I. Background

Genome-wide cell-free DNA prenatal screening continues to increase our insight into karyotypic findings not previously recognized. Here we present data from the first two years of clinical testing for expanded cfDNA screening, including genome-wide aneuploidy detection and subchromosomal copy number variants (CNVs) larger ≥1Mb.

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 al1. Sequencing data were analyzed using a novel algorithm as described by Lehrke et al2. Statistical analysis of the average risk screening cohort employed a two-sample, two-sided proportional z-test to compare submission rates from May – December 2016 to January – August 2017. p-value = 0.001.

III. Results

Average fetal fraction 9.8%
Average maternal age 34.3 years
Overall positivity rate 4.7%
Average TAT 4.5 business days / 6.7 calendar days
Average gestational age 15 weeks 1 day

MaterniT® GENOME
Overview of positive cases (Aug 9, 2015 – Nov 2, 2017 (n=1,957 positives))

Abnormal findings identified across the entire genome
Every chromosome is represented among the positive cases (n=1,957)

Size distribution of subchromosomal CNVs
Excluding whole chromosome aneuploidies (n=382 samples)

Testing Indications per test requisition (n=41,634)

Similiar to prior reported trends, 49% of all positives showed ultrasound findings (USF) (either in isolation or combined with another high risk indication), yielding an increased 11% positivity rate among this cohort. Likewise, 21.2% of all positives report multiple high risk indications, yielding an increased 13% positivity rate among this cohort. Late gestational age (≥40 weeks) testers continued to account for a disproportionate fraction of positive results (24%), with the vast majority (81%) reporting USFs. CNV size range holds steady at ≤100MB to >100MB, with the majority 10-20MB. In addition, 6% of all positives came from the ‘average risk’ cohort, yielding a 2.9% positivity rate.

IV. Conclusions

Previously reported trends in genome-wide cfDNA prenatal screening results remain consistent, including a higher positivity rate among pregnancies with ultrasound findings and multiple high risk indications, as well as a higher proportion of late gestational age screening compared to targeted screening. The overall positivity rate as well as positive result distribution among the various result categories remains constant. However, the growing emergence of an ‘average risk’ screening cohort is noted, with the statistically significant increase (p-value = <0.001) in size since our last report ~6 months ago. This may indicate a growing acceptance and appreciation for genome-wide cfDNA screening among risk patients and providers alike. This cohort exhibits many expected attributes, such as a younger average maternal age, lower average gestational age, and lower positivity rate. While a lower proportion of age related trisomies is intuitive (including common and esoteric trisomies), this in turn leads to a higher proportion of sex chromosome aneuploidies and microdeletions reported among the positive results in this cohort. Copy number variants were noted to be consistent in proportion with the larger screening population, as expected given the independence of maternal age and prevalence of CNVs.

Key points:
• While genome-wide cfDNA screening is most common among the ‘high risk’ pregnancy population, a growing ‘average risk’ cohort is quickly emerging.
• The majority of subchromosomal CNVs are sizeable events, averaging 10-20MBs.
• Subchromosomal CNVs are proportionally equally common among ‘high risk’ and ‘average risk’ positive results.

V. References