PRENATAL ARRAY GUIDELINES

prepared by the BeSHG Workgroup on Prenatal Testing on 10.12.2020

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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.

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]Kalia SS, Adelman K, Bale SJ, Chung WK, Eng C, Evans JP, Herman GE, Hufnagel SB, Klein TE, Korf BR, McKelvey KD, Ormond KE, Richards CS, Vlangos CN, Watson M, Martin CL, Miller DT. Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics. Genet Med 2016. PMID: 27854360.