Genome-wide cfDNA: Emerging data trends in 28K clinical samples

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I. Background

Recent adoption of genome-wide cell-free DNA prenatal screening provides unique insight into placental findings not previously recognized. Here we present data from our first 28,760 clinical samples for expanded cfDNA screening, including genome-wide aneuploidy identification and subchromosomal copy number variants (CNVs) ≥ 7Mb.

II. Methods

Maternal blood samples submitted to Sequenom® Laboratories for MaterniT® GENOME testing were subjected to DNA extraction, library preparation, and genome-wide massively parallel sequencing as described by Jensen et al. Sequencing data were analyzed using a novel algorithm as described by Lefkowitz et al.

III. Results

The gestational age (GA) of samples submitted for genome-wide cfDNA show a subtle shift towards later testing (compared to ‘traditional’ cfDNA samples), with a slight upturn at ~20 weeks, coinciding with typical timing for prenatal anatomy ultrasounds. Samples drawn ≥ 20 weeks are commonly referred with abnormal ultrasound findings (USFs), per 71% of the cohort’s test requisitions. Interestingly, ≥ 20 weeks GA samples yield disproportionately high CNV positive results (17% of cohort positives).

Overall, 51% of total positive results noted USFs per test requisitions, and we observed a 10% positivity rate among samples with abnormal ultrasound findings. Esoteric aneuploidies are seen across all risk categories, but show disproportionately higher rates of abnormal serum screening (16%) per test requisitions.

IV. Conclusion

In over 28,000 samples submitted for the MaterniT® GENOME test, the overall positivity rate remained relatively low at 4.8%. Of note, a quarter of these positives reported out abnormalities typically not included on traditional cfDNA tests, consistent with expectations based on large-scale placenta cytotrophoblast study data. Among samples from patients with an abnormal ultrasound finding, positivity rates more than doubled. While copy number variants tend to coincide with complex prenatal cases (e.g. multiple high risk indications, USFs, history of translocation), esoteric aneuploidy was less risk specific, though showed a tendency toward abnormal serum values as a likely byproduct of altered placental functioning.

V. References