Prenatal Genome Testing Sparks Debate

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NEW TECHNOLOGIES THAT ALLOW scientists to rapidly analyze a person’s genome for potentially deleterious variations are now being used by at least 1 company and an academic medical center for prenatal testing, igniting a debate among scientists about the clinical value and ethical implications of the procedure.

As data emerge from early clinical studies that use microarray comparative genomic hybridization for prenatal diagnosis (Sahoo T et al. *Genet Med*. 2006;8[11]:719-727 and Shaffer LG et al. *Prenat Diagn.* 2008;28[9]:789-795), proponents of the testing are beginning to offer this expensive service more broadly. But because such tests may provide parents with ambiguous information, some scientists question their clinical value and express concern that the procedure offers false assurances to parents at a vulnerable time.

COPY NUMBER VARIATIONS

Microarray comparative genomic hybridization allows scientists to scan an individual’s genome and rapidly identify copy number variations, which occur when an individual has an unusual number of copies of a particular section of their DNA.

To do this, scientists expose a glass slide embedded with single-stranded fragments of DNA, called an array, to a mixture of fluorescently labeled single-stranded DNA, half from the individual being tested and labeled with one color, and an equal amount of control DNA labeled with another color. The DNA from the control and the individual being tested will then bind to DNA fragments on the array, and the color of those fragments will vary based on the relative amount of DNA from each. For example, if the individual has more copies of a particular section of DNA than the control, the color of the patient’s DNA will show up stronger. Conversely, if the patient is missing a copy of a particular section of DNA, the control sample color will be brighter. These results are read by a laser scanner and analyzed by computer.

Because the process is automated, scientists have used it to scan genomes of hundreds or even thousands of patients and matched controls to identify DNA duplications or deletions linked to disease. Now, at least 2 laboratories are using the technique to scan the DNA of fetuses to determine if they have any copy number variations that have been associated with disease, or whether they possess novel copy number variations that might cause disease.

Arthur Beaudet, MD, chair of the department of molecular and human genetics at Baylor College of Medicine in Houston, and colleagues have used this technology to analyze more than 300 samples of fetal DNA collected from mothers undergoing amniocentesis or chorionic villus sampling. Some of the women were patients at Baylor; others were referred by physicians at other institutions. Beaudet and his colleagues previously disclosed that their department offers extensive laboratory testing, including this test, and that the department derives revenue from these activities. Additionally, Baylor College of Medicine owns equity in Spectral Genomics, which markets arrays similar to those used for prenatal testing.

Another company, Signature Genomics, based in Spokane, Washington, has created its own microarray-based prenatal test. So far, the company has analyzed samples from 380 fetuses sent by their mother’s physicians, according to Lisa G. Shaffer, PhD, the head of the company and a former colleague of Beaudet’s at Baylor.

Baylor charges about $1600 for the test (not including the costs associated with collecting the sample) and Signature Genomics charges about $1850. The charge for conventional prenatal testing, which relies on a skilled technician examining fetal chromosomes for abnormalities as small as 5 to 10 megabases, ranges nationwide from $500 to $700, according to Beaudet. But the arrays can be used to...
detect chromosomal variations at sizes of 0.05 to 0.1 megabases—100 times smaller than those detected by traditional methods.

**UNCERTAINTY**

Kathy Hudson, PhD, director of Johns Hopkins University’s Genetics and Public Policy Center in Washington, DC, said comparative genomic hybridization potentially could increase the specificity of prenatal chromosomal analysis, but noted that much of the vast amount of information that could be generated is not clinically relevant. While having too much or questionable information in other medical arenas may not be as problematic, providing such information to prospective parents—even when found through more traditional means—is the subject of great debate and concern.

“The dilemma in prenatal testing is that the information is used to make really profound decisions about whether to continue or terminate a pregnancy, Hudson said. “The information is really important.”

Experience with the use of microarrays to help physicians assess patients with disabilities of unknown etiology is providing scientists with insights into the potential and limitations of the technology for prenatal testing. Jan M. Friedman, MD, PhD, professor of medical genetics at the University of British Columbia in Vancouver, said the arrays can detect at least twice as many harmful variations as the traditional tests. However, the tests can also identify variants of unknown clinical significance, said Friedman.

Some variants may be benign. It is not uncommon to identify dozens of benign variants in a given individual’s genome, Friedman noted. “As a geneticist, that blows my mind,” he said. “There’s a lot of buffering and redundancies we didn’t previously appreciate.”

Physicians evaluating a patient can take several steps to determine whether a variant is benign or related to his or her disability, explained Friedman. First, they may try to determine whether the variation was passed down from a parent. If either of the individual’s parents has the variant and is unaffected it is unlikely to be the cause. If the missing or duplicated section of DNA is small, it is also less likely to be the cause. Scientists may also examine whether any genes within the missing or duplicated regions have previously been linked to the type of disability under consideration. Some of these techniques also can be used when evaluating variants identified prenatally, but the scientists will have little, if any, information about whether there are unfavorable phenotypic consequences of having a variant because many conditions cannot be detected in utero or may not develop until years after birth.

Even when a harmful variant in a fetus is identified by microarray analysis, there may be uncertainty about its clinical implications. Some variations are known to cause conditions with well-defined clinical outcomes, such as Down syndrome. When such a disease-associated variation is identified in a fetus, physicians can counsel parents about the possible range of symptoms and characteristics associated with the disorders or provide advice regarding caring for such a child.

However, many of the harmful or potentially harmful variants identified are rare and less well studied. Physicians may have little information about the clinical prognosis for patients with such variants. “We often don’t know as much about [the variation] to tell parents what to expect in the future, which is what a family needs to know,” said Friedman.

Beaudet argues that providing parents with more information is better and that the goal of such prenatal testing should be to identify as many disabilities as possible. Based on his experience, Beaudet said, “95% of the time you are dealing with pretty black-and-white information, and fairly serious disabilities.”

Even when the results are less clear, he believes such information is still useful to families. For example, he noted that a pair of genome-wide association studies published in late July identified 3 rare copy number variants that are associated with a small increased risk (about 1.15 fold) of developing schizophrenia (Stefansson H et al. Nature. doi:10.1038/nature07229 [published online ahead of print July 30, 2008] and the International Schizophrenia Consortium. Nature. doi: 10.1038/nature07239 [published online ahead of print July 30, 2008]).

“If we were to find a fetus with one of these possibilities, we would inform [the parents]. We would give these published references to their genetic counselor or obstetrician,” Beaudet said.

But Hudson questioned whether using data from unvalidated association studies to create a genetic test, without carefully considering the risks and benefits, is appropriate medical practice.

“Do we want to spend important and limited health care resources to provide information to already anxious parents about a minuscule risk for a condition that would present itself in teen years or later?” she said.

Beaudet said parents can be counseled prior to testing that in addition to identifying serious disabilities, the technology can also identify variants of uncertain significance, and they can decide whether or not they want to have that information.

**ETHICAL CONCERNS?**

But some geneticists question whether such a consumer-driven approach is appropriate from an ethical or public health standpoint.

“You have to be careful in prenatal testing not to cause anxiety,” said Caroline Mackie Ogilvie, MD, of the cytogentic department at Guy’s and St Thomas’ National Health Service Trust in London. “Parents are very vulnerable,” she noted.

Ogilvie is conducting a pilot trial of using only a rapid polymerase chain reaction–based test for Down syndrome in at-risk women from the southeast region of England who chose to undergo an amniocentesis or chorionic villus sampling. The testing is less expensive and offers faster results than...
Friedman agreed that it is premature to offer this type of prenatal testing outside of the context of a clinical trial or limited circumstances in which a severe malformation may be detected in a fetus and such testing might provide some insight about the cause.

LIMITED OVERSIGHT
Currently, federal regulation of microarray prenatal testing is limited. Under the so-called homebrew exemption, laboratories do not have to seek approval from the US Food and Drug Administration (FDA) for a test they have created as long as it is administered only by that laboratory. FDA approval would, however, be required if the laboratories that created the tests wished to market them for use by other laboratories. Under the Clinical Laboratory Improvement Amendments, the Centers for Medicare & Medicaid Services provide some oversight for the quality of laboratory testing, such as the qualifications of personnel and the handling of samples.

But Friedman said he believes professional organizations should take a leadership role in determining the best clinical applications for such tests. One reason such guidance is needed is the disturbing prospect that parents may decide to terminate a pregnancy on the basis of genetic variants that confer a very small increased risk of developing conditions in which nongenetic factors are clearly involved, such as cardiovascular disease.

Moreover, the prospect of shifting the focus of prenatal testing from providing definitive identification of disorders that have severe clinical consequences to purportedly reassuring parents that a fetus is normal is troubling, said Friedman.

“It is not sensible to demand [confirmation] that there is no risk for anything in a fetus—it’s impossible to get that,” he said.