Expanding Noninvasive Prenatal Testing (NIPT) to Average Risk: MaterniT® 21 PLUS Performance in the Average Risk vs. High Risk Population

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INTRODUCTION

The use of noninvasive prenatal testing (NIPT) as a screening tool for fetal aneuploidy has been well established in high risk pregnancies. More recently, NIPT has been expanded to the average risk obstetric population, which is reflected in recent ACMG guidelines[1]. Here we compare the laboratory and clinical performance of >16,000 average risk MaterniT® 21 PLUS samples to the known MaterniT® 21 PLUS high risk experience.[2]

METHODS

Maternal blood samples submitted to Sequenom Laboratories for MaterniT® 21 PLUS testing were subjected to DNA extraction, library preparation, and whole genome massively parallel sequencing as described by Jensen et al.[3] Samples that did not meet the AGOC CO #640 criteria were considered average risk.[4]

RESULTS

Table 1. Demographics

	Average Risk	High Risk
Number of Samples	16,585	>400,000*
Average Maternal Age (years)	30.3	35.1
Average Gestational Age	12 weeks, 5 days	14 weeks, 5 days
Median Fetal Fraction	9.72%	10.3%
Non Reportable Rate (Technical)	0.35%	0.60%
Non Reportable Rate (QNS)**	0.54%	0.75%

*410,459 of 418,671 total samples included T18 & T13 analysis starting in February 2014.
**Quantity Not Sufficient (low fetal fraction)

Table 2. Positivity Rate

Condition	Average Risk	High Risk
Trisomy 21	0.31%	1.4%
Trisomy 18	0.08%	0.42%
Trisomy 13	0.10%	0.19%
Cumulative Positivity Rate of Common Aneuploidies	0.49%	2.01%

Image 1. Maternal Age Distribution – Average Risk

This image represents the number of completed MaterniT® 21 PLUS assays based on maternal age in the average risk cohort.

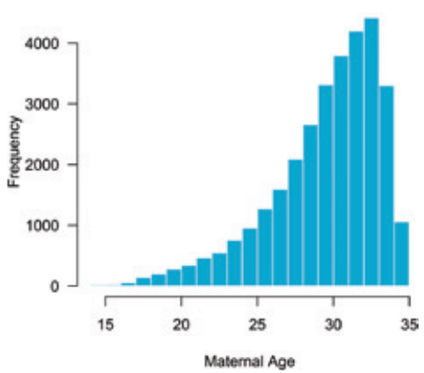

Table 3. Average Risk Performance based on *Ad Hoc* Feedback

Chromosome	MaterniT® 21 PLUS samples reported as negative	MaterniT® 21 PLUS samples reported as positive	False negatives communicated to Sequenom Laboratories	False positives communicated to Sequenom Laboratories
21	16,387	51	0	0
18	16,425	13	0	0
13	16,422	16	0	1

Chromosome	Relative Sensitivity	Relative Specificity	*Analytical PPV
21	>99.9%	>99.9%	>99.9%
18	>99.9%	>99.9%	>99.9%
13	>99.9%	99.9%	93.7%

*In addition to sensitivity and specificity, clinical PPV is dependent on condition prevalence and *a priori* risk.

CONCLUSION

Over 16,000 average risk MaterniT® 21 PLUS tests have been ordered. While the positivity rate in the average risk group is lower than in high risk (0.49% vs. 2.01%), it is still above what would be expected given aneuploidy incidence in women <35 years old. This is most likely due to the skewed maternal age distribution observed in this average risk cohort (see **image 1**). Overall, performance in the average risk cohort much resembles that seen in high risk pregnancies. It is important to differentiate analytical positive predictive value (PPV) based on *ad hoc* outcomes versus clinical PPV, when counseling average risk patients with an abnormal NIPT result. When compared to current serum biochemical screening protocols, expanding NIPT into the average risk population would allow for markedly improved screening performance of common aneuploidies.

REFERENCES

1. Gregg AR, Skotko BG, Benkendorf JL, et al., Noninvasive prenatal screening for fetal aneuploidy, 2016 update: a position statement of the American College of Medical Genetics and Genomics. *Genet Med* 2016; 18:1056-1065.
2. McCullough R, High volume clinical laboratory noninvasive prenatal testing: results from >400,000 patients. Poster presented at: International Society of Prenatal Diagnosis; 2015 Jul 12-15; Washington D.C.
3. Jensen TJ, Zwiefelhofer T, Tim RC, et al., High-throughput massively parallel sequencing for fetal aneuploidy detection from maternal plasma. *PLoS One* 2013; 8(3):e57381. doi:10.1371/journal.pone.0057381. Epub 2013 Mar 6.
4. ACOG practice committee opinion number 640: Cell-free DNA screening for fetal aneuploidy. *Obstet Gynecol* 2015; 126:e31-37.