Health & Medicine

Looking for the Telltale Gene

A new genetic test allows parents to peer into their unborn children's medical future. Are we ready for this knowledge? A Columbia study looks for answers.

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Trishia Bermudez and her son, Matthew. Photo by Jorg Meyer

Trishia Bermudez was thrilled to find out that she was pregnant last spring. She loved her baby bump and her expectant glow. And she was delighted by the sense of awe and possibility that her growing baby inspired in family and friends. “Everyone is excited for you about the new life you’re bringing into the world,” she

says.

During a routine ultrasound at about twenty weeks, Bermudez's doctor noticed a potential problem. The baby's kidneys appeared to be enlarged, which is sometimes a sign of a kidney disorder. In the worst case, it could mean death in the womb or within the first year of life.

Bermudez's doctor sent her immediately to the Center for Prenatal Pediatrics at Columbia University Medical Center (CUMC), one of the nation's premier institutions for treating high-risk pregnancies.

There, another ultrasound suggested that her baby's kidneys were fine, having swelled only temporarily. But it revealed a missing nasal bone, an enlarged placenta, and a shortage of amniotic fluid around the fetus. These were likely signs of a chromosomal abnormality in the baby. Bermudez sat down with Ashley Mills, a genetic counselor who specializes in translating complex information about a fetuses' DNA to parents. Mills offered Bermudez a routine procedure known as amniocentesis, which requires inserting a long needle into the abdomen to collect amniotic fluid. It is unpleasant and somewhat risky — about one in three hundred amniocenteses results in miscarriage — but it would allow doctors to examine her baby's DNA.

Bermudez agreed, despite her fear of needles. A physician extracted amniotic fluid, created a cell culture, and examined the stained cells under a microscope. The results were encouraging: no genetic mistakes could be seen. This ruled out the possibility that her baby would have Down syndrome, Turner syndrome, or any of the dozens of other conditions that are caused by the sorts of genetic mistakes that are easy to spot on a slide.

But Mills also offered to analyze Bermudez's baby's DNA using a computer-based technique that probes even deeper into the genome. Microarray analysis, as it is called, can detect mistakes in genetic code that are one hundred times smaller than those seen under a microscope. These tiny deletions and duplications are the sort that have been linked to autism, developmental delays, schizophrenia, and many other complex conditions. The test therefore provides parents a more detailed picture of their baby's health than has ever been available before.

"I thought if we went ahead with the test, maybe we'd get some concrete answers about what was going on with my body and my baby," says Bermudez.

Bermudez agreed to the test. This time, scientists did find something alarming: a missing piece of DNA on chromosome 3. This was a bad sign, but precisely what it meant for the baby was unclear.

“I sat with her for a very long time delivering the news,” says Mills. “I explained that I would have to do lots of research to give her some reliable information.”

Over the next several weeks, Mills studied the area of the genome where Bermudez’s baby had a deletion. There were nine genes in the region that were particularly worrisome, having been implicated in autism, diabetes, cataracts, abnormal blood clotting, epilepsy, leukemia, lymphoma, Parkinson’s disease, and obesity. To narrow down the prognosis, Mills pored over medical literature in hopes of finding references to other people with a DNA deletion that resembled this one. She found none. So she telephoned genetics labs around the country, asking if any other researcher had come across a similar case. Again, no luck.

“This meant that I couldn’t give her percentages or statistics on the likelihood that anything in particular would happen,” says Mills. “All I could say was that, based on the location and size of this deletion, the child would almost certainly have health problems. But what kind of problems? And when? What will he be like when he’s two? When he’s five? It was impossible to say. That’s very difficult news to deliver.”

Mills and Bermudez discussed the baby’s prognosis over a series of visits. They became close, and spent some of their time just chatting and laughing. But the heart of the meetings consisted of Mills preparing Bermudez for the likelihood that her baby would have special needs.

“Every time I went back for a visit, it was something sad,” Bermudez says. “I was coming home and crying and telling my fiancé about it. He felt like we couldn’t enjoy what the pregnancy was really about, which was bringing a new life into the world.”

Over the next few years, more and more women will face the decision of whether or not to test their unborn children for genetic abnormalities. The new test comes with emotional risks because it will sometimes pick up oddities in a baby’s DNA that are too subtle for geneticists to base any firm conclusions upon, thus leaving parents feeling anxious and helpless.

Ronald Wapner, the director of reproductive genetics at CUMC and vice chairman for research in the department of obstetrics and gynecology, is leading a federally

funded study that has provided thousands of women with the powerful new genetic test that was used on Bermudez's baby. The purpose of his study is to determine if this test generates information that is useful to doctors and parents, and therefore should be offered to all expectant mothers.

"This might mean that a doctor is able to diagnose a genetic disorder in the womb and treat it properly as soon as the child comes into the world," Wapner says. "Or it could mean helping a mother make a more informed choice about whether or not to continue with her pregnancy."

A more difficult question, however, is this: will parents be glad they received this information? Or will they regret ever having peeked at their baby's DNA?

Searching for signs

Prenatal genetic testing emerged in the 1970s, when obstetricians started to recommend amniocentesis for pregnant women over the age of thirty-five. The first common condition that scientists learned to preemptively diagnose was Down syndrome, which stood out because it is caused by the presence of a whole extra chromosome. Soon, they were also spotting the large chromosomal anomalies that cause Tay-Sachs disease, sickle-cell anemia, and several disorders of the neural tube, which is the embryo's precursor to the brain and spinal cord.

Wapner, a sixty-five-year-old obstetrician who came to Columbia from Drexel University in 2005, has been trying to improve prenatal diagnosis his entire career. In the early 1980s, he was instrumental in developing chorionic villus sampling (CVS), a procedure in which fetal cells are extracted from a woman's placenta rather than from her amniotic fluid. CVS can be done at an earlier stage of pregnancy — in the first trimester, versus the second — and is now a popular alternative to amniocentesis, although some women still get amniocentesis because it is easier for physicians to administer and is more widely available.

Wapner's most important contribution, though, may turn out to be his advancement of microarray analysis, the genetic test that Bermudez underwent last summer. The idea is simple: rather than limiting oneself to what can be spotted visually, why not use computers to identify the minutest discrepancies in a baby's DNA? The technology is not new. By the time Wapner proposed examining fetal tissue this way

in 2006, physicians had been analyzing the DNA of sick children by microarray for a few years. The technique was especially useful in spotting rare disorders that pediatricians had trouble diagnosing any other way.

“Say you have a youngster with a seemingly random combination of learning difficulties and physical problems, like a heart defect and cleft palate,” says Wapner. “If you do the microarray, you may discover he has a small piece of chromosome 22 missing. That indicates it’s DiGeorge syndrome. And it means he’s got a 25 percent chance of developing schizophrenia. So now you can be on the lookout for that, too.”

With such a sophisticated tool, however, came thorny ethical questions. Obstetricians knew from experience that many pregnant women who opt for genetic testing are those who, after having received a troubling result on an ultrasound, are considering abortion. The method of analysis using microscopes, which is called karyotyping, was generally considered a useful tool for helping them to make this decision because it identified large, clearly defined genetic defects. The microarray test, on the other hand, would detect not only the genetic signatures of rare diseases like DiGeorge syndrome but also many other DNA flaws whose impact on the body were not yet fully understood. This raised the possibility that babies could be aborted for having slight, potentially harmless DNA irregularities.

At the same time that Wapner and several other scientists were developing a prenatal version of the test, however, rapid progress was being made in linking subtle DNA mistakes with specific conditions. These advances emboldened Wapner — a tall, wild-haired native of Wilmington, Delaware — and a few of his influential colleagues, including Baylor University’s Art Beaudet, Emory University’s David Ledbetter, and Washington State University’s Lisa Schaffer, to articulate a new vision for prenatal genetic testing, one driven not merely by the desire to help women decide whether or not to abort high-risk pregnancies but also by the hope of diagnosing and treating a number of disorders as early in life as possible.

“Imagine if parents and doctors knew from day one that a child was going to be susceptible to autism,” Wapner says. “They might catch it sooner and provide him early intervention, which can be critical. There are all sorts of things a physician can do with this information.”

In the spring of 2007, the National Institute of Child Health and Human Development awarded Wapner a $5.4 million grant to lead the first-ever clinical study on the use

of microarray testing for pregnant women. The project, based at CUMC and involving twenty-eight partner institutions, would enroll 4,400 women to be tested. All participants would have a reason for needing special testing, such as advanced age (over the age of thirty-five), an indication of Down syndrome, or aberrations on an ultrasound. They would stipulate upfront how much information they wanted researchers to disclose to them. For instance, a woman could say that she wanted to learn about her baby's genetic susceptibility to conditions that would affect him or her as a child but not adult-onset conditions like Alzheimer's or heart disease. They could also ask researchers not to inform them of genetic flaws whose health ramifications were a total mystery.

"We knew this was going to be a stressful and anxiety-inducing situation for people," says Wapner. "We didn't want to needlessly upset them."

The final results, long awaited by obstetricians and genetic counselors, were published in the *New England Journal of Medicine* this past December. They showed that the microarray test caught dangerous genetic errors in 6 percent of fetuses who appeared to be developing abnormally in ultrasound images but for whom a karyotyping test indicated no broken DNA. "That's a lot. That's huge," Susan Klugman, director of reproductive genetics at Montefiore Medical Center in the Bronx, told the Associated Press. Even among fetuses who appeared healthy in both ultrasounds and karyotyping, the new test found that 1.7 percent of them actually had at least one genetic error that has been linked to disease.

On the basis of those results, which were widely reported last winter, Wapner and his colleagues at CUMC's Center for Prenatal Pediatrics are now offering the microarray to all pregnant women who request a genetic test.

"Lots of people are now asking for it," he says. "We find this exciting. It will make a big difference in how we can counsel patients."

Guideposts to care

December 5, the day the Columbia study was released to the public, was busy and triumphant for Wapner. In his office that morning, surrounded by framed diplomas, orchid plants, and a bag of potting soil, he reflected on the dramatic advances that have taken place in his field.

“When I started practicing in the early 1970s, we didn’t even have ultrasound,” says Wapner, who still sees patients two days per week. “Now I’m decoding babies’ genomes. And with change comes fear, of course. Some people, practitioners included, are afraid of change, and they are afraid of new information.” The new test will sometimes pick up oddities in a baby’s DNA that are too subtle for geneticists to base any firm conclusions upon.

One lesson Wapner has learned over the years, he says, is that you can never predict how people will respond to the prospect of having their baby’s genome read. Some prefer as little information as possible, even if their baby is at high risk for disease. Others request every detail and agonize over the odds. Wapner says that it is up to his patients to decide how much information they can handle. His job, as he sees it, is to dig up every bit of data he can provide them. “When they sit down and face their own situation,” he says, “I find they really are able to comprehend it and deal with it.”

Ana Zeletz, a former pediatric nurse from South Orange, New Jersey, didn’t think twice about participating in Wapner’s study. When she was thirteen weeks pregnant, an ultrasound had revealed extra fluid behind her baby’s neck, which sometimes indicates Down syndrome. A standard chromosomal test had come back normal, which ruled out Down syndrome as an explanation. But the new microarray test found a small DNA deletion that has been linked to kidney problems, diabetes, cognitive and developmental delays, and reproductive-system malformations.

Nobody could tell Zeletz precisely how her child would be affected, or even if she would be. “It was definitely heartbreaking,” says Zeletz. “But my husband and I decided we could deal with this.”

Jillian was born in October 2010, nearly seven pounds and, by all appearances, healthy. But the parents and their doctors were on the lookout for any signs of trouble. Eventually, they found some: Jillian displayed problems walking independently in her second year. So Zeletz and her husband, Stu, enrolled her in physical therapy when she was just seventeen months old. They say the microarray-test results encouraged them to seek those services, whereas they might otherwise have shrugged off Jillian’s motor delays as an example of the natural variety that exists in the timing of child-development milestones.

“I feel like it did help,” says Zeletz. “If other issues come up, I won’t be having to say to someone, ‘No, there really is a problem; she won’t grow out of it.’ It will give me more confidence in my gut instincts, and we won’t ever be chasing the problem. We’ll always be ahead of it. That does offer peace of mind.”

A science in its infancy

Human DNA is notoriously imperfect. Everyone’s genes contain typos, and most are harmless. In the Columbia study, 88 percent of the deletions and duplications detected in the genome were known to be benign.

Now that more and more DNA flaws are being linked with diseases, a new question arises: what are the chances that a flaw will lead to its associated disease? Few DNA mistakes harm us in ways that are consistent and easily traceable, like the way an extra copy of chromosome 21 will cause Down syndrome. Consider the tangled web of genetic factors involved in autism, for example. Scientists now suspect that variations in more than two hundred genes can contribute to the disorder. A child need not have all these genes to develop autism; nor does it seem likely that the presence of any one of them can ensure that he will be afflicted. Rather, a child may develop the condition only if he is carrying one or more of these broken genes and then is exposed to certain pollutants, viral infections, or chemicals that amplify the genes’ pathogenic effects.

One day, scientists hope, we will understand how these factors interact. Then a pediatrician may be able to tell a parent, based upon a child’s unique genetic profile, which environmental risks to most carefully avoid.

Wapner clearly sees his work as contributing to this future of personalized medicine. “Microarray testing will help us get to the point where we’ll be able to alter the course of a child’s health before any illness is even apparent,” he says.

Scientists are nowhere near this point yet, however. Neurological and developmental disorders in particular are proving difficult to trace to their genetic origins. In the case of autism, for example, geneticists have so far identified only 10 to 20 percent of the total number of genes thought to be involved in the condition. None of these genes is understood well enough to base any prognoses upon.

“There are limitations to what we can predict,” says Ashley Mills, the genetic counselor. “That is true of nearly all genetic conditions. We cannot completely predict how that baby is going to develop and live.”

Few of the women who took part in the Columbia study were prepared to deal with this type of ambiguity. This is apparent from follow-up interviews that the researchers conducted with some of the seventy-nine women whose unborn children were found to be carrying potentially dangerous mutations. In the interviews, many of the women said that when they agreed to participate they had failed to appreciate how murky the results could be.

“You know, they’re telling me there’s something wrong, but they can’t tell me what,” said one woman. “We wanted to know what that would mean for our son in the future. And they really couldn’t tell us.”

Said another: “I started to get really panicky that the child that I was carrying was going to be severely autistic, with seizures and schizophrenia. I would look online, and I met with a geneticist and talked to an autism expert. And frankly, nobody could really tell me. I ended up going to a crisis counselor because it was very stressful.”

About one-quarter of the women who received troublesome results would terminate their pregnancies. Of those who carried their baby to term, many now say they regret having learned about their child’s genetic flaws because the knowledge gives them so much anxiety.

“They watch their babies like hawks, always waiting for the other shoe to drop,” says Barbara Bernhardt, a genetic-counseling expert at the University of Pennsylvania’s Perelman School of Medicine, whom Wapner hired to conduct the follow-up interviews.

These comments worry Paul Appelbaum, the director of CUMC’s division of law, ethics, and psychiatry. He wonders: if parents are constantly watching to see if something is wrong with their child, will this affect the natural bonding process? And what are the implications for parents’ psychological well-being?

“These are questions that nobody has ever confronted before,” he says. “We essentially have no data yet. So we need to proceed cautiously.”

Over the next few years, Wapner and his colleagues will be keeping track of the families whose children they identified as having dangerous genetic abnormalities, in part to answer these types of questions. And they are now providing more lengthy counseling sessions to people who request microarray tests, to make sure they are comfortable with the prospect of receiving vague results.

“We definitely had to improve some parts of our process, which is probably no surprise, given that nobody had ever done this before,” Wapner says. “Now we’re explaining to parents the test’s limitations, as well as its benefits, much more carefully up front, before they take it.”

Some physicians have suggested that the microarray test ought to be reserved for specific circumstances, such as following a troublesome ultrasound, until more research is done. But Wapner bristles at the notion of limiting the test’s availability in any way.

“Were people who found out there was something wrong with their baby nervous and upset?” he says. “Yeah, of course they were. But what’s the solution? To deny adults information that is readily available about their baby? That’s ridiculous. Clearly, this isn’t right for every woman. But I firmly believe that the test should be offered to every woman so that she can make that decision for herself.”

Exaggerated risks?

Most babies are genetically healthy. In the Columbia study, no dangerous genetic flaws were detected in 98 percent of cases.

“You know what the response of these parents is?” says Wapner. “Happiness and excitement. That’s what most people are getting — reassurance that their baby is OK.”

The same December day that his study made news, Wapner left his office, ate a quick lunch with his staff, changed out of his gray-striped button-down shirt and into blue scrubs, and extracted placental tissue from Maria Lopez, thirty-six and pregnant with twins, for a microarray analysis.

Maria and her husband, John, whose names have been changed for this article, wanted the test performed because they were concerned about their twins. John's nephew is on the autism spectrum, and Maria's mother has schizophrenia, leaving her unable to function socially or to develop deep bonds with her children and grandchildren. "I would not wish it upon anyone," says Maria.

Thankfully, the test showed no significant abnormalities. Had the microarray results suggested a chance of either autism or schizophrenia in their unborn children, Maria would have considered termination.

Wendy Chung, a genetic researcher and pediatrician at CUMC, understands this. Chung treats children with special needs, some of whom can't walk or talk, and she has witnessed the strain on parents. Babies suffer, parents get divorced, families are financially ruined. Like Wapner, she believes that parents deserve to get as much information as they want about the health of their unborn children as soon as they want it.

"Many couples have said to me, 'I wish I had had the opportunity to understand this earlier,'" says Chung.

But the question on many scientists' minds is this: will parents decide to terminate pregnancies based on imperfect information?

Much as Chung supports prenatal genetic testing — she is now collaborating with Wapner to improve microarray tests for heart disease, obesity, and diabetes — this is an issue that troubles her deeply. She worries, for instance, that genetic counselors and physicians who translate test results for parents may be inadvertently exaggerating children's risks of health problems.

"A lot of the genetic data that is available has come from children who showed signs of health issues and were tested as a result," she says. "So you have to ask: how many people in the general population have some of the same DNA mistakes and yet are perfectly healthy? We just don't know. And that means our data is biased toward the worst-case outcomes."

Robert Klitzman, a prominent bioethicist and clinical psychiatrist at CUMC, is similarly worried that parents may abort babies who might have grown up healthy. And he raises other concerns. If genetic testing becomes more widespread, will there eventually come a time when the parents of children with special needs will be

regarded as irresponsible for not having tested them in the womb? Could this, in turn, have implications for the public funding of special-education services?

“We’re entering a brave new world that I’m not sure we’re entirely ready for,” Klitzman says. “To me, there’s a large question about whether we should do more research before we now offer this to absolutely everyone, regardless of whether the fetus or future child may be at any risk.”

Today, the prenatal microarray test is offered at dozens of medical institutions around the country, many of which are participating in Wapner’s research: every time a woman receives a positive result on a microarray test at one of these partner clinics, the woman is given the choice of taking part in his study. Those who agree may be interviewed about their experience, and if they bring their baby to term, its health may be tracked for the first few years of life.

“This is going to generate more information about what effects those tiny DNA deletions and duplications have on a child’s health,” Wapner says. “And then, five or ten years from now, there will be fewer and fewer DNA mistakes about which we can’t make predictions. We’re studying this topic from every angle possible.”

In the meantime, Wapner’s own staff at CUMC’s Center for Prenatal Pediatrics continues to provide the test for ten to fifteen women per week. Some of these women arrive because a doctor spotted something mysterious on an ultrasound. Others have a history of illness in their family and seek assurance that their baby won’t inherit the same disease from which relatives have suffered. Others are simply meticulous information gatherers and want the peace of mind that comes with knowing their baby is healthy.

“I’ve seen women who are afraid to have a baby because their first child has a severe disorder,” Wapner says. “Often I’m able to report back to them: ‘This baby is fine; he’s not carrying the same gene.’ So that’s a life that might not have entered this world if it weren’t for the test.”

Leaning forward in his swivel chair, folding his hands as he reflects, Wapner says: “I think that overall, the good dramatically outweighs the harm.”

Tomorrow never knows

For Trishia Bermudez, the good may well have outweighed the harm. The information she received about her baby was upsetting, but it didn't derail her pregnancy. Bermudez feels strongly that even the most sophisticated science cannot forecast human destiny. "You can have all these speculations and run all these tests," she says, "but you can't really tell how a child will turn out until he's out of the womb."

On October 24, 2012, Bermudez became a mother. Matthew weighed three pounds, fifteen ounces. He has his mother's mouth and his father's curly hair. Dad has already signed him up to play for the Knicks. As for Bermudez, "I'm just looking for him to be a happy and healthy kid and to enjoy life as it's meant to be. That's all I hope for."

Nobody can say for certain how sick or healthy Matthew will be tomorrow or decades in the future. For now, he is cooing and smiling, and his mother is drinking in every minute. "I love him dearly, no matter what the situation turns out to be," she says. "He's my son, and I love him unconditionally."

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