WGS-based NIPS Without a Fetal Fraction Threshold: What are the Clinical Outcomes of No-Calls?

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BACKGROUND

- Noninvasive Prenatal Screening (NIPS) for aneuploidies via cell-free DNA analysis (cfDNA) has been rapidly incorporated into prenatal care since 2011. NIPS "no-calls," i.e., cases in which a result cannot be generated, can occur for a number of reasons, including a low number of mapped reads or DNA quality that does not pass quality control (QC) requirements.
- Laboratories also commonly issue no-calls when the fetal fraction (FF) of a sample falls below an imposed threshold. The Myriad Prequel Prenatal Screen utilizes a customized whole-genome sequencing (WGS) approach to NIPS and does not impose an FF threshold, yielding many fewer no-calls than methodologies that require a threshold.
- Here we describe the outcomes associated with the no-calls issued by our

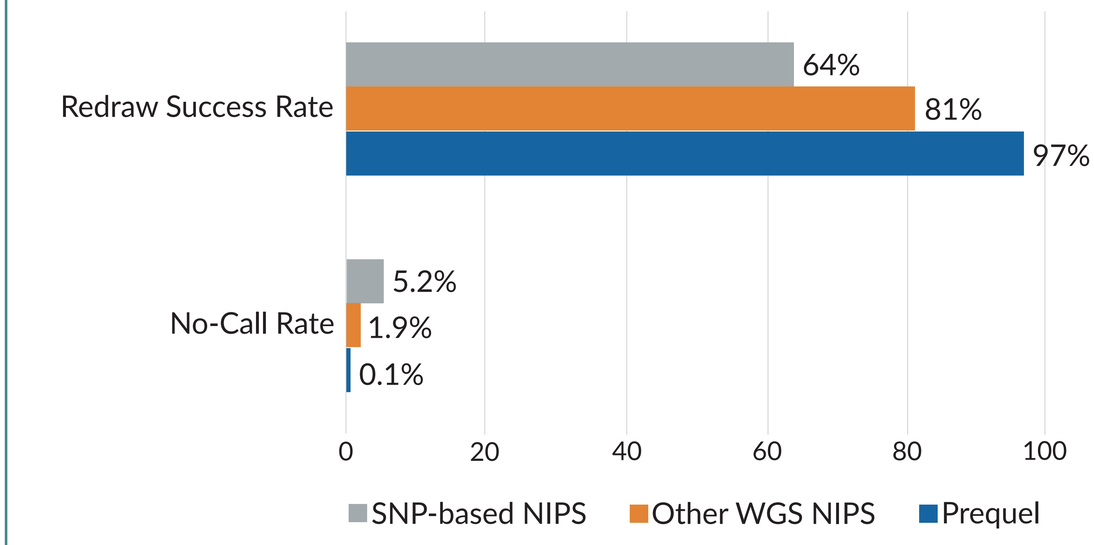
METHODS

- We retrospectively analyzed results from 58,105 patients who underwent NIPS over an 8-month period to assess clinical performance in singleton pregnancies.
- In the total cohort of 58,105 patients, we actively sought outcomes for all positive results and 18% of randomly selected negative results.
- We also actively sought outcome information for all patients who received a no-call in this cohort.
- Outcomes and concordance were determined by diagnostic methods (chromosome analysis and/or physical exam of the neonate). We incorporated voluntarily reported diagnostic outcomes as well as those outcomes that were actively sought.
- Concordance was determined by two board-certified genetic counselors.

RESULTS

- 99.9% of samples received a result with a single round of testing on Prequel. Only 0.1% of patients (n=57) received a no-call due to technical reasons, including low cfDNA yield, DNA quality that did not pass QC requirements, and hemolyzed samples.
- Thirty-nine of these patients (68%) pursued a redraw, and 18 (32%) did not.
- Thirty-seven patients (65%) received test results after a single redraw, while 2 (3.5%) experienced a repeat no-call. Of those with a repeat no-call, 1 patient pursued a second redraw and received negative screen results, and the other did not pursue a second redraw. No patient pursued more than two redraw attempts.
- Of patients receiving results after redraw, 36 of 38 (95%) screened negative, and no false negatives were reported.
- In the larger cohort of >58k women, we found that all false negatives were voluntarily reported by the provider, with no additional cases of false negatives identified via our active outcomes collection process for these results (3,258). There were specifically no false negatives reported for any of the successful redraw samples.
- Two screen-positive redraw results were confirmed to be false positives.
- No known aneuploidies were reported in those receiving no-calls in this cohort.
- Our data indicates that the number of patients choosing redraw after Prequel no-call is consistent with other literature; however, redraw success rate was higher for Prequel than has been reported by other laboratories (Figure 1).[1,2,3]
- While other studies indicate that no-call results are enriched for chromosome anomalies, no such anomalies were reported in this cohort.[3,4] While all providers experiencing a no-call on Prequel were strongly encouraged to report abnormalities in these patients, a limitation of this study is the incomplete follow-up for those patients that did not choose to pursue a redraw.

Figure 1. Comparison of Test Failure Metrics



NIPS, non-invasive prenatal screening; SNP, single nucleotide polymorphism; WGS, whole-genome sequencing.

CONCLUSIONS

- Fewer than 1 in 1000 patients received a no-call with the Prequel NIPS.
- Most patients who received a no-call chose to pursue a redraw, of which 97% received a result; however, 32% did not pursue a redraw.
- While these data compare favorably to other published reports of no-calls, the drawbacks of no-calls such as delayed time to results, potential for increased patient anxiety and potential to limit reproductive options underlines the importance of a low no-call rate.
- More research is needed to quantify the rate of aneuploidy in no-calls for laboratories that do not employ a fetal fraction threshold, in general, and for Prequel, specifically.
- These data are useful for counseling patients who experience no-call results and allows for counseling tailored to the specific testing laboratory. Future data may also allow for

References: **1.** Dar, P. et al. *Am. J. Obstet. Gynecol.* 211, 527.e1–527.e17 (2014). **2.** McCullough, R. M. et al. *PLoS One* 9, e109173 (2014). **3.** Ryan, A. et al. *Fetal Diagn. Ther.* 40, 219–223 (2016). **4.** Norton, M. E. et al. *N. Engl. J. Med.* 372, 1589–1597 (2015).

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