Noninvasive genetic test for Down syndrome and Edwards syndrome highly accurate

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Current screening strategies for Down syndrome, caused by fetal trisomy 21 (T21), and Edwards syndrome, caused by fetal trisomy 18 (T18), have false positive rates of 2 to 3%, and false negative rates of 5% or higher. Positive screening results must be confirmed by amniocentesis or chorionic villus sampling, which carry a fetal loss rate of approximately 1 in 300 procedures. Now an international, multicenter cohort study finds that a genetic test to screen for trisomy 21 or 18 from a maternal blood sample is almost 100% accurate. The results of the study are published online in the *American Journal of Obstetrics and Gynecology*.

The trial evaluated a novel assay known as Digital Analysis of Selected Regions (DANSR) that analyzes fetal cell-free DNA, small DNA fragments which circulate in maternal blood. Unlike similar tests that analyze DNA from the entire genome, DANSR analyzes only the chromosomes under investigation for a more efficient and less expensive process. The results are evaluated with a novel analysis algorithm, the Fetal-fraction Optimized Risk of Trisomy Evaluation (FORTE), which considers age-related risks and the percentage of fetal DNA in the sample to provide an individualized risk score for trisomy detection.

A total of 4,002 pregnant women from the United States, the Netherlands, and Sweden were enrolled in the NICE (Non-Invasive Chromosomal Evaluation) study. The mean maternal age was 34.3 years and the cohort was racially and ethnically diverse. Blood samples were taken before the women underwent invasive testing for any indication, and 774 samples were excluded prior to analysis. Of the 3,228 samples that underwent analysis, 57 cases were excluded due to low fetal cfDNA in the sample and 91 samples were excluded due to failure of the assay. The classification of samples as High Risk or Low Risk using the DANSR and FORTE method was compared with the results from amniocentesis and CVS.

The DANSR and FORTE method identified 100% of the 81 T21 cases as High Risk, and there was one false positive among the 2,888 normal cases, for a false-positive rate of 0.03%. Of the 38 T18 cases, 37 were classified as High Risk and there were 2 false positives among the 2,888 normal cases, for a sensitivity of 97.4% and a false positive rate of 0.07%.

Prior studies of cfDNA have been case-control studies, comparing detection in subjects identified with T21 or T18, to a selected group of those with normal karyotypes. The current study included a large cohort of subjects undergoing invasive prenatal diagnosis. This allowed the researchers to assess the potential impact of other complex and unusual abnormalities on cfDNA test results. Overall, the presence of other chromosomal variants did not interfere with the detection of T21 or T18. While the study included primarily high-risk women, all women undergoing invasive prenatal diagnosis for any indication were eligible, so the cohort represents a broader population than reported in previous studies.

"The improvement in sequencing efficiency achieved by the DANSR platform provides a more affordable, scalable approach to cfDNA analysis with high throughput and potential for widespread clinical utility," says lead investigator Mary E. Norton, MD, director of perinatal research, Lucile Packard Children's Hospital at Stanford University. "Cell-free DNA offers high accuracy with a single blood test. It is potentially suitable as a replacement for current, relatively inefficient aneuploidy screening."

More information: "Non-Invasive Chromosomal Evaluation (NICE) Study: Results of a Multicenter, Prospective Cohort Study for Detection of Fetal Trisomy 21 and Trisomy 18," by M.E. Norton, H. Brar, J. Weiss, et al. (doi: 10.1016/j.ajog.2012.05.021). It is available online in advance of publication in *American Journal of Obstetrics & Gynecology*.

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