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Over a half million noninvasive prenatal tests: a clinical laboratory experience

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I. Introduction

The adoption of noninvasive prenatal testing (NIPT) for screening has been rapid, resulting in a paradigm shift in patient management. Here, we describe the laboratory experience and clinical performance of the test, including for select subchromosomal deletions. Here, we describe the laboratory experience and clinical performance of the MaterniT® 21 PLUS test, including for select subchromosomal deletions.

II. Methods

Over 600,000 maternal blood samples submitted to Sequenom Laboratories for MaterniT® 21 PLUS testing were subjected to DNA extraction, library preparation, and genome-wide massively parallel sequencing as described by Jensen et al.[1] Testing includes aneuploidies of chromosomes 13, 18, 21, X, Y and selected subchromosomal events. Statistical analysis of this large patient cohort was undertaken.

III. Results

The predominant indication for testing in this large cohort was advanced maternal age (56.7%), followed by abnormal ultrasound findings (9.5%) and positive serum screening (6.1%). Compared with 2015, when only 3.7% of samples were from average risk pregnancies, in 2016 20.2% of samples were from average risk pregnancies. Overall, the positivity rate in singletons for trisomy 21 was 1.23%, 0.39% for trisomy 18, and 0.19% for trisomy 13. More than 26,000 cases (~4.05%) were reportedly multifetal.

The average turnaround time was 5.5 calendar days, and the test had a total non-reportable rate, including DNA quantity not sufficient (QNS) of 1.48%. Estimated performance based on ad hoc clinical outcome show that sensitivity and specificity meet or exceed the original clinical validation studies. Additionally, positive predictive values (PPV) of subchromosomal findings for all events range from 44.4%-100%.

Table 1. Singleton performance based on ad hoc feedback

Summary of clinical outcome received from clinician, and estimated analytical performance based on this feedback.

Chromosome	Number of MaterniT 21 PLUS cases reported as negative	Number of MaterniT 21 PLUS cases reported as positive	Number of false negatives communicated to Sequenom Laboratories	Number of false positives communicated to Sequenom Laboratories
21	606,614	7,485	42	60
18*	611,703	2,396	34	60
13*	612,955	1,144	7	79

Chromosome	Relative Observed Sensitivity	Relative Observed Specificity	Relative Observed Positive Predictive Value
21	99.4%	>99.9%	99.2%
18	98.6%	>99.9%	97.5%
13	99.3%	>99.9%	93.1%

*T13 and T18 testing started in Feb. 2012

Table 2. Multifetal performance based on ad hoc feedback

Summary of clinical outcome received from clinicians, and estimated analytical performance based on this feedback.

Chromosome	Number of MaterniT 21 PLUS cases reported as negative	Number of MaterniT 21 PLUS cases reported as positive	Number of false negatives communicated to Sequenom Laboratories	Number of false positives communicated to Sequenom Laboratories
21	24,148	372	7	3
18	24,395	125	3	1
13	24,464	56	0	7

Chromosome	Relative Observed Sensitivity	Relative Observed Specificity	Relative Observed Positive Predictive Value
21	98.1%	>99.9%	99.2%
18	97.6%	>99.9%	99.2%
13	>99.9%	>99.9%	87.5%

Table 3. MaterniT® 21 PLUS test: Laboratory experience

Demographics	
Number of tests to date	>600,000
Average gestational age	14 weeks, 2 days
Multifetal pregnancy	4.05%
Average fetal fraction	10.2%
Not reportable (technical)	0.53%
Not reportable (QNS)	0.95%

Table 4. MaterniT® 21 PLUS Test: Microdeletions included with the Enhanced Sequencing Series (ESS)

ESS	Total	Confirmed True Positive*	Suspected**	No Info	Confirmed False Positive	PPV***
22q del	82	46	23	13	0	84.15-100%
5p del	23	11	3	5	4	60.87-82.61%
15q del	26	17	0	9	0	65.38-100%
1p del	11	6	2	1	2	72.73-81.82%
4p del	15	8	4	3	0	80.00-100%
11q del	9	4	0	4	1	44.44-88.88%
8q del	7	3	1	1	2	57.14-71.43%
Total	173	95	33	36	9	

*True positives were confirmed by diagnostic testing (i.e. CVS, Amnio, Postnatal, Karyotype, Microarray, FISH, etc.).

**Suspected includes cases with findings that align with the predicted result, but without diagnostic confirmation (i.e. ultrasoundings, physical exam, etc.).

***PPV estimate range: Lower bound assumes "No information" patients are false, upper bound assumes "No information" patients are true. Specifically: PPV upper bound=(True Positive)+(Suspected)+(No Information)/Total and PPV lower bound=(True Positive)+(Suspected)/Total

Figure 1. Positivity rates: Singletons

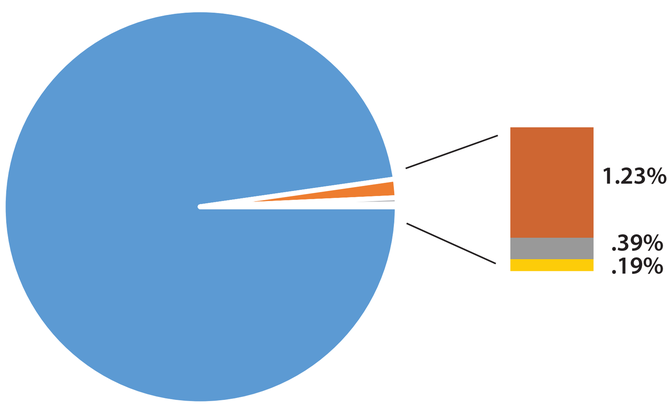
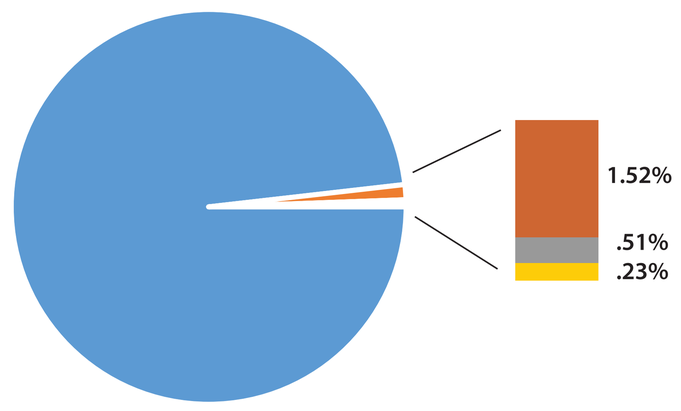


Figure 2. Positivity rates: Multifetal gestations



IV. Conclusions

MaterniT®21 PLUS offers pregnant patients accurate and reliable screening for fetal aneuploidy. This laboratory developed test has demonstrated positivity rates for trisomy 21, 18 and 13 that mirror those found in large studies on high-risk populations that underwent invasive testing. The addition of subchromosomal events was shown to perform well, with good clinical correlation. Operational performance demonstrated a robust and efficient process that has met or exceeded performance from the original clinical validation studies.

V. References

1. 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.

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