High-throughput fetal-fraction amplification increases analytical performance of noninvasive prenatal screening

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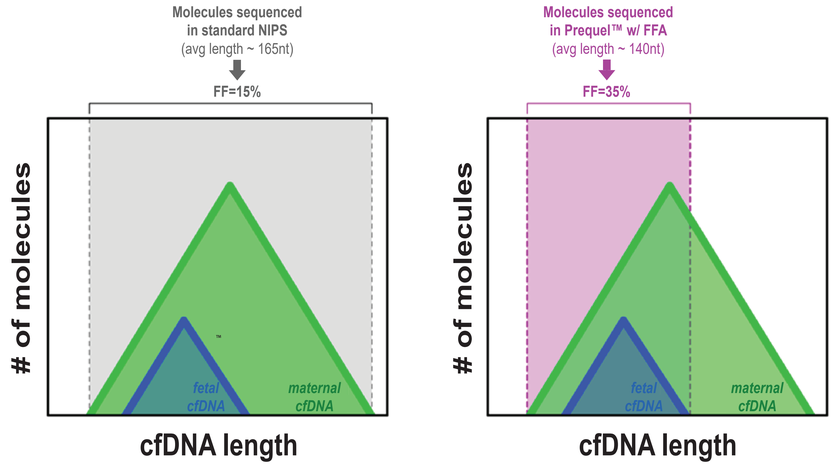
INTRODUCTION

- The percentage of a maternal cell-free DNA (cfDNA) sample that is fetal-derived (the fetal fraction; FF) is a key driver of the sensitivity and specificity of noninvasive prenatal screening (NIPS).
- On certain NIPS platforms, >20% of women with high body-mass index (and >5% overall) receive a test failure due to low FF (<4%).

METHODS

- A scalable fetal-fraction amplification (FFA) technology powered by cfDNA size selection that is routinely applied to all samples undergoing whole-genome sequencing (WGS)-based NIPS in our laboratory was analytically validated on 1,264 samples tested with and without FFA (Figure 1).
- FF levels were also explored in a retrospective cohort of >22,000 clinical samples to which FFA was applied.

Figure 1. FFA increases the relative concentration of fetal-derived cfDNA fragments via size selection.



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RESULTS

- Zero samples in the combination of our validation cohort and our retrospective patient cohort had FF<4% when screened with FFA, whereas 1 in 25 of these same patients had FF<4% without FFA (Figure 2).
- The average increase in FF was 3.9-fold for samples with low FF (2.3-fold overall) and 99.8% had higher FF with FFA (Figure 3).
- Microdeletion identification improved dramatically, even for short anomalies: the expected sensitivity for the 22q11.2 microdeletion associated with DiGeorge Syndrome is 95.6% when aggregated across the FF levels achieved with FFA (Table 1).
- In >22,000 production samples tested with FFA, 99% of samples had FF >8.1% (Figure 4A) with an average FF >20%. Even in samples with high BMI and early gestational age (Figure 4B), >99% of samples still had FF>4%.

Figure 2. Fetal fraction amplification (FFA) technology increases fetal fraction (FF) across all BMI levels.

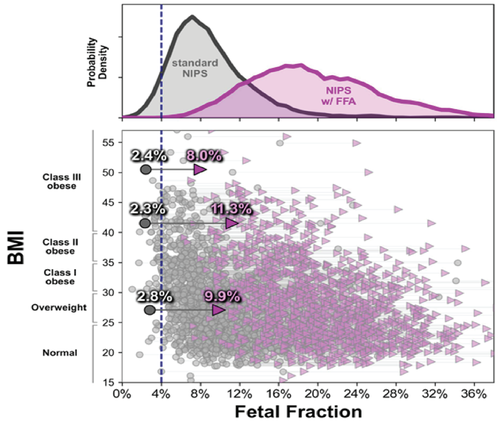


Table 1. Estimated analytical performance.

	Analytical Sensitivity	Analytical Sensitivity
Common aneuploidies (aggregate)	99.988% ± 0.004%	99.968% ± 0.005%
T21	99.990% ± 0.005%	99.996% ± 0.001%
T18	99.990% ± 0.002%	99.996% ± 0.001%
T13	99.978% ± 0.005%	99.976% ± 0.005%
RAAs (aggregate)	99.695% ± 0.305%	99.981% ± 0.010%
Microdeletions (aggregate)	97.172% ± 0.054%	99.767% ± 0.012%
DiGeorge Syndrome (22q11.2)	95.633% ± 0.071%	99.949% ± 0.005%

Figure 3. FFA increases FF for 99.8% of samples tested and most appreciably for low-FF samples.

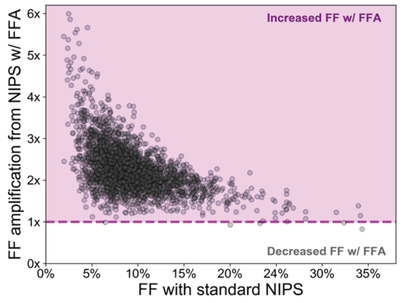
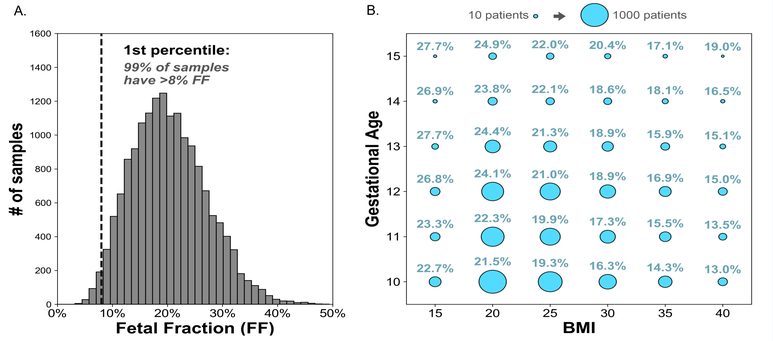


Figure 4. FFA performance tested in >22,000 samples.



CONCLUSION

- FFA transforms low-FF samples into high-FF samples. By combining FFA with WGS-based NIPS, a single round of NIPS can provide nearly all women with confident results about the broad range of potential fetal chromosomal abnormalities across the genome.

For additional information see our original research article: Welker, N.C., Lee, A.K., Kjolby, R.A.S. *et al*. High-throughput fetal fraction amplification increases analytical performance of noninvasive prenatal screening. *Genet Med* (2020).