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Trends from over 85,000 genome-wide cell-free DNA tests

Jill Rafalko, Samantha Caldwell, Eyad Almasri, Erica Soster, Kimberly Fanelli, Vanessa Nitibhon
Laboratory Corporation of America®, La Jolla, CA

I. Objective

Genome-wide cell-free DNA (cfDNA) screening has been clinically-available in the United States since 2015. Here, we review over 85,000 consecutive clinical samples submitted for testing, spanning two versions of the laboratory assay. The current study analyzes testing trends from when genome-wide cfDNA analysis became available: assay version 4 (AV4) to assay version 5 (AV5).

II. Study Design

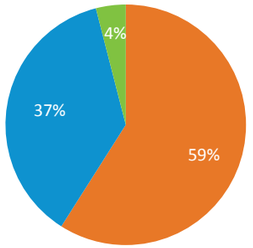
Maternal blood samples submitted for genome-wide cfDNA testing were subjected to DNA extraction, library preparation, and genome-wide massively parallel sequencing as previously described by Jensen et al.[1] Sequencing data were analyzed using a novel algorithm to detect aneuploidies and other subchromosomal events as described by Lefkowitz et al.[2]

Retrospective analysis of demographic information, laboratory reporting metrics, and positive screening results was performed for the overall cohort (n=86,902) and then samples were divided and analyzed by assay version (47,981 samples from AV4 and 38,921 samples from AV5).

III. Results

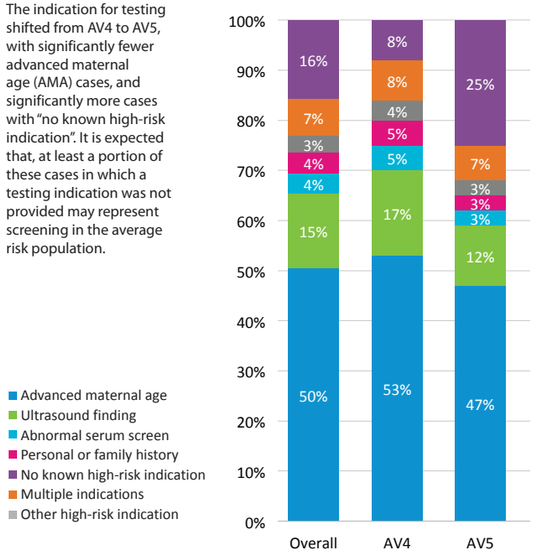
Gestational age distribution at time of cfDNA draw (n=85,945)

The gestational age of samples stayed relatively consistent over time, with the majority (59%) of samples submitted for testing during the first trimester of pregnancy, and only 4% during the third trimester.



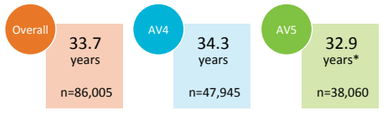
Indication for testing (n=86,902)

The indication for testing shifted from AV4 to AV5, with significantly fewer advanced maternal age (AMA) cases, and significantly more cases with "no known high-risk indication". It is expected that, at least a portion of these cases in which a testing indication was not provided may represent screening in the average risk population.



Statistically significant changes for all testing indications from AV4 to AV5 (p<.05)

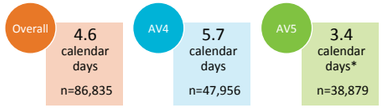
Average maternal age



The average maternal age of patients submitting samples for genome-wide cfDNA screening decreased significantly between assay versions, from 34.3 to 32.9 years.

**Statistically significant decrease in average maternal age from AV4 to AV5 (p<.0001)*

Turnaround time

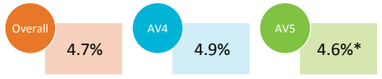


The average turnaround time for testing decreased significantly from 5.7 calendar days with AV4 to 3.4 calendar days with AV5.

**Statistically significant decrease in turnaround time from AV4 to AV5 (p<.0001)*

Average fetal fraction of reportable samples

Positivity rate



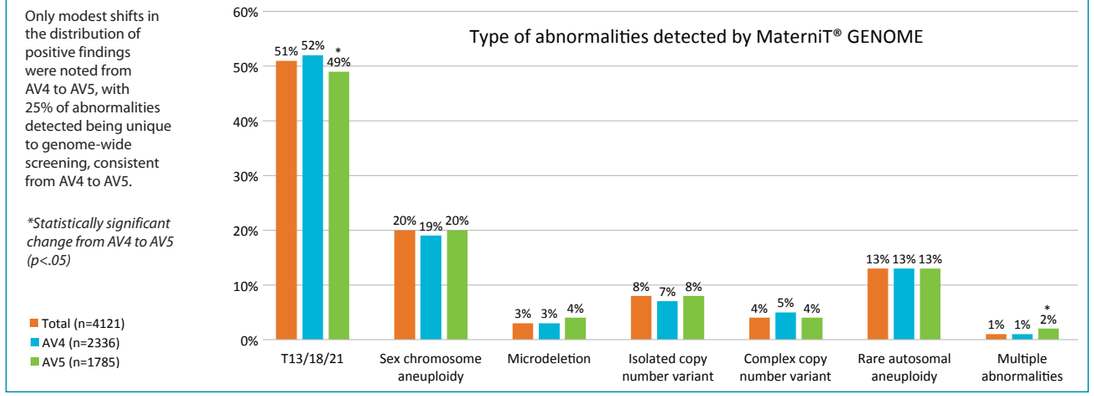
The overall positivity rate of genome-wide cfDNA screening was 4.7%, with a statistically significant decrease in positivity rate from AV4 (4.9%) to AV5 (4.6%).

**Statistically significant decrease in positivity rate from AV4 to AV5 (p<.05)*

Type of positive findings

Only modest shifts in the distribution of positive findings were noted from AV4 to AV5, with 25% of abnormalities detected being unique to genome-wide screening, consistent from AV4 to AV5.

**Statistically significant change from AV4 to AV5 (p<.05)*



IV. Conclusions

Over 5 years of genome-wide cfDNA screening has seen a significant decrease in the average maternal age of patients tested, and an increase in patients screened with "no known high-risk indication". As the proportion of presumably average risk patients has increased, the positivity rate of testing has correspondingly decreased. However, the frequency of findings unique to genome-wide cfDNA screening has remained constant over time at 25%.[3] Significant improvements in turnaround time have been seen from one assay version to the next.

KEY POINTS:

- From AV4 to AV5, genome-wide cfDNA screening has seen:
  - A significant *decrease* in the average maternal age of patients tested
  - A significant *increase* in the number of patients being screened with "no known high-risk indication", which may represent screening in the average risk population
  - A significant *decrease* in positivity rate, likely due to the influx of presumably average-risk screening
  - A significant *decrease* in test turnaround time
- After 5 years of testing, a consistent 25% of abnormalities identified by genome-wide cfDNA screening would have been missed by traditional cfDNA analysis.

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 Gynec*. doi: http://dx.doi.org/10.1016/j. ajog.2016.02.03.
3. Boomer T, Soster E, Caldwell S, et al. Genome-wide cfDNA screening: Trends and lessons from >40,000 samples. Poster presented at the *22nd International Conference on Prenatal Diagnosis and Therapy* (ISPD); 2018 July 8-11; Antwerp, Belgium.

Poster presented at the *SMFM 41st Annual Pregnancy Meeting*; 2021 January 25-30.