gw webinar

COMPARISON OF GENOME-WIDE VERSUS TARGETED cfDNA TESTING FOR FIRST-LINE PRENATAL SCREENING: REAL-WORLD DATA

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A **GenomeWeb/Roche** White Paper

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This white paper is based on a webinar presentation by Dr. Elisa Bevilacqua, a Senior Medical Consultant OBGYN and PhD Researcher at Brugmann University Hospital in Belgium.

Dr. Bevilacqua began with an overview of prenatal screening and methods of cell-free DNA (cfDNA) analysis. She then presented real-world data from a head-to-head comparison of a targeted and a "home-brew" genome-wide cfDNA (HB-GW) test, including a discussion of the clinical impact of findings beyond the common trisomies. She closed her discussion with recommendations for best strategies for cfDNA screening during pregnancy.

Noninvasive prenatal testing (NIPT) based on cfDNA has been available since 2011 and has quickly become an established tool for common trisomy screening. Dr. Bevilacqua noted that cfDNA testing provides a 99 percent detection rate for trisomy 21 and a false positive rate of 0.04 percent. "This is the real benefit of NIPT for common trisomies," she said. "A very low false positive rate and a real reduction in the invasive procedure rate."

There are currently two major cell-free DNA NIPT technologies: genome-wide (GW) and targeted. GW screening uses massively parallel sequencing (MPSS), resulting in a shallow analysis depth across all chromosomes.

"With this test, we can detect common trisomies, but also rare autosomal trisomies (RAT), rare autosomal monosomies (RAM), [and] large partial imbalances (PI)," said Dr. Bevilacqua.

In comparison, a targeted test provides high analysis depth on a subset of chromosomes and critical regions. The test can detect specific common trisomies and, if selected, microdeletions.

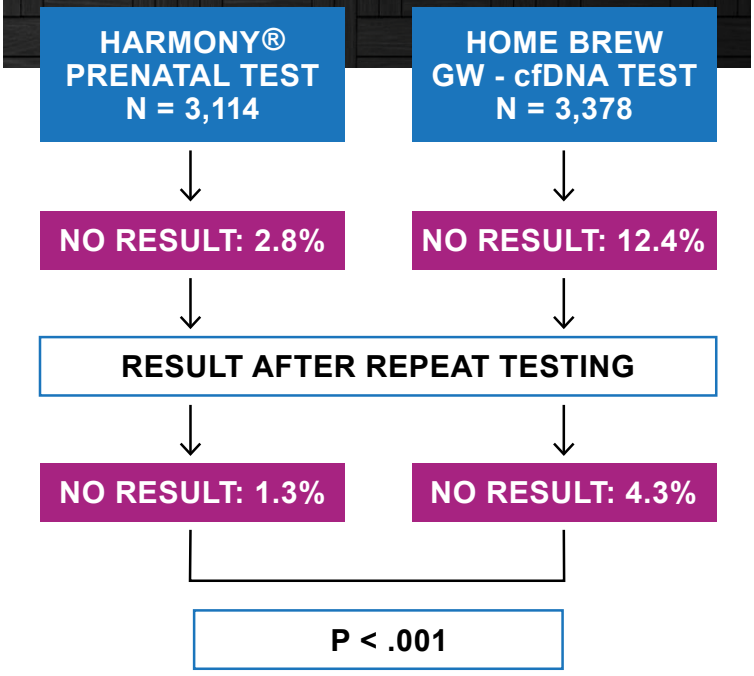
HEAD-TO-HEAD COMPARISON: TARGETED AND GENOME-WIDE ANALYSIS

Dr. Bevilacqua presented a retrospective observational study comparing a targeted cfDNA test, the Harmony prenatal test, with a "home brew" genome-wide (HB-GW) test using an Illumina platform[1].

Results of all NIPTs performed in the two largest maternity hospitals in Brussels between July 2017 and April 2019 were analyzed. Of 6,487 pregnancies, 3,114 received the Harmony targeted test and 3,378 had the HB-GW test. Authors compared performance, failure (no-call) rates, turn-around-time (TAT) between the two tests, and evaluated the clinical relevance of incidental HB-GW findings.

While sensitivity and false-positive rates for the common trisomies did not significantly differ between the two methods, the Harmony test demonstrated a significantly lower no-call rate and shorter TAT compared to the HB-GW test *(see figure 1)*.

FIGURE 1 Failure rates for the Harmony and home-brew tests.



Turnaround time also differed: 98.2 percent of Harmony results were available in less than seven calendar days, compared to 58 percent for the HB-GW test.

The HB-GW test reported abnormal results beyond the common trisomies (RAT, RAM, SCA, PI) in 28 of 3,378 women (about 0.8 percent). "Notably, for all 28 cases with an additional finding of NIPT, there was a normal physical follow-up, and an apparently normal baby at birth," said Dr. Bevilacqua.

Analysis showed that women undergoing the HB-GW test had a greater than 5 percent chance of being advised to undergo an invasive procedure, as a result of the 4.3 percent failure rate and the additional 0.8 percent rate of findings beyond common trisomies.

Dr. Bevilacqua noted that this data indicates that the GW approach fails to meet the main goals of NIPT, which are to decrease false positive rates, frequency of invasive procedures, and maternal anxiety. She pointed out that another study, called TRIDENT-2, in which researchers in the Netherlands investigated NIPT as a first-tier screening test, had similar conclusions[2]. In that study, 94 percent of RATs and more than 70 percent of PIs were not confirmed in screen-positive pregnancies.

"Presently, TRIDENT-2 shows that the benefits of screening for all genetic imbalances do not seem to outweigh the potential harms and that clinical implementation, even in a research setting, may be questionable ethically," said Dr. Bevilacqua.

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GENOME-WIDE TESTING: HARM OR BENEFIT?

GW cfDNA analysis can detect a variety of genomic imbalances, "but we cannot detect these relevant conditions without also detecting a lot of other large non-recurrent partial imbalances that may be difficult to interpret," explained Dr. Bevilacqua.

In January 2020, leading experts signed a position statement[3] raising several concerns regarding the use of GW-cfDNA testing, including the increased screen-positive rate of a test that was initially meant to reduce unnecessary invasive testing, lack of accurate information for counseling and informed consent, and ethical challenges surrounding clinical decision-making based on unclear results. Indeed, no international society currently recommends a genome-wide NIPT approach.

Dr. Bevilacqua stated that "we should not forget, or underestimate, the emotional impact and effort of providers managing the uncertainty of NIPT results."

CONCLUSIONS

Before implementing GW-cfDNA into a screening program, the benefits and harms must be weighed carefully and more robust data and management strategies should be available. Currently, when genome-wide assessment is desired, amniocentesis with array-CGH should be performed.

"NIPT is a screening test," Dr. Bevilacqua said. "It is not a diagnostic. No matter the manner of clinical implementation and the methodology used, NIPT does not replace ultrasound examinations, or diagnostic procedures. If an anomaly is found, an invasive procedure should be the gold standard."

Dr. Bevilacqua concluded that in the ideal country, the best way to perform screening for aneuploidy should be a first-trimester ultrasound scan, followed by a targeted NIPT. "The two tests should be used together," she said. "If the ultrasound is normal, we should perform the NIPT. Ultrasound information will help us to manage the NIPT results. If an anomaly is detected at ultrasound, an invasive procedure should be proposed instead of NIPT."

REFERENCES

1: de Wergifosse S, Bevilacqua E, Mezela I, et al. Cell-free DNA analysis in maternal blood: comparing genome-wide versus targeted approach as a first-line screening test, *The Journal of Maternal-Fetal & Neonatal Medicine*, 2019. DOI: 10.1080/14767058.2019.1686478.

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