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

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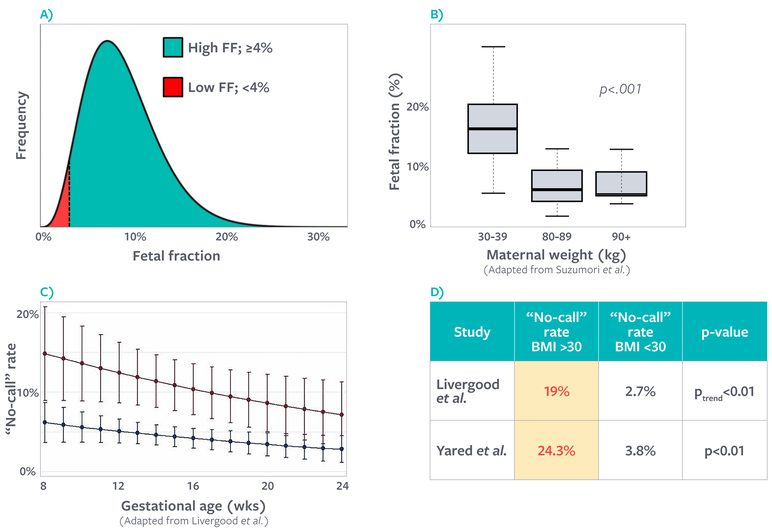
Introduction

Fetal fraction (FF) is one of the many factors that influences the performance of noninvasive prenatal screening (NIPS).[1] Low FF is associated with early gestational age, a compromised placenta (e.g., from triploidy and certain aneuploidies), and high Body-Mass Index (BMI).[2] By far, the most common of these is high BMI: patients with high BMI constitute >25% of US pregnancies.[3,4] While the majority of pregnancies have a FF>4%,[1] women with high BMI are much more likely to have lower FF,[1,5] impacting the performance of NIPS due to test failures, or "no-calls," based on the low FF (Figure 1). When BMI is >30 (considered obese), studies have shown "no-call" rates of 19-24.3% — an unacceptably high rate of test failure for widespread use.[6,7]

The most recent American College of Genetics and Genomics statement recommends "offering aneuploidy screening other than NIPS in cases of significant obesity."[8] There are several drawbacks of this approach: **1)** most women with a high BMI actually do not have a low FF (Figure 2 and ref 6, 7); **2)** there is no known association between aneuploidy and BMI and; **3)** heeding this recommendation would necessitate treating >25% of the patient population clinically different based on their weight alone.

We sought to examine whether high-BMI patients benefit from NIPS using whole-genome sequencing (WGS) without a strict FF cut-off versus standard maternal serum screening for the purpose of common aneuploidy screening.

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



D)

Study	"No-call" rate BMI >30	"No-call" rate BMI <30	p-value
Livergood *et al.*	19%	2.7%	P_{trend}<0.01
Yared *et al.*	24.3%	3.8%	p<0.01

Figure 1: A) Depiction of population-wide distribution of FF. A beta distribution fit to empirical FF values is plotted. **B)** The distribution of FF associated with maternal weight, demonstrating an inverse relationship. Adapted from Suzumori *et al*; **C)** Higher "no-call" rates in women with a high BMI vs. normal BMI across gestational ages. While FF increases with increasing gestational age, leading to lower "no-call" rates, the difference between "no-call" rates in women with a high BMI (maroon) vs. a normal BMI (blue) is largely maintained. Adapted from Livergood *et al*; **D)** Clinical experience studies show significantly higher "no-call" rates in women with obesity vs. women without obesity.

Study design

51,737 consecutive patients who provided their height and weight and received WGS-based NIPS were stratified into standard BMI classes. FF 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 FF values — the product of **1)** the sensitivity for a given FF and depth based on a model of WGS NIPS11 and **2)** the BMI-specific probability of observing a patient at that FF from Figure 2. The analysis did not involve a "no-call" threshold on FF.

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

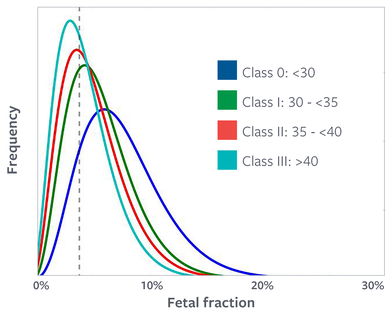


Figure 2: Obesity is defined by BMI classes based on CDC definitions, as noted.[10] FF has a known distribution and patient cohorts are defined by their BMI class, fitting that Beta-distribution. This parameterization is important to be able to calculate precise amounts of patients in each cohort within each FF window. The higher the class of obesity the higher the frequency of low FF, but in all classes the majority of the population still fall above 4% FF, as indicated by the dashed line. Of note, however, is that a significant percentage of patients in each of these classes would end with a "no-call" if using a FF cut-off as a sole metric consistent with the clinical experience studies by Livergood *et al.*[6] and Yared *et al.*[7]

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

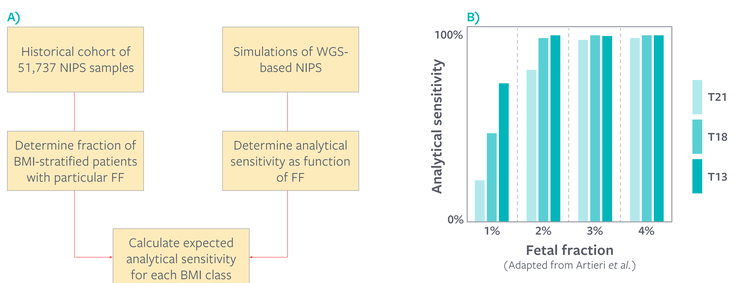


Figure 3: A) Study Design Retrospective cohort of NIPS samples stratified by FF and BMI class. **B)** Analytical sensitivity for common aneuploidy using WGS at various FF levels.[11]

Results

The distribution of FF over various classes of BMI demonstrates that a large proportion of women with high BMI would have a FF <4%, which would result in a high test-failure rate if FF alone were used as cut-off. This is consistent with similarly high test failure rates seen by others.[6,7,12]

As BMI increases, NIPS sensitivity drops due to downward shifts in the FF distribution: non-obese analytical sensitivity for T21 is 99.8%, whereas for class III it is 95.4%.[11] Nevertheless, even those patients with class III BMI have expected T21 sensitivity in excess of that obtainable via standard maternal serum screening (92.9%).[13]

Obesity class (BMI)	WGS NIPS Chr21 Analytical Sensitivity	MSS Chr21 Analytical Sensitivity
Class 0 (<30)	99.79%	92.9%
Class 1 (30 - <35)	98.78%	92.9%
Class 2 (35 - <40)	97.62%	92.9%
Class 3 (>40)	95.41%	92.9%

Table 1: With WGS, NIPS has superior analytical sensitivity over maternal serum screening for trisomy 21 in patients with any class of obesity.[11,13]

Conclusion

Due to their systematically lower FF, high-BMI patients are subjected a higher "no-call" rate for NIPS methodologies that have a minimum-FF threshold.[6,7] 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 FF such as whole-genome sequencing,[10] allowing providers to offer the same high level of care to all of their patients, regardless of body habitus.

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