NIPS for patients with high BMI: evaluating the impact of whole genome sequencing

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Introduction
Fetal fraction (FT) is one of the many factors that influences the performance of noninvasive prenatal screening (NIPS).1 Low FT is often associated with a compromised placenta (e.g., from triplody and certain aneuploidies), and high body mass index (BMI). By far the most common of these high FT patients with high BMI constitute 25% of US pregnancies.1 While the majority of pregnancies have a FT>4%, women with high BMI are much more likely to have lower FT, impacting the performance of NIPS due to test failures, or "no-calls," based on the low FT.2,3 When BMI is >30 (considered obese), studies have shown "no-call" rates of 19-24%—an unacceptable high rate of test failure for widespread use.4

The most recent American College of Genetics and Genomics statement recommends "offering amniocentesis otherwise than NIPS in cases of significant obesity."2 There are several drawbacks of this approach: 1) Most women with a high BMI actually do not have a low FT (Figure 2 and ref 6, 7), 2) There is no known association between amniocentesis and BMI, and 3) heeding this recommendation would necessitate treating >25% of the patient population clinically different based on their BMI, impacting the performance of NIPS due to test failures, or "no-calls," based on the low FT (Figure 7). Of note, however, is that a significant percentage of patients in each of these BMI classes would end with a "no-call" if using a FF cut-off of 4%. Nevertheless, even those patients with class III BMI have expected T21 sensitivity in excess of that obtainable via standard maternal serum screening (51%).8

Study design
9,137 consecutive patients whose height and weight and received WGS-based NIPS w ere stratified into standard BMI classes. FT closely follows a beta distribution, allowing parameterization across classes (Figure 2). For each BMI group, the aggregate analytical sensitivity (Figure 3) was calculated by summing — over the range of FT values — the product of the FT sensitivity for a given FT and depth based on a model of WGS NIPS.11 and the BMI-specific probability of observing a test at that FT from Figure 2. The analyses did not involve a "no-call" threshold on FT.

Results
The distribution of FT over various classes of BMI demonstrates that a large proportion of women with high BMI would have a FT<4%, which would result in a high test failure rate if FT alone were used as a cut-off. This is consistent with similarly high test failure rates seen by others.9,10 As BMI increases, NIPS sensitivity drops due to downward shifts in the FT distribution: non-class analytical sensitivity for T21 is 95%, whereas for class III it is 94.5%.11,12 However, even those patients with class III BMI have expected T21 sensitivity in excess of that obtainable via standard maternal serum screening (51%).8

Conclusion
Due to their systematically lower FT, high-BMI patients are subjected a higher "no-call" rate for NIPS methodologies that have a minimum-FT threshold.1 The alternative of using other screening methodologies such as MSS is suggested by professional guidelines;9 in either case, a class of patients could be subjected to a lower quality of care. However, we demonstrate that NIPS alone is a superior option for high-BMI patients when using methods that maintain high sensitivity at low FT such as whole-genome sequencing, allowing providers to offer the same high level of care to all of their patients, regardless of body habitus.


References
1. "No-call" rate
5. "No-call" rate
9. "No-call" rate

Figure 1: Previous studies demonstrate that high BMI is associated with lower FT and higher "no-call" rates.

Figure 2: Distribution of FT over various classes of BMI.

Figure 3: Evaluating the analytical sensitivity of WGS for patients with high BMI.

Table 1: WGS NIPS demonstrates superior analytically over standard maternal screening for low FT in patients with any class of obesity.

Figure 4: Depiction of population-wide distribution of FT. A) Beta distribution fit to empirical FT values is plotted. B) The distribution of FT associated with maternal weight, demonstrating an inverse relationship. Adapted from Leong et al et al. C) Higher "no-call" rates in women with a high BMI versus normal BMI were noted. D) FT increases with increasing maternal age, leading to lower "no-call" rates, the difference between "no-calls" values actually higher in women with a high BMI (adjusted for maternal age). E) Clinical experience shows significantly higher "no-call" rates in women who are seriously underweight or seriously underweight without obesity.