Early Performance Analysis for 22q11.2 Deletion Syndrome Detection Using a Whole-Genome Sequencing-Based Noninvasive Prenatal Screen

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Introduction

- Prenatal detection of microdeletion syndromes enables pregnancy management and early intervention in affected newborns.
- 22q11.2 deletion syndrome—also known as DiGeorge Syndrome—is the most frequent chromosomal microdeletion disorder, estimated to occur in approximately 1 in 2,500-4,000 births.
- Unlike multiple marker screening, noninvasive prenatal screening (NIPS) technology can detect fetuses affected by microdeletion syndromes.
- By increasing fetal fraction (FF) by more than two-fold on average, fetal fraction amplification (FFA) may further enhance NIPS detection of microdeletions.
- Limited studies on the clinical performance of NIPS for 22q11.2 deletion detection report positive predictive values (PPV) between 20%-50%. However, no reports have included clinical performance using FFA.
- Here, we sought to describe the performance of 22q11.2 deletion screening using a whole-genome sequencing (WGS)-based NIPS platform that leverages FFA.

Methods

- We retrospectively analyzed data from patients who consented to being involved in research and who underwent WGS-based NIPS (Prequel™, Myriad Genetics, Inc) between June 2019 and August 2022. Most samples were processed after the implementation of FFA, which launched on July 27, 2020, as a standard part of the NIPS assay.
- For cases in which a 22q11.2 deletion was detected, pregnancy outcome data were requested from ordering providers via a routine HIPAA-compliant process for continuous quality improvement.
- Concordance was evaluated between the NIPS assay result and molecular diagnostic testing results for 22q11.2 deletion, including by karyotyping, fluorescence in situ hybridization (FISH) studies, or chromosomal microarray obtained by chorionic villus sampling, amniocentesis, products-of conception analysis or postnatal sampling.
- All samples with diagnostic confirmation were used to calculate the PPV, defined as true positives/(true positives + false positives). The confidence interval (CI) was estimated using the Exact Binomial Test.

Results

- 13 cases that screened positive for 22q11.2 deletion had completed molecular diagnostic testing.
- FFA was a standard part of the NIPS assay at the time that eleven of these thirteen cases were processed.
- Among these 13 screen-positive cases, twelve were confirmed as true positives, and one false positive.
- The resulting PPV was 92.3% (95 percent CI PPV=64.0% to 99.8%). Among true positives, gestational age at time of NIPS testing ranged from 10 weeks 0 days to 35 weeks 0 days.
- The mean fetal fraction of true positives was 21.15% (range 5.9% to 36.4%), near the mean FF level of all samples tested with FFA more generally, suggesting that the cohort of 22q11.2 positives is not biased toward unusually high-FF samples.
- For the false positive, the gestational age at time of NIPS testing was 10 weeks 5 days, and the fetal fraction was 10.4% assessed prior to FFA enhancements on the assay for the single false positive.

Figure 1. 22q Deletion Screen Positive Cases with Pregnancy Outcome Data

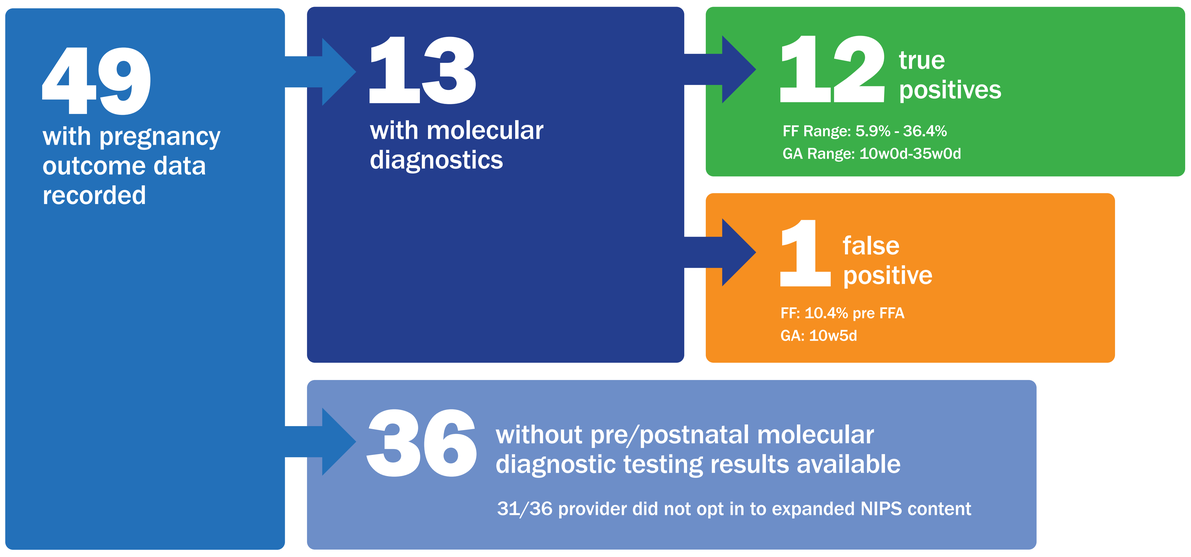

Table 1. Outcomes of Screen Positives with Molecular Confirmation

Case #	Result	GA at Draw	Fetal Fraction	Indication for Screening	Pregnancy Outcome	Clinical Notes
1	**True Positive**	28w3d	31.7% (FFA)	Abnormal U/S	Term delivery	TOF identified by U/S
2*	**True Positive**	22w2d	26.2% (FFA)	High Risk Pregnancy	Term delivery	VSD and other heart defects on U/S
3*	**True Positive**	12w0d	27.2% (FFA)	AMA, Abnormal maternal serum screen	TAB	Pyelectasis on U/S
4	**True Positive**	26w3d	30.0% (FFA)	Abnormal U/S	Pre-term delivery	TOF and other heart defects on U/S
5*	**True Positive**	19w3d	11.8% (FFA)	AMA	Term delivery; preeclampsia	Craniosynostosis noted on U/S
6*	**True Positive**	10w0d	23.3% (FFA)	AMA, High Risk pregnancy	TAB	Multiple heart defects on U/S
7	**True Positive**	35w0d	20.7%	Abnormal U/S	Pre-term delivery	Complex fetal heart defects, IUGR and other abnormalities on U/S. Infant died at 5mo.
8	**True Positive**	23w3d	14.2% (FFA)	CHD detected on U/S	Term delivery	TOF, IUGR on U/S
9	**True Positive**	18w5d	27.3% (FFA)	Hx of previous infant with congenital anomalies	Term delivery	ASD and other heart defects noted on postnatal echo
10	**True Positive**	11w6d	5.9% (FFA)	Screening for genetic and chromosomal anomalies	Infant death	TOF noted. Infant died at 29h.
11*	**True Positive**	24w6d	14.2% (FFA)	Abnormal U/S, bilateral UTD, VSD	Term delivery	VSD and other heart defects on U/S
12*	**True Positive**	34w4d	36.4% (FFA)	Abnormal U/S, chromosome abnormality suspected in fetus	Pre-term delivery	Multiple CHD, Polyhydramnios, IUGR, multiple congenital anomalies noted on U/S
13	**False Positive**	10w5d	10.4%	Supervision of normal first pregnancy	Fetal demise: 18w5d	Malformed male fetus, immature placenta with ONTD

GA, Gestational Age; Hx, History; FFA, Fetal Fraction Amplification; U/S, Ultrasound; TOF, Tetralogy of Fallot; IUGR, Intrauterine Growth Restriction; AMA, Advanced Maternal Age; FISH, Florescent in Situ Hybridization; CMA, Chromosomal Microarray; ASD, Atrial Septal Defect; VSD, Ventricular Septal Defect; UTD, Urinary Tract Dilation; TAB, Therapeutic abortion; ONTD, Open Neural Tube Defect; CHD, Congenital Heart Defect; NA, Not available

*Case where provider did not opt in to reporting on expanded NIPT content

Conclusions

- Early analysis of outcomes for 22q11.2 deletion performance using a WGS-based NIPS with FFA suggests a PPV substantially higher than previous studies have reported.
- This improvement in PPV likely arises from higher FF levels from FFA, which facilitates detection of small deletions in cell-free fetal DNA.
- These initial results suggest that 22q11.2 screening performance with FFA in WGS-based NIPS is consistent with that of other reportable anomalies recommended by guidelines (e.g., for trisomy 13), warranting possible inclusion of 22q11.2 deletion screening in routine NIPS.
- Outcomes collection for additional cases is ongoing, which is expected to improve the certainty of these results.