Prenatal genetic test offers more information, raises questions

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The latest advance in prenatal genetic testing purports to offer parents more detailed information than ever about the child they are expecting. But for some, the new answers could lead to another round of questions.

The technology allows doctors to detect small or subtle chromosomal changes in a fetus - such as missing or extra pieces of DNA - that could be missed by standard tests.

Most parents will get results confirming a normal pregnancy. But some will learn that their baby has a birth defect, a developmental problem or other medical condition, and in a small number of cases the test will detect things that no one knows quite how to interpret.

The information can allow parents to prepare for early intervention and treatment, but it also could raise questions about terminating the pregnancy or lead to nagging worry over uncertain results.

The Reproductive Genetics Institute in Chicago, which has helped pioneer the rapidly developing field of prenatal diagnosis and testing, recently began offering the procedure - array comparative genomic hybridization, or array CGH for short - to any pregnant woman who wants it.

"The technology has been available for a number of years ... but it has almost never been used prenatally," said Dr. Norman Ginsberg, an obstetrician specializing in prenatal genetic testing at the institute. "We

think this is the beginning of the next generation of how we'll look at things."

Other medical experts see the technology as promising but have concerns about using it as a first-line test because of the potential drawbacks and the lack of published research. The availability of array CGH also raises fundamental, sometimes delicate, questions for parents.

How much do they want to know about their child's genetic makeup before he is born? How will they deal with the uncertainty of some test results, such as detection of chromosomal changes that have not been associated with diseases? Should the technology be used to identify diseases in their children that would not emerge until adulthood?

"This technology is giving genetic counselors and physicians a challenge in that there is more to discuss with patients, and it gives patients a lot more to think about in terms of what kinds of information they want to know about their baby prior to delivery," said Jennifer Hoskovec, director of prenatal genetic counseling services at the University of Texas Medical School at Houston.

Array CGH is just one of the newer microarray technologies expected to become widely available to parents.

Scientists last week reported that they had successfully sequenced the genome of a baby in the womb using a noninvasive procedure that avoids the risk of miscarriage because it does not require penetrating the sac of amniotic fluid that protects the fetus. Researchers instead drew blood from the mother 18 weeks into the pregnancy and took a sample of saliva from the father.

Scientists have long known that fetal DNA appears in the mother's blood plasma a few weeks after conception, rises during gestation and normally

vanishes after the baby is born.

From the samples, researchers were able to determine if the fetus' genome contained single-letter changes in the DNA code that can cause a genetic disorder. They also could identify which mutations were inherited from each parent and which were new, said the authors of the report in Science Translational Medicine.

Many experts say this type of prenatal testing eventually could provide parents with a simple, risk-free way to screen for genetic disorders.

The hope for array CGH for prenatal testing is that it can give parents more information than previously available through the more commonly used procedure, karyotyping. Comparing the two techniques, a major study funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development found that array CGH is reliable and does a better job of detecting chromosome deletions and duplications.

"It is equally effective in identifying the things that karyotype now identifies," said the principal investigator, Dr. Ronald Wapner, director of reproductive genetics at New York-Presbyterian/Columbia University Medical Center. "But microarray is superior in identifying lots of other things that are too small to be seen on a karyotype."

The researchers have submitted the results of their research - the first large study on array CGH for prenatal testing - to a medical journal.

Among pregnancies in which routine chromosome testing was normal, microarray analysis turned up a clinically significant chromosomal abnormality - one clearly linked to medical or developmental problems - in 1.7 percent, or about 1 in 70. In another 1 percent to 2 percent, the changes detected were of uncertain clinical significance, meaning it's unclear whether they would have health repercussions.

"Microarrays are not unusual in this respect from other tests we offer in medicine," said Lisa Shaffer, chief scientific officer and co-founder of the Washington-based Signature Genomics, which says it was the first laboratory to offer microarray genetic testing. "Most tests have a gray zone where you may find something and you don't know what it means. Sometimes we get results that we just don't have enough information to say whether or not it will affect the baby."

Chromosomes are tightly bundled packages of DNA that carry our genetic information. Since the 1970s, the standard method of prenatal genetic diagnosis has been karyotyping, which involves using a microscope to examine chromosomes from the amniotic fluid or from the mother's placenta.

Microarray tests, such as array CGH, can detect differences too small to be seen that way, though no test can detect all chromosomal changes or genetic disorders.

"Over the next five to six years, we'll be able to sequence the DNA and get even more information," Wapner said. "There's no question that technology is moving rapidly forward."

Genetic testing often is done if an ultrasound identifies a physical abnormality, if the woman has a history of problem pregnancies, if a maternal blood test indicates increased risk for a chromosome abnormality or if she will be 35 or older when she delivers.

But Dr. Lee Shulman, clinical director at the Reproductive Genetics Institute and director of clinical genetics at Northwestern University's Feinberg School of Medicine, said genetic abnormalities can occur regardless of the mother's age.

"All women need to be aware that there is a risk so that they can choose

whether or not they want to have a (prenatal genetic) test, which is invasive, to determine whether their baby is affected," Shulman said.

The cost averages about $1,500 to $3,000 but depends on the type of microarray analysis, the lab and whether insurance will cover all or part of it. Aetna, for example, considers the technology experimental and does not pay for its use for prenatal genetic diagnoses.

In April, the genetics committee of the American College of Obstetricians and Gynecologists reaffirmed its 2009 policy on array CGH. Despite some advantages, it states, the test's usefulness as a first-line tool is still unknown and the technology is not a replacement for current tests.

"We think conventional karyotyping is still the first-line preferred test for prenatal diagnosis," said committee chairwoman Dr. Nancy Rose. "Array CGH is a great adjunct tool in a fetus with birth defects detected in an ultrasound, if the karyotype is normal, as a second-line test to evaluate the fetus."

Sarah Benedict chose to undergo array CGH before her son Andrew was born in March.

"I like to have information and be able to plan for things," said Benedict, who lives in Hinsdale. "I just wanted to know that everything was OK, especially at age 44. The risks are higher than when you are younger. For me, it was a question, not if I was going to do prenatal testing, but which one was right for me."

To reduce the chances of unclear results, she opted for a microarray that is more precise than standard karyotyping but not the most comprehensive available.

The results came back normal, though it showed two changes in regions of genes that contain long repetitive DNA sequences. These changes are thought to be due to normal human genetic variation and have no known clinical relevance.

Benedict was reassured. Andrew was born at a healthy weight and size and is doing well, she said.

"There was a time when (abortion opponents) called this kind of genetics testing 'search and destroy,' " Ginsberg said. "Now we say what we do is 'search and treat.' We are not looking to necessarily terminate pregnancies."

Hoskovec, a spokeswoman for the Chicago-based National Society of Genetic Counselors, said half of her patients decline array CGH, mostly because they lack insurance coverage but also because some find the level of detail uncomfortable.

Still, she expects that, over time, array CGH will become widely used.

"As long as the counseling piece is there to help parents make informed decisions about this information, I support it," Hoskovec said. "I think it's fantastic that we are able to provide patients with information we couldn't provide them with in the past. But I tell them, just because we can provide this information, it doesn't mean we need to."