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Genome-wide cfDNA screening: Trends and lessons from >40,000 samples

Theresa Boomer, Samantha Caldwell, Eyad Almasri, Jenna Wardrop, Sidra Boshes, Michelle Hackbardt, Phillip Cacheris, Ron McCullough
Sequenom®, Inc., Laboratory Corporation of America® Holdings

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I. Background

Genome-wide cell-free DNA prenatal screening continues to increase our insight into placental 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 ≥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.[1] Sequencing data were analyzed using a novel algorithm as described by Lefkowitz et al.[2]

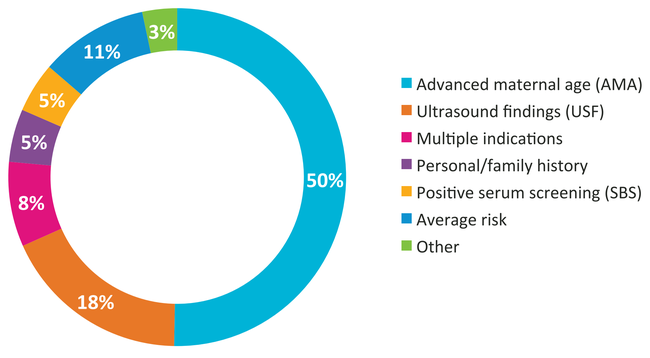
Statistical analysis of the average risk screening cohort employed a two-sample, two-sided proportional z-test to compare submission rates from May – December 2016 to January – August 2017: z= -18.62, p-hat$_1$=0.047, p-hat$_2$=0.106, p-hat overall=0.076, p value=<0.001.

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

Similar 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.[3] Likewise, 21.2% of all positives report multiple high risk indications, yielding an increased 13% positivity rate among this cohort. Late gestational age (GA) testers (>=20 weeks, 14% of samples submitted) continue to account for a disproportionate fraction of positive results (24%), with the vast majority (81%) reporting USFs. CNV size range holds steady at <10Mb 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.

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



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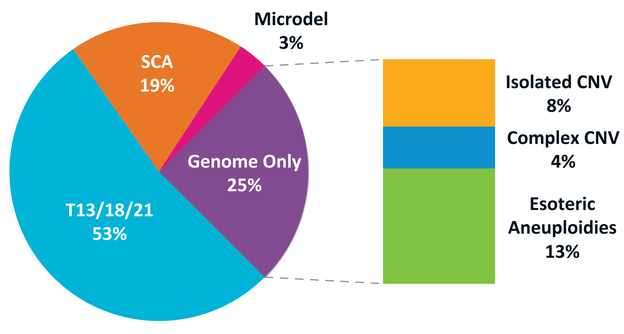
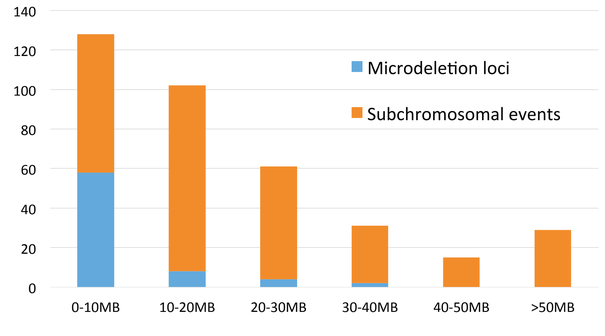
Overview of positive cases | Aug 31, 2015 – Nov 2, 2017 (n=1,957 positives)



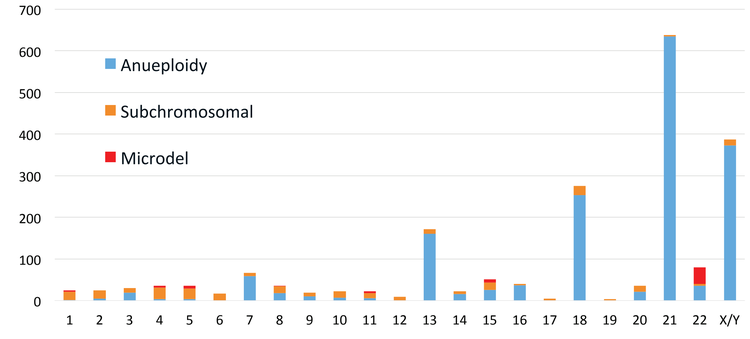
Size distribution of subchromosomal CNVs

Excluding whole chromosome aneuploidies (n=302 samples)



Abnormal findings identified across the entire genome

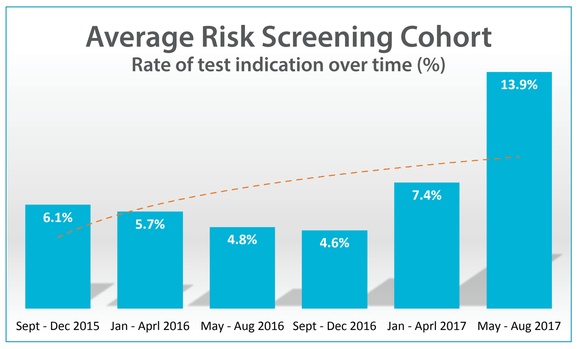
Every chromosome is represented among the positive cases (n=1,957)



Average Risk Screening Cohort	
Average fetal fraction	9.0%
Average maternal age	32.2 years
Overall positivity rate	2.9%
Average gestational age	14 weeks 3 days

Average Risk Screening Cohort

Rate of test indication over time (%)



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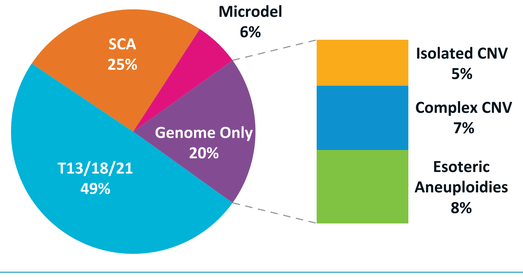
Average risk positive cases | Aug 31, 2015 – Nov 2, 2017 (n=123 positives)



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 a statistically significant increase (p-value <0.001) in size since our last report ~6 months ago.[3] This may indicate a growing acceptance and appreciation for genome-wide cfDNA screening among average 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 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.

V. References

1. Jensen TJ, Zwiefelhofer T, Tim RC, et al. High-throughput massively parallel sequencing for fetal aneuploidy detection from maternal plasma. *PLoS One*. 2013;8(3):e57381. doi: 10.1371/journal.pone.0057381. Epub 2013 Mar 6.
2. Lefkowitz RB, Tynan J, Liu T, et al. Clinical validation of a non-invasive prenatal test for genome-wide detection of fetal copy number variants. *Am J Obstet Gynecol*. doi: http://dx.doi.org/10.1016/j. ajog.2016.02.03.
3. Boomer T, Caldwell S, Almasri E, et al. Genome-wide cfDNA: Emerging data trends in 28K clinical samples. Poster presentation at the *NSGC annual meeting*, 2017 Sept 13-16; Columbus, OH.

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Poster presented at the *ACMG Annual Clinical Genetics Meeting*; 2018 April 10-14; Charlotte, NC.