

New prenatal test, chromosomal microarray, proposed as standard of care

December 5 2012

A large, multi-center clinical trial led by researchers from Columbia University Medical Center (CUMC) shows that a new genetic test resulted in significantly more clinically relevant information than the current standard method of prenatal testing. The test uses microarray analysis to conduct a more comprehensive examination of a fetus's DNA than is possible with the current standard method, karyotyping—a visual analysis of the fetus's chromosomes. Results were published in the Dec. 6, 2012, issue of *The New England Journal of Medicine (NEJM)*.

The prospective, blinded trial involved 4,400 patients at 29 centers nationwide; the data took four years to compile. The study involved women with [advanced maternal age](#) and those whose fetuses were shown in early screening to be at heightened risk for Down syndrome, to have structural abnormalities (as seen with ultrasound), or to have indications of other problems. Ronald J. Wapner, MD, professor and vice chairman for research at the Department of [Obstetrics and Gynecology](#) at CUMC and director of reproductive genetics at NewYork-Presbyterian/Columbia, was principal investigator. This is the first and only study to prospectively compare karyotyping with microarray in a blinded head-to-head trial.

The trial found that microarray analysis, which compares a fetus's DNA with a normal (control) DNA, performed as well as karyotyping in identifying common aneuploidies (an abnormal number of chromosomes—an extra or missing chromosome causes genetic disorders such as Down syndrome and [Edwards syndrome](#)); it also

identified additional abnormalities undetected by karyotyping.

Among fetuses in which a growth or structural anomaly had already been detected with ultrasound, microarray found clinically relevant chromosomal deletions or duplications in one out of 17 cases (6%) that were not observed with karyotyping. In cases sampled for advanced maternal age or positive screening results, microarray analysis picked up an abnormality in one out of every 60 pregnancies (1.7%) that had a normal karyotype.

"Based on our findings, we believe that microarray will and should replace karyotyping as the standard for evaluating chromosomal abnormalities in fetuses," said Dr. Wapner. "These chromosomal micro-deletions and duplications found with microarray are often associated with significant clinical problems."

As with karyotyping, microarray requires fetal cells obtained via an invasive procedure such as amniocentesis, where fetal cells are taken from the amniotic fluid, or chorionic villus sampling, where cells are taken from the placenta. Parents deciding whether to take these tests must weigh a number of factors, including their individual risk of fetal abnormalities, possible procedure-induced miscarriage, and the consequences of having an affected child. Work is underway to develop a non-invasive test, the same information seen by microarray, using a blood sample taken from the mother but is not yet available.

"We hope that in the future—when microarray can be done non-invasively—every woman who wishes will be offered microarray, so that she can have as complete information as possible about her pregnancy," said Dr. Wapner.

Second Paper Published in Same Issue of *NEJM* re: Microarray in Stillbirth

In a second paper published in the same issue of *NEJM*, about the use of microarray in stillbirth, results showed that microarray produced a clinical relevant result in 87% of 532 cases, which were analyzed with both karyotyping and microarray. In contrast, standard methods for analyzing a stillbirth, which include karyotyping, have been shown in previous research to fail to return information in 25% of cases.

"Microarray was significantly more successful at returning clinically relevant information because, unlike karyotyping, it does not require cultured cells. Viability does not come into play at all—DNA can be extracted from tissue that is no longer living," said study senior author, Brynn Levy, MSc(Med), PhD, associate professor of pathology and cell biology, and co-director of the Division of Personalized Genomic Medicine at CUMC, and director of the Clinical Cytogenetics Laboratory at New York-Presbyterian/Columbia. "Not being able to explain why a stillbirth occurred can be very hard for families. These findings are important because they give us a significantly more reliable method to provide information to families and their physicians."

"The primary benefit of using microarray analysis rather than karyotype analysis is the greater likelihood of obtaining results," said Uma Reddy, MD, MPH of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) of the National Institutes of Health, first author of the paper. "Microarray analysis is especially useful in stillbirth cases in which the karyotype has failed or there is a birth defect present. However, microarray analysis is currently more expensive than karyotyping – and this may be a barrier to some."

The study used data compiled by NICHD's Stillbirth Collaborative Research Network (SCRN), a population-based study of stillbirth in five geographic catchment areas.

Clinical Significance of Chromosomal Abnormalities

Growing by Leaps and Bounds

Both microarray and karyotyping reveal clinically relevant information about conditions that can be life-threatening for a newborn baby or that can signal a possible health threat that might be treatable. However, as with all current [genetic testing](#) including karyotyping, the results may reveal findings that have not been described in the literature or in which the exact implications are known.

"While the vast majority of abnormalities found with microarray are associated with known conditions, not all are. But with time, knowledge and understanding of what these abnormalities mean will continue to grow," said Dr. Wapner. "When we started this study five years ago, the incidence of findings we did not understand was about 2.5%—now, with more information, that has fallen to 1.5%."

Dr. Wapner is currently leading phase two of his microarray study. Supported by the NICHD (NIH Grant No. 2U01HD055651-06; Project No. GG006961), he has begun a five-year study to follow children born to mothers who underwent microarray, to learn the clinical implications of micro-deletions or duplications that are not yet understood.

"Unfortunately, it is sometimes difficult to predict the full spectrum of some diseases indicated by a particular deletion or duplication," said Dr. Wapner. "Genetic medicine is about obtaining genomic information about an individual and predicting what affect it will have on that person. But we are all different—so genetic abnormality in one person may behave differently than in someone else. For example, an inherited disease could be mild in the mother but severe in her child. We are studying what these mean clinically, and science continues to catch up with our ability to obtain the information."

More information: Dr. Wapner's paper is titled, "Chromosomal

Microarray Compared with Karyotyping for Prenatal Diagnosis." An abstract was presented in Feb. 2012 at the Society for Maternal-Fetal Medicine annual meeting.

Provided by Columbia University Medical Center

Citation: New prenatal test, chromosomal microarray, proposed as standard of care (2012, December 5) retrieved 25 April 2024 from <https://medicalxpress.com/news/2012-12-prenatal-chromosomal-microarray-standard.html>

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