More research is needed prior to the implementation of genome-wide cell-free DNA testing in specific populations (Response to letter L19-020A: Confined placental trisomy detection through cell-free DNA in the maternal circulation: Benefit for pregnancy management)

We thank Li *et al* for the response to our recent publication "Expanding the indications for cell-free DNA in the maternal circulation: clinical considerations and implications."[1] The authors present interesting information regarding the use of genome-wide cell-free DNA testing in a small number of patients with early-onset intrauterine growth restriction (IUGR) and propose potential benefit to patient counseling and treatment based on the prenatal identification of confined placental mosaicism (CPM) for rare autosomal trisomies using cell-free DNA.

Although we recognize that, theoretically, genome-wide cell-free DNA testing may help elucidate the background of certain pregnancy complications, more research is needed prior to its generalized use in the clinical care of pregnant women. The clinical performance of genome-wide cell-free DNA tests, including sensitivity and specificity, has not been adequately described.[1] Placental mosaicism is a documented cause of cell-free DNA results that are discordant with fetal genetic status,[2] but the ability of cell-free DNA testing to identify placental mosaicism has not been described. Li et al propose that a cell-free DNA test result indicative of CPM for a rare autosomal trisomy may have an impact on clinical management. However, a negative result should be interpreted with caution, as the residual risk for placental mosaicism is unknown. As such, it is unclear whether patients with a negative result should be managed any differently from those with a positive result.

The potential benefits of a screening program must be carefully weighed against potential harms to patients prior to implementation in clinical practice. Rare autosomal trisomies and large copy number variants assessed by genome-wide noninvasive prenatal tests are exceedingly rare conditions for which the natural history cannot be reliably predicted in the prenatal period. Professional societies do not currently recommend this testing in the general pregnancy population.[1] It remains to be seen whether genome-wide cell-free DNA testing has clinical utility in specific high-risk populations. ■

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