When edge cases aren’t so “edgy” anymore: Providing prenatal cfDNA screening to the masses

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Introduction
Non-invasive prenatal screening (NIPS) via cell-free DNA has reached a point of relative maturity, in terms of both technology and market. This growth means what were formerly edge cases are now routine and need to be mitigated, not by limiting access based on age or body habitus, but rather by addressing the limitations of widely used methodologies. Here we address how NIPS can robustly handle patients with obesity, low fetal fraction (FF), and confounding maternal CNVs, as well as how to deliver results and counseling at scale.

Fetal Fraction and Sensitivity for High-BMI Patients
Guidelines recommend “offering aneuploidy screening other than NIPS in cases of significant obesity”, limiting access for nearly 1 in 4 patients. We couple a retrospective fetal fraction analysis from 51,737 anonymized samples with computational simulations of whole-genome sequencing (WGS) to calculate expected sensitivity for patients in each BMI class. We find that NIPS is a reasonable option for high-BMI patients with methods that improve performance at low FF, thereby allowing providers to offer the same high level of care.

Maternal CNVs Are a Known Cause of False Positives
Maternal CNVs (mCNVs) are a known cause of false positives. Retrospective analysis and simulations were used to characterize the relationship between features of mCNVs (chromosome, size, type) and risk for a false call. High-specificity in NIPS can be achieved using a suite of best practices, including algorithmic omission of outlying segments, fine-tuned quality-control metrics and manual call review.

Conclusions
Using appropriate methodology, computational analysis, software tools and thoughtful consideration of technical challenges, we demonstrate how to provide a robust, accessible and scalable prenatal screening experience for all patients.