of variant that was at first NOT reported as unsolicited finding because of its evaluation to be a class 1, 2, or 3 variant, but was later proven to be (likely) pathogenic (class 4 or 5). Only on rare occasions, will the laboratory be able to identify the individual patient(s) in whom such 'upgraded' variant was observed, as most often hospital information systems solely store the information of the genetic variant without identifiable patient information. There is no duty for the laboratory to actively retrace information that would lead to the identification of the patient(s) in whom this variant was uncovered (1,2).

In contrast, if a patient was disclosed a variant that (due to reclassification or otherwise progressive insights) is no longer considered of medical relevance, it is good clinical practice to recontact the

patient and inform the patient on these novel insights. By informing the patient that the variant is no longer of clinical relevance, it allows for preventing further harm (by alleviating uncertainty, anxiety and concerns, detrimental social and societal impact, as well as futile medical intervention).

Policy rule 2: Unsolicited 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 unsolicited finding must be respected, provided that during pre-test counselling, the patient willingly signed to 'opt-out'. For minors aged 12 to 16 years, the minor and (both) parents must jointly support the decision to 'opt-out'.*

- The healthcare professional has a duty to inform the patient on the risks and health care problems that can be intervened with medical interventions ('do well', 'respect for autonomy', 'right to know'). In-keeping with the duty to practice good clinical care, the patient should be informed on an unsolicited finding, provided that the unsolicited finding 1) results in a disease or condition in the patient, and 2) leads to subsequent actions of the patient, such as follow-up diagnostic testing, preventatives measures or treatment.
  The referring clinician fails to provide good clinical care if he does not inform his patient on such unsolicited findings (unless the patient has willingly signed 'the opt out' and invoked his right not to know).
- To assess if there are guidelines to medically intervene with the natural course of disease the unsolicited finding predisposes to, one has a duty to always consult the most recent literature.
- For chromosomal class 4 and 5 variants e.g. (mosaic monosomy X or Klinefelter syndrome), medical interventions almost always exist. It is important to check the consent and context before deciding on disclosure.
    - Consent: did the patient choose an opt-out? Use of ISCN nomenclature should be avoided to hide the finding.
    - Context: for example; Klinefelter in elderly does not have to be reported
- The right to 'opt-out' is a consequence of respecting patient's autonomy and the option should be offered during pre-test counselling. The option can be overruled in rare occasions (WGBO 449).
- If a patient chose to opt out for the disclosure of unsolicited findings, the laboratory should ideally mitigate all risks of uncovering such findings. The technical feasibilities to prevent this are limited and not always possible.
- For children under the age of 12, unsolicited findings will only be disclosed if they increase the risk on a childhood or adolescent onset disorder, and if medical intervention is available. Parents of patients are not revoked the right not to know.
- Unsolicited findings in children under the age of 12 that are the cause of an adult-onset disorder for which medical interventions exist, should be evaluated on a case-by-case basis.
    - Arguments favouring non-disclosure may include the child's right to an open future, and protection of the future child's autonomy. That is, the child has not reached the legal age yet to make his own well-informed decision, and invoke his right not to know when disclosing.
    - Arguments favouring disclosure may include the rational that one cannot ensure that the information reaches the patient (at an age where he can legally make his own well-informed decision to opt-in or opt-out). The patient may therefore miss out on this important information. For patients with an intellectual disability, it should be noted

that, despite reaching the legal age to make their own informed decision, they may never reach a level of mental competence to make this decision. Not disclosing the unsolicited finding may prevent the patient and his parents to take appropriate (preventative) medical actions.

- In the case of a trio-based analysis, an unsolicited finding can be uncovered in either one of the parents and will in principle, be disclosed to allow for appropriate medical intervention.

Policy rule 3: Unsolicited findings predisposing to diseases WITHOUT opportunities for medical intervention will NOT be disclosed

In the advice of the Healthcare council (3), no duty to inform on unsolicited findings that are 'not actionable' has been described. The healthcare professional has a duty to inform, when the information leads to improvement of health related outcomes. If a patient shares the interest in knowing about these potential findings, it should be explained that the genetic test that is being performed is not aimed at uncovering these findings.

Policy rule 4: Unsolicited findings related to carrier status that imply a risk on a genetic condition in offspring will NOT be reported, unless the patient or blood relatives have a possible 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'.*

- Disclosure of unsolicited l findings related to carrier status does generally speaking NOT benefit the health or well-being of the patient himself. It, however, IS of potential medical relevance to his (unborn) children, or to the (unborn) children of his blood relatives. Knowledge on carrier status allows the patient or his blood relatives to make well-informed reproductive choices, which benefit the health and well-being of the unborn child. Hence, incidental findings with a high relative risk on a genetic disease, manifesting in unborn progeny, can therefore be disclosed.
- A threshold for disclosure of carrier status was set to have at least 25% chance of having affected progeny, for example when both parents are identified as a carrier of the same variant (carrier status for autosomal recessive disorders), but also the carrier status for an X-linked disorder in females.
- A deliberate choice was made to use a threshold based on the risk of affected progeny (e.g. at least 25%) rather than a threshold based on carrier frequency in the population (e.g. 1/60), as this is independent of ethnicities-specific alleles and diseases. The latter would require a disproportionate effort to gain detailed knowledge per variant which pragmatically cannot be achieved.
- When carrier status has been identified in one parent, the laboratory specialist has no duty to actively look for carrier status in the other parent. Not identifying a disease causing variant in the other parent does not exclude a positive carrier status. Also, this would align with secondary findings which are not being looked for in the Netherlands.
- As a consequence of these choices, individual carrier status is not disclosed as an incidental finding, not even if it concerns a disorder with a relative high frequency of carriers in the population (e.g. CF). Based on a carrier frequency of 1/30 in the population, the risk of the offspring of an individual with a pathogenic CF variant (as incidental finding) is less than 1% (1/2 x 1/30 x ½ = 1/120 = 0.8%). In practice, this risk is likely to be even lower, as often both parents are

tested in WES, with the variant only being observed in 1 parent (for example, if the most frequent pathogenic CF variant, delta-F-508, is only present in one parent, one may also deduce that the other parent does not carry this variant, leaving a risk of this parent being a carrier of less than 1/30).

- Couples with an *a priori* increased risk to have a child with a genetic disorder (because of, for instance, ethnicity, geographical descent and/or consanguinity), or couples who wish to be able to gain more insight into their carrier status for genetic diseases, can be referred for counselling and preconception carrier testing (PCT). This sort of dedicated test is better suited to determine the couple's risk of affected offspring.
- If the laboratory identifies carrier status in a child and one of his parents, there is no duty for the laboratory to actively search for the presence or absence of a (likely) pathogenic variant in the other parent (possibly resulting in a 25% risk of affected offspring). The absence of carrier status may lead to false assumptions as it cannot be assured the assay used did not miss the detection of a (likely) pathogenic variant. Unsolicited findings do not fully cover the possibility of shared carrier status of autosomal recessive conditions.

These are three scenario's in which the recurrence risk is hard to predict. In these scenario's, disclosure will depend on consent and context:

- Balanced chromosomal translocations/inversions/structural variants
- Mosaic variants (risk of gonadal mosaicism)
- Premutations

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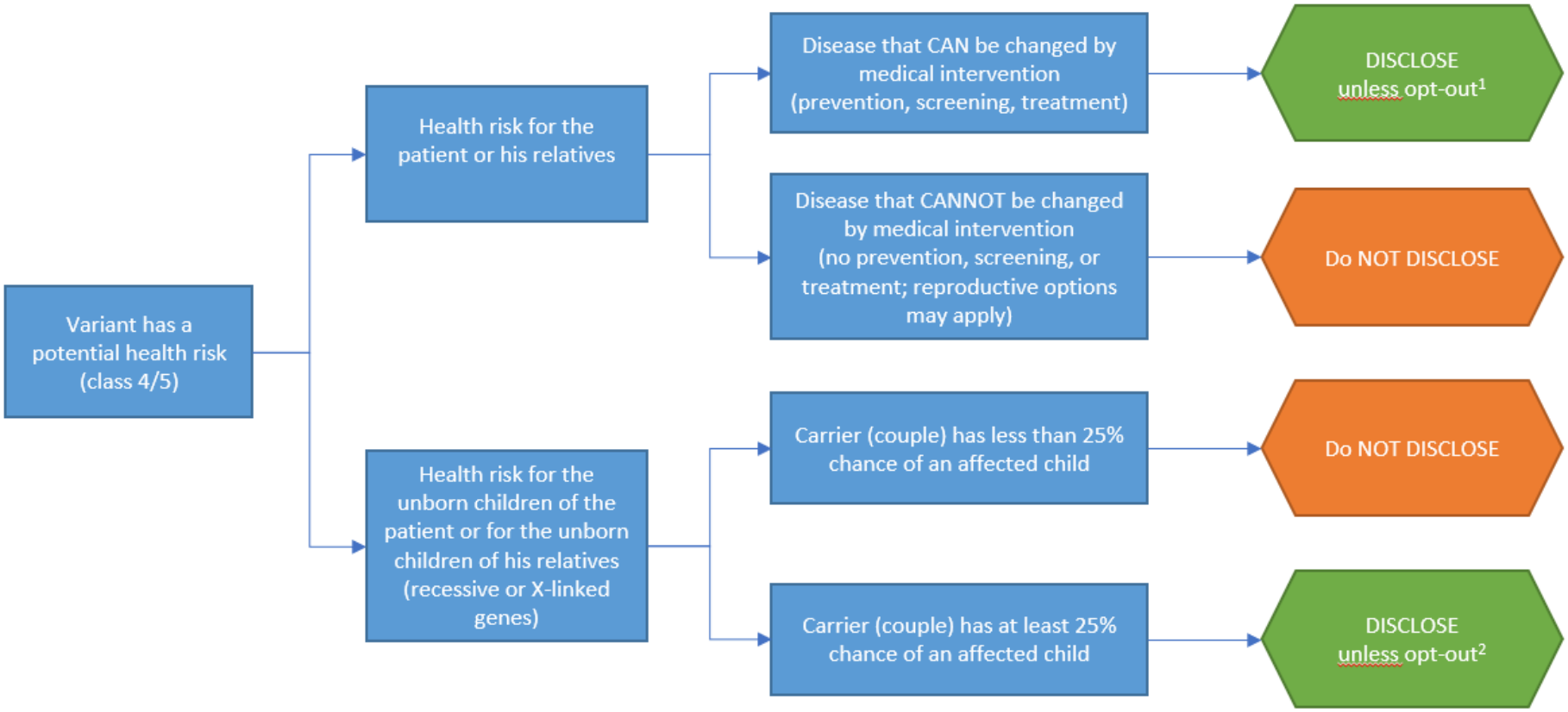
Appendix 2: Flowchart for the disclosure of unsolicited findings during clinical genetic diagnostic testing



[1] If the patient is <12 years old and disease manifests during childhood: no opt-out possible.

[2] Both parents must jointly support the decision to opt-in or to opt-out.