Key Summary of Published Article

Improving the Positive Predictive Value of Noninvasive Prenatal Screening (NIPS)

Background

- Noninvasive prenatal screening provides higher detection rates for fetal aneuploidies (the presence of an abnormal number of chromosomes) than do traditional screening methods, such as maternal serum screening.[1]
- For pregnant women at high risk for fetal aneuploidy, the literature reports that using cell-free DNA (cfDNA)-based prenatal screening has the following positive predictive values (PPVs): >90% for trisomy 21, 40% to 68% for trisomy 18, and 45% to 57% for trisomy 13.[2-4]
- **Objective:** The investigators evaluated the performance characteristics of a technologically enhanced cfDNA-based prenatal screening assay (QNatal® Advanced) that incorporates follow-up karyogram analysis in cases with initially abnormal data (elevated "z scores"). They also evaluated initial clinical experience with the assay.

Methods

- An automated cfDNA-based prenatal screening assay for trisomies 21, 18, and 13 was developed. The assay incorporated GC correction to enhance discrimination and Illumina version 4 chemistry.
- The assay was verified (2,085 samples from pregnancies with known aneuploidy status) and validated (667 samples; 552 from women with known singleton and 115 from women with known twin pregnancies).
- These samples included cases of trisomies 21, 18, and 13 and a sex chromosome aneuploidy.
- Results from the first 10,000 clinical samples were analyzed: 180 abnormal results were identified, including trisomies 21, 18, and 13, and Turner syndrome (loss of an X chromosome).

Results

- In verification and validation sets, the assay provided 100% discrimination between affected and unaffected pregnancies for trisomies 21, 18, and 13 (analytical sensitivity and specificity >99.9% for each aneuploidy).
- The assay demonstrated a low "no-call" rate in clinical samples: results could not be reported in 0.88% of samples, including 0.59% because of low fetal fraction and 0.29% because of technical issues.
- In several clinical samples with elevated z scores, follow-up karyogram analysis revealed that the elevations were due to presumably benign maternal duplications rather than true fetal abnormalities. These cases were reported as negative for fetal trisomy.
- The high analytical specificity of the test, and the reduction in false-positive results due to maternal duplications and other factors (eg, uterine fibroids and other maternal copy number variants), yielded high PPVs in cases with clinical follow-up: 100% (41/41 cases) for trisomy 21; 96% (23/24 cases) for trisomy 18; and 69% (9/13 cases) for trisomy 13.

Conclusions

- This technologically advanced cfDNA-based prenatal screening assay demonstrates excellent discrimination between affected and unaffected pregnancies for trisomies 21, 18, and 13.
- Identifying and excluding cases of maternal duplications (and other confounding factors), rather than reporting them as fetal aneuploidies, resulted in high PPVs in clinical practice.

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