Prenatal array guidelines

prepared by the BeSHG Prenatal Committee on 14.09.2023

approved by the College for Medical Genetics on 02.02.2024

CLASSIFICATION OF VARIANTS WITH REGARD TO PATHOGENICITY

- **Pathogenic**

  CNVs known to be associated with a phenotype (e.g. del22q11.2, del4p, del15q11-13, etc.) or CNVs resulting in a known effect on gene function and known phenotypic effect are communicated.

- **Benign variants without functional consequences**

  Variants repeatedly found in the normal population and not enriched in individuals with abnormal phenotypes are not communicated.

- **Unclassified variants (UV)**

  In principle, unclassified variants are not communicated and parental analysis is not performed, unless one expects that this will add to the interpretation of the UV and to the decision to communicate this CNV. Examples include CNVs with a higher degree of suspicion that they may cause a phenotype (size, number of genes, percentage of overlap with reported pathogenic CNVs, phenotype associated with the reported CNV, number of cases described…), the presence of ultrasound anomalies, family history etc.

In case of uncertainty, **the ad hoc committee** is consulted for advice. This is done before the final protocol is issued.

SUSCEPTIBILITY CNVs

CNVs that are risk factors for developmental disorders will, in principle, not be communicated, unless the risk is sufficiently large and/or the CNV is associated with structural malformations for which ultrasound follow-up is indicated. The list of susceptibility loci is available on the website of the College for Genetics: https://www.college-genetics.be/nl/voor-de-professionele/good-practice-et-richtlijnen-voor-beroepsbeoefenaars/richtlijnen.html.

Communicating other susceptibility CNVs may be appropriate when this is expected to influence the management of pregnancy by parents or physicians (e.g. family history, ultrasound anomalies).

INCIDENTAL FINDINGS

Only highly penetrant monogenic disorders are considered, with validated evidence on the phenotype associated with the deletion or duplication. Four categories are distinguished:

- **Late-onset genetic disorders with clinical utility:**

  CNVs causing late onset disorders, typically cancer caused by the deletion of a tumor suppressor gene, will be communicated if undeniable health benefit can be expected for the patient (fetus or parent) according to the latest guidelines[1] from the American College of Medical Genetics (ACMG).
- **Late onset disease without therapeutic possibilities:**

  The responsible clinician takes the decision after consulting the ad hoc committee. If no consensus can be reached, the responsible clinician decides and communicates the decision to the ad hoc committee.
- **Carriership for X-linked recessive disorders** will be communicated, both de novo or inherited.
- **Carriership for autosomal recessive disorders** will not be communicated.

A non-exhaustive list of the reporting policy of possible fetal aberrations detected by aCGH can be found in the annex document "Reporting policy of fetal CNVs detected by aCGH upon invasive prenatal testing" on the website of the College for Genetics: https://www.college-genetics.be/nl/voor-de-professionele/good-practice-et-richtlijnen-voor-beroepsbeoefenaars/richtlijnen.html.

PRE- AND POST-TEST COUNSELING

Providing pretest information on the different test results is strongly recommended and is summarized in an information leaflet. The parents are not given an option to choose which information they wish to be returned. In case of an abnormal result (irrespective of which type) the parents should be offered extensive genetic counseling, without unnecessary delay.

---

[1] David T Miller, Kristy Lee, Noura S Abul-Husn, Laura M Amendola, Kyle Brothers, Wendy K Chung, Michael H Gollob, Adam S Gordon, Steven M Harrison, Ray E Hershberger, Teri E Klein, C Sue Richards, Douglas R Stewart, Christa Lese Martin; ACMG Secondary Findings Working Group. ACMG SF v3.2 list for reporting of secondary findings in clinical exome and genome sequencing: A policy statement of the American College of Medical Genetics and Genomics (ACMG). Genet Med 2023. PMID: 37347242.

Version history

Version	Date prepared by BeSHG Prenatal Workgroup	Date approved by College of Medical Genetics	Updates
V2013	20.04.2013	03.05.2013	New document: no history available.
			Detailed guidelines published in paper PMID 24534801.
V2018	21.12.2017	12.01.2018	Only annex with summary of guideline is retained..
			Communication of de novo unclassified variant was removed.
			ACMG guidelines: reference to paper PMID 27854360.
			List of susceptibility CNVs summarized in annex table.
V2021	10.12.2020	05.02.2021	Link to the list of susceptibility loci was updated (website of the College for Genetics).
			Carriership for AR disorders will not be communicated (no exceptions).
V2023	14.09.2023	02.02.2024	Referral to annex document with reporting policy of a non-exhaustive list of possible fetal aberrations detected by aCGH.
			ACMG guidelines: reference to paper PMID 37347242.