Trial aims to advance prenatal diagnosis of genetic defects

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Reproductive genetics researchers at Columbia University Medical Center (CUMC) are leading a multicenter prospective clinical study investigating the effects of chromosomal abnormalities (duplicative or missing material) found prenatally through microarray analysis. The goal of the study is to gain further information on genetic variances previously not well reported in the medical literature and share it with parents during pregnancy.

Led by principal investigator Ronald J. Wapner, MD, professor and vice chair for research at CUMC's Department of Obstetrics and Gynecology and director of reproductive genetics at NewYork-Presbyterian Hospital/Columbia, the research is the next phase of a project to advance clinicians' ability to diagnose in utero conditions such as developmental delays, structural abnormalities, and treatable or life-threatening diseases.

"Parents of children found to have a genetic variance want a better understanding of what it means. Our goal is to give them as much information and support as possible—from detailed genetic counseling to ways to connect with other people expecting children with the same variance," said Dr. Wapner.

In December 2012, Dr. Wapner and colleagues published in the New England Journal of Medicine (NEJM) findings of a trial involving 4,400 patients at 29 centers nationwide. That study showed that microarray analysis of a fetus's DNA gave significantly more clinically relevant

information than the standard method of analysis, known as karyotyping—a visual analysis of the fetus's chromosomes. [Click here for a news release about that study.]

In the current study—which has ongoing clinical recruitment—data on babies included in the NEJM article will be augmented by data on patients recruited by 10 major prenatal diagnostic centers around the country that offer microarray to all their patients. Each center aims to recruit 1,000 patients. Of the anticipated 10,000 or so microarray analyses, the researchers aim to follow 300–600 children born with genetic variances, for at least three years. (See below for more about microarray.)

"While the majority of abnormalities found with microarray are associated with known conditions, in many cases the full implications of findings are not well understood, and about 1.5 percent are unidentified. The goal is to fill in these knowledge gaps," said Dr. Wapner. "Ours is the only study of its kind that is identifying genetic variances in utero and following the kids over time to see how the abnormalities present and to gather as much clinical information about them as possible, such as the severity of problems and life expectancy."

"When we counsel parents now, we can give them only limited information, drawn from what we know about children who have undergone genetic testing. But these children often represent the severe end of the spectrum," said Dr. Wapner. "There might be people who, because they had no symptoms, were never identified as having a variance, limiting the prognostic information we are able to give parents."

NewYork-Presbyterian/Columbia is the primary recruitment center. The other centers participating in the study are: the Center for Fetal Medicine, Northwestern University, Cedars Sinai Medical Center, San

Francisco Perinatal, Carnegie Hill Imaging, Montefiore Medical Center, Mount Sinai Medical Center, Lenox Hill, and North Shore LIJ.

A majority of the labs in the country that do prenatal microarray have agreed to refer patients to the website, where they will be able to self-enroll in the study. "We hope to capture almost all the available microarray data," said Dr. Wapner.

Website to Collect, Share Information in Real Time with Parents, Clinicians

Trial data will be collected and shared in real time with parents and clinicians via the website http://www.prenatalarray.org, where expectant parents undergoing testing can learn how microarray works and what it looks for; parents of a child with a variance can find information about their baby's variance and connect with other parents of babies with the same variance; and physicians, genetic counselors, and other clinicians can input and research real-time information on the clinical impact of the variance.

"We will link genetic anomalies with structural abnormalities—connecting the genotype (the genetics, or errors) with the phenotype (what you see)," said Dr. Wapner. "This will help us to better understand the basis of birth defects—things that run together, what genes to look for, and so on."

Software to better categorize ultrasound findings and relate them to the phenotype is provided by a genetics software-as-a-service company called Cartagenia, a collaborator on this work. As medical science continues to advance, Dr. Wapner and his colleagues hope and expect that this data pool (and web tracking system) will continue to improve genetic surveillance.

A web-based portal designed and hosted by David Ledbetter, PhD, and W. Andrew Faucett, MS, collaborators at Geisinger Health System in Danville, Pa., enables secure two-way communication with patients. This allows researchers to conduct surveys about patients' attitudes and opinions about testing; it can also help them to understand how the patients dealt with learning that their child has a genetic variance.

More About Microarray

Microarray requires fetal cells obtained through an invasive procedure (offered to high-risk pregnant women), such as amniocentesis, in which fetal cells are taken from the amniotic fluid, or chorionic villus sampling, in which cells are taken from the placenta. Pregnant women are deemed high risk if they have advanced maternal age (age 35 or older) or if their fetuses are shown through early screening to be at increased risk for Down syndrome, to have structural abnormalities (as seen with ultrasound), or to have indications of other problems. Parents deciding whether to undergo 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.

Wendy Chung, MD, PhD, associate professor of pediatrics (in medicine) at Columbia University Medical Center and director of clinical genetics at NewYork-Presbyterian/Columbia, is supervising the evaluation of the children.

The data are being housed at the George Washington University data center. Researchers at the University of Pennsylvania are leading the counseling and psycho-social portions of the study.

Provided by Columbia University Medical Center