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Diagnostic testing trends after genome-wide cell-free DNA prenatal screening results

Kimberly Fanelli, MS, CGC, Erica Soster, MS, CGC, Jill Rafalko, MS, CGC
Integrated Genetics, Laboratory Corporation of America®, Westborough, MA

I. Introduction

The American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal-Fetal Medicine (SMFM) outlined prenatal diagnostic testing guidelines for patients, and recommended microarray as a first-line test when fetal structural anomalies are identifed.[1] Historically, patients interested in more genetic information but reticent to undergo diagnostic testing were only able to choose from traditional cell-free DNA (cfDNA) testing, biochemical screening, or ultrasound evaluation during pregnancy. Genome-wide cfDNA prenatal screening has been clinically available since 2015, providing an option for patients who decline diagnostic testing. Genome-wide cfDNA offers additional information about fetal chromosomal abnormalities beyond common aneuploidies, sex chromosome aneuploidies, and select microdeletions. Previous studies have shown that 25% of positive results are unique to genome-wide cfDNA and could be missed by traditional methods of cfDNA testing.[2] Given the fact that genome-wide cfDNA could help to identify complex genetic issues (i.e. confined placental mosaicism, uniparental disomy, etc), diagnostic ordering trends were examined following this screening.

II. Methods

Maternal blood samples were submitted to Sequenom Laboratories® for genome-wide cfDNA screening. All samples were subjected to DNA extraction, library preparation, and genome-wide massively parallel sequencing.[3] Clinical outcomes were requested from ordering providers as part of routine follow-up of cases, or matched to corresponding diagnostic testing samples from the internal diagnostic testing laboratory. Out of a cohort of approximately 55,000 genome-wide cfDNA samples submitted, approximately 1,600 had diagnostic specimen and/or testing information that was reported or matched. Those specimens or diagnostic tests that could not be confirmed were categorized as unspecified/other and statistical analysis was performed.

III. Results

A list of genome-wide cfDNA samples associated with diagnostic testing and specimen information was compiled. Diagnostic specimen types included: chorionic villi, amniotic fluid, postnatal peripheral or cord blood, placenta, products of conception (POC), maternal/parental peripheral blood, and unspecified/other. Tests ordered included: fluorescence *in situ* hybridization (FISH), karyotype, microarray, uniparental disomy (UPD) studies, and unspecified/other.

- The majority of cfDNA samples were associated with one specimen type (93.4%) and one test type (87.5%). (**Figure 1, Figure 2**).
- Of the cfDNA samples with only one test type, karyotype (58.4%) was ordered more frequently than microarray (10.8%). (**Figure 2**)
- Amniotic fluid (60.7%) was the most common single specimen type sampled. (**Figure 3**)
- 21.3% of cfDNA cases had diagnostic testing on a single postnatal, POC, or placental specimen only. (**Figure 3**)
- Maternal/parental (64.3%) and placental (60.9%) studies often coincided with testing on an additional specimen type, while chorionic villi (89.2%), amniotic fluid (93.9%), POC (89.7%), and postnatal studies (84.4%) were often the only specimen type sampled. (**Figure 4a-4g**)

Figure 1. Genome-wide cfDNA samples with diagnostic specimen and test information (n=1,655)

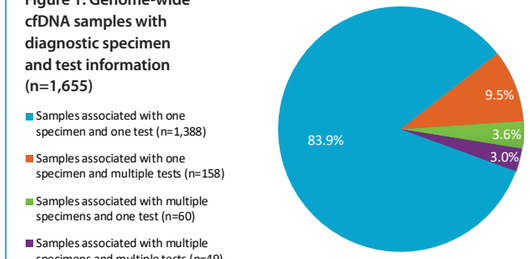


Figure 2. Genome-wide cfDNA samples with diagnostic testing (n=1,655)

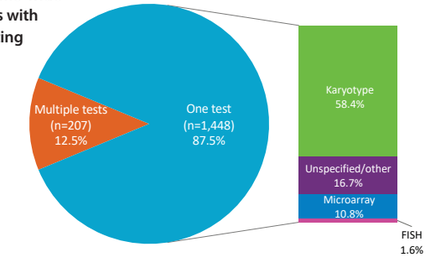


Figure 3. Genome-wide cDNA samples with a single diagnostic specimen type (n=1,546)

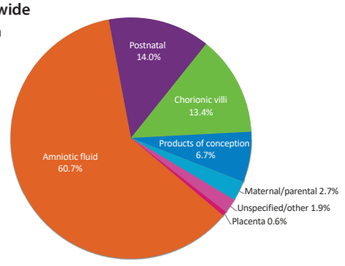
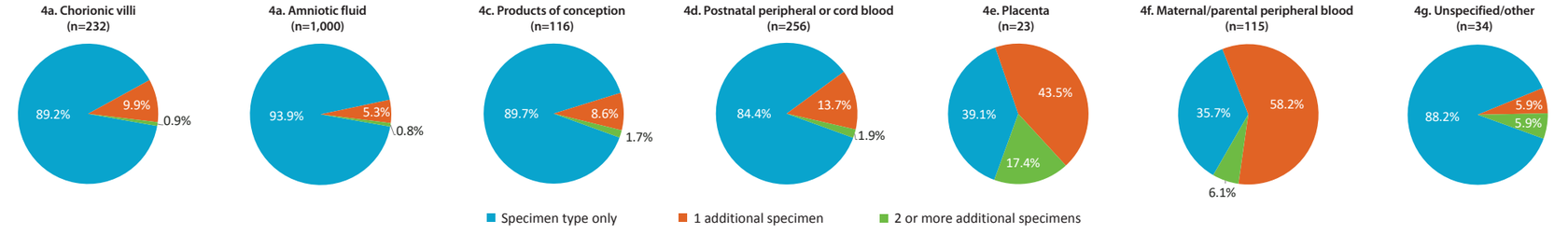


Figure 4. Genome-wide cfDNA samples associated with different specimen types



IV. Conclusions

The data shows the majority of providers are ordering testing on a single specimen and test type following genome-wide cfDNA screening. Additional testing at other laboratories or institutions could have been performed but not captured during data collection. Providers ordering only one test type were greater than 5 times more likely to order karyotype over microarray, despite the joint ACOG and SMFM guidelines discussing microarray's higher resolution and diagnostic yield.[1] Positive, negative, and non-reportable genome-wide cfDNA results were included in the data compilation with associated diagnostic and specimen type. The increased number of karyotypes ordered may be related to an increased number of genome-wide cfDNA results positive for common aneuploidies, precluding the need for microarray analysis. Future studies can analyze whether the type of genome-wide cfDNA result correlates to the type of diagnostic testing ordered.

Greater than 20% of single specimens were not associated with a prenatal sample. This observation suggests that some patients may have chosen to defer testing until the postnatal period, or after a pregnancy loss, instead of pursuing diagnostic testing during pregnancy. Genome-wide cfDNA could be a viable option for these patients.

Key Points:

- Over 20% of women who opted for genome-wide cfDNA did not proceed with diagnostic testing during pregnancy.
- Providers were 5-times more likely to order karyotype over microarray, despite the lower diagnostic yield and resolution with karyotype.
- Maternal/parental and placental studies were likely to coincide with additional specimen types.

V. References

1. Committee on Genetics and the Society for Maternal-Fetal Medicine. Committee Opinion No.682: Microarrays and Next-Generation Sequencing Technology: The Use of Advanced Genetic Diagnostic Tools in Obstetrics and Gynecology. *Obstet Gynecol*. 2016 Dec;128(6):e262-e268. doi: 10.1097/AOG.0000000000001817. PMID: 27875474.
2. Boomer T et al. Genome-wide cfDNA screening: Trends and lessons from >40,000 samples. Poster presented at: ISPD 22nd International Conference on Prenatal Diagnosis and Therapy; 2018 Jul 8-11; Antwerp, Belgium.
3. 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.

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