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Copy-Number Variation and False Positive Prenatal Aneuploidy Screening Results: The Authors Reply

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THE AUTHORS REPLY

Kingsley et al. argue that experimental and algorithmic aspects of their method minimize the effect of maternal copy-number variants on noninvasive prenatal screening. To illustrate their approach, they provide data excluding outlying estimates of fetal chromosome copy numbers that may be affected by maternal copy-number variants. Along similar lines, van den Boom et al. summarize results of their algorithm that was adjusted to mitigate the effect of maternal copy-number variants in interpretation of the results of noninvasive prenatal screening. They discuss the additional effect of maternal copy-number variants on nontargeted chromosomes as well as on the targeted chromosome. As we noted in the Discussion section of our article, various cell-free DNA (cfDNA)-based non-invasive prenatal screening methods may be more or less influenced by maternal copy-number variants, depending on both experimental considerations (e.g., shotgun vs. targeted sequencing) and algorithmic considerations (e.g., whether the algorithm underlying a particular test accounts for copy-number variation). We appreciate these descriptions of the authors' approaches to maternal copy-number variants and agree that continued technological refinement is crucial as noninvasive prenatal screening moves forward.

Jivan et al. describe a case of a false positive result of cfDNA-based noninvasive prenatal screening. This result was found to be due to maternal acute myeloid leukemia with multiple cytogenetic abnormalities. Though other cases of false positive results on noninvasive prenatal screening that were attributable to cancer have been reported,^{1–3} these results have not implicated leukemia specifically. Cases such as this one underscore the complexity of interpretation of noninvasive prenatal screening, given the potential of cfDNA to derive from multiple sources and therefore to reflect either true fetal genetic factors, confined placental mosaicism, or a maternal condition, including cancer or a previously unrecognized maternal genetic condition. In this rapidly changing field, continual evaluation of noninvasive prenatal screening and its clinical delivery to account for our expanding knowledge is crucial.

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