Recent adoption of genome-wide cell-free DNA (cfDNA) prenatal screening provides unique insight into placental findings not previously recognized. Here we present data from our first 200,000+ samples for expanded DNA sequencing, including genome-wide identification of amplifications and subchromosomal copy number variants (CNVs) >7 Mb, with specific attention to complex chromosomal rearrangements.

I. Background

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

II. Methods

Complex CNV samples show an enrichment of:
- 45% as a sole indication (vs. 20% in the general MaterniT® GENOME screening population)
- 67% overall, adding in the subset of multiple indications that include ultrasound findings

High risk personal and/or family histories

- 20% as a sole indication (vs. 12% in the general MaterniT® GENOME screening population)

Multiple high risk indications

- 100% as a sole indication

III. Results

Identification of complex chromosomal rearrangements via cfDNA prenatal screening marks a new and valued high risk patients often use such information for diagnostic testing plans, deciding to wait for pending and likely concordant, 3% (2/64) unknown/lost to follow-up, and 5% (3/64) discordant.

Table 1: Substantive fetal confirmation was reported in the majority (56%, 36/64), with 23% (15/64) pending and likely concordant, 3% (2/64) unknown/lost to follow-up, and 5% (3/64) discordant.

Table 2: Complex CNV report interpretations

IV. Conclusions

Identification of both balanced translocation and inversion carriers earlier in their reproductive lives can assist with improved pregnancy surveillance, maximizing patient options and overall medical management.

Key points:
- Patients at risk for fetal unbalanced chromosomal rearrangements during pregnancy (e.g. translocations, insertions, inversions) can benefit from early cfDNA genome-wide screening.
- Novelly, a quarter of the patients yielding positive complex chromosomal rearrangements had no known family or personal history, nor overt ultrasound findings at the time of screening.
- New discovery of families at risk of carrying a recombinant chromosomal event via cfDNA screening can clarify future reproductive risks as well as maximize surveillance options.

V. References