



BELGIAN GUIDELINES FOR MANAGING INCIDENTAL FINDINGS DETECTED BY NIPT

prepared by the BeSHG Prenatal Committee on 05.09.2019

approved by the College for Medical Genetics on 06.09.2019

NIPT by means of whole genome sequencing may result in incidental findings such as whole chromosome aneuploidies other than trisomy 13, 18 or 21 or subchromosomal abnormalities. In reporting incidental findings, emphasis should be on the risk on causing potentially serious harm for maternal or fetal health when this finding is not reported. Therefore, incidental findings should only be reported if (i) they are considered technically valid, (ii) there is validated evidence on the associated phenotype and (iii) they are considered clinically relevant and actionable.

Incidental findings should be managed according to the guidelines outlined below. In case of uncertainty, the responsible clinical geneticist takes the decision after consulting the ad hoc committee. If no consensus can be reached, the responsible clinical geneticist decides and communicates his decision to the ad hoc committee. For all reported incidental findings, referral for genetic counselling is required.

Fetal incidental findings

1. **Fetal autosomal aneuploidies** other than trisomy 13, 18 or 21 will be communicated, stating the possibility of confined placental mosaicism in the report. Ultrasound follow-up is recommended. Follow-up amniocentesis can be offered to exclude fetal mosaicism and, if applicable, uniparental disomy (chromosome 6, 7, 11, 14, 15 and 20).
2. **Fetal subchromosomal abnormalities**, if considered technically valid, will be communicated when they are in concordance with the Belgian invasive prenatal testing guidelines. Follow-up amniocentesis is indicated to confirm the finding.

Maternal incidental findings

Five groups of maternal incidental findings can be distinguished. Follow-up amniocentesis can be indicated, since NIPT cannot confirm or exclude the presence of the detected aberration in the fetus.

1. Copy number variations (CNVs) causing disorders with validated evidence on the phenotype. Only those that are considered clinically relevant and actionable* (detailed ultrasound follow-up, adjusted delivery management...) will be reported.
2. CNVs proven to be risk factors for developmental disorders with reduced penetrance and/or variable expression. The predictability of the future phenotype resulting from such CNVs remains very poor. Therefore, these susceptibility CNVs will not be reported.
3. CNVs causing late-onset genetic disorders that are still asymptomatic in the mother. Disorders with clinical utility, typically cancer caused by the deletion of a tumor suppressor gene, will be reported according to the latest guidelines¹ from the American College of Medical Genetics (ACMG), as undeniable health benefit can be expected for the mother and/or relatives when communicated.
4. CNVs that have no consequence for the mother but, if inherited, are potentially harmful for the fetus in the current or in a future pregnancy:
 - a. Carriership for autosomal recessive disorders will not be communicated, unless the disorder is frequent, i.e. carrier frequency >1/50 (CFTR, SMA and GJB2/6).
 - b. Carriership for severe X-linked recessive disorders** will be communicated, irrespective of the sex of the fetus.
 - c. Carriership of a mosaic CNV will be communicated if it poses a risk for highly penetrant developmental disorders in the fetus.
5. NIPT may lead to the incidental finding of a malignancy in the mother. This will be communicated.

* Representative examples are the 22q11 deletion between LCR-A and LCR-D causing VCFS and the recurrent 17p12 deletion causing HNPP. The reciprocal 17p12 duplication causing CMT1A will not be reported. If it has not yet been diagnosed, it is a predictive test of a condition for which no preventive measures exist.

** STS and SHOX deletions will not be reported, since these are not considered severe, and the potential benefit does not outweigh the potential distress caused by communicating this result.

¹Kalia 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.

