

# NONINVASIVE PRENATAL TESTING IN THE GENERAL OBSTETRIC POPULATION: CLINICAL PERFORMANCE AND COUNSELING CONSIDERATIONS IN OVER 85,000 CASES

Taneja P, Snyder HL, de Feo E, et al. *Prenat Diagn.* 2015;doi:10.1002/pd.4766.

## Study Objective

To provide clinically relevant information for appropriate patient counseling and update performance statistics as compared with the initial clinical experience publication.

## Study Design

Retrospective study of 86,658 consecutive clinical samples received for NIPT testing, subsequent to those previously published.

## Results

- Whole cohort (n=86,658):
  - Aneuploidy Detected in 2.2% of samples as compared with 4.0% in Futch et al.<sup>†</sup> (p-value <0.0001)
  - Aneuploidy Suspected in 0.3% of samples as compared with 2.8% in Futch et al.<sup>†</sup> (p-value <0.0001)
- Putative false positive frequency in Aneuploidy Detected cases (n=120): 0.1%; Putative false positive frequency in Aneuploidy Detected/Aneuploidy suspected cases (n=261): 0.3%
- Putative False negative frequency (n=15): 0.02%.
- Testing now predominantly offered in first trimester, compared with second/third trimesters in Futch et al.<sup>†</sup> (p-value <0.0001)
- Technical test cancellation: 0.1% as compared with 0.7% in Futch et al.<sup>†</sup> (p-value <0.0001)
- Average turnaround time: 3.3 business days as compared with 5.1 business days in Futch et al.<sup>†</sup> (p-value <0.0001).

<sup>†</sup>Futch et al. *Prenat Diagn.* 2013;33(6):569-574.

“ Increasing utilization of NIPT has highlighted the importance of evaluating and communicating clinical performance and test limitations. ”

Observed clinical performance in the CLIA laboratory and validation performance metrics (MELISSA study)<sup>§</sup>

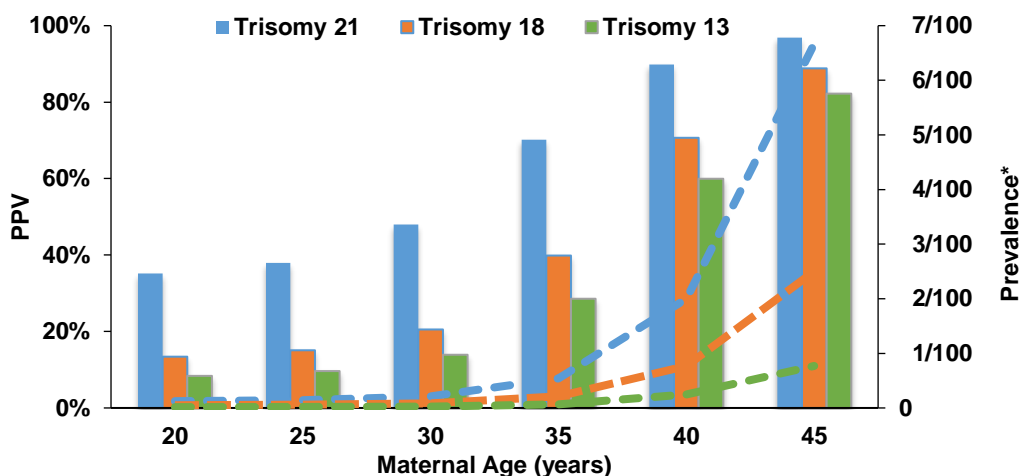
Condition	CLIA Laboratory		Validation Study <sup>§</sup>	
	Observed Sensitivity (Range)	Observed Sensitivity (Range)	Sensitivity	Specificity
Trisomy 21	99.49% (98.66–99.53%)	99.49% (98.66–99.53%)	100%	99.76%
Trisomy 18	97.23% (94.20–98.15%)	97.23% (94.20–98.15%)	97.37%	99.57%
Trisomy 13	97.98% (95.56–98.87%)	97.98% (95.56–98.87%)	87.50%	100%

<sup>§</sup>Illumina. Analytical Validation of the veriFi® prenatal test: Enhanced Test Performance for Detecting Trisomies 21, 18, and 13 and the Option for Classification of Sex Chromosome Status. *Illumina White Paper.* 2012

Observed positive predictive values by condition, based on cytogenetically confirmed cases

Variable	Trisomy 21	Trisomy 18	Trisomy 13	Overall
AD/AS Samples	85.5% (443/518)	51.2% (130/254)	41.0% (43/105)	70.2% (616/877)
AD Samples	92.8% (439/473)	74.3% (127/171)	50.0% (42/84)	83.5% (608/728)

**Positive predictive value (PPV) counseling tool.** Positive predictive values (bars) based on estimated prevalences at 10 weeks of gestation\* (dashed lines) by maternal age and observed sensitivities and specificities for NIPT. PPV, positive predictive value.



\* Estimated prevalences at 10 weeks of gestation were derived from Gardner, Sutherland, and Shaffer. *Chromosome abnormalities and genetic counseling*: Oxford University Press, 2012.

### Key Summary Points

- Demographic changes observed since the Futch *et al*<sup>1</sup> study:
  - More patients undergoing testing in the first trimester (p<0.0001)
  - Lower test positive rate for chromosomes 21 and 18 (p<0.0001)
  - Changing indications, with more patients lacking clearly defined high-risk indications
- Test modifications implemented in the CLIA laboratory since the Futch *et al*<sup>1</sup> study have facilitated:
  - A refinement in borderline result classification, reducing AS cases to 0.3% from 2.6%<sup>1</sup> (p<0.0001)
  - Faster turn-around times, now 3.3 business days
  - Lower technical cancellation rates, 0.1% compared with 0.7%<sup>1</sup> previously (p<0.0001)
  - Putative false positive frequency in AD cases is 0.1%, and in AD/AS cases is 0.3%
  - Putative false negative frequency is 0.02%
- We developed a PPV chart for clinicians to use as a guide to a patient's NIPT PPV based on maternal age alone

<sup>1</sup>Futch *et al. Prenat Diagn.* 2013;33(6):569-574.