Chapter 3

Maternal malignancies detected with noninvasive prenatal testing

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To the Editor

Dr Bianchi and colleagues [1] described the incidental detection of occult maternal malignancies with noninvasive prenatal testing (NIPT). The authors evaluated 8 pregnant women who received an abnormal NIPT result discordant with the actual fetal genotype.

Five of these women received an NIPT result with at least a monosomy for chromosome 18, and 1 received a result suggestive for monosomies of chromosomes 13, 18, and 21. For routine NIPT, the authors used whole-genome massively parallel sequencing with targeted analysis (Illumina). Overrepresentation or underrepresentation of chromosomes 13, 18, 21, X, and Y was evaluated by “…constructing a ratio between the normalized coverage on each chromosome of interest and the sum of normalized coverage on a respective set of reference chromosomes…” [1] with the number of reference chromosomes typically being between 2 and 6 per target chromosome.

After the malignancies were reported to the laboratory, the data of the 8 cases were analyzed genome-wide, revealing copy-number variants that affected multiple chromosomes. In their discussion, the authors stated that “the data presented here underscore the necessity of performing a diagnostic procedure to determine the true fetal karyotype whenever NIPT results reveal chromosome abnormalities” [1].

We agree with the authors that aberrant NIPT results should be confirmed, but we think NIPT results suggestive for an autosomal monosomy should neither be reported to the patient nor confirmed with invasively obtained fetal material without prior additional data analysis because a fetal autosomal monosomy is unlikely. Moreover, for data analysis, the prenatal test used in the study relied on a small set of reference chromosomes for each target chromosome; aberrations of the reference chromosomes might lead to incorrect conclusions for the target chromosomes, such as shown in this study for reference chromosome 8 and target chromosome 18.

Therefore, we suggest the use of algorithms that, instead of relying on only a few reference chromosomes, rely on a broader panel of reference chromosomes or genomic regions, such as the publicly available WISECONDOR algorithm [2, 3] or the algorithm described by Bayindir et al. [5].

These algorithms rely on regions across the genome as reference and produce genome-wide results. They do not overcome the rare problem of detecting maternal aberrations, but do provide immediate insight into the data before such data are reported to pregnant women.
References


