

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) or a possible maternal hematological malignancy (chromosome 8 and 22).
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 guidelines<sup>1</sup> 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.
  - 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 (see also fetal incidental findings §1). This will be communicated.

A non-exhaustive list of the reporting policy of possible maternal incidental findings detected by NIPT can be found in the annex document “Reporting policy of maternal incidental findings detected by NIPT” 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>.

\* 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.

<sup>1</sup>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.

## Version history

Version	Date prepared by BeSHG Prenatal Workgroup	Date approved by College of Medical Genetics	Updates
V2017	26.01.2017	03.02.2017	No history available
V2018	21.12.2017	12.01.2018	Examples added for CNVs causing highly penetrant disorders with validated evidence on the phenotype associated with the deletion of duplication: del22q11A-D, del17p12 (HNPP), dup17p12 (CMT1A). Fetal aneuploidies instigating UPD analysis adapted (chr. 6 and 20 added, chr. 20 removed)
V2019	05.09.2019	06.09.2019	Three general criteria for reporting incidental findings are added to the first paragraph. Group 1 of maternal incidental findings is revised (only CNVs that are clinically relevant and actionable are to be reported); examples are updated and moved to footnote (17p12 duplication will no longer be reported if not yet diagnosed). Examples of X-linked recessive disorders are added in a footnote (STS and SHOX deletions will not be reported).
V2021	10.12.2020	05.02.2021	Group 4 of maternal incidental findings is revised (AR disorders will not be communicated, without exceptions).
V2023	14.09.2023	02.02.2024	Referral to annex document with reporting policy of a non-exhaustive list of maternal incidental findings detected by NIPT.
	14.12.2023		Follow-up for possible maternal hematological malignancy in case of trisomy 8 or trisomy 22.