DEEP DIVE

The problems with prenatal testing for autism

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Illustration by Cinyee Chiu

When Maureen Bennie's son, Marc, was 10 months old, he started missing developmental milestones. He had had feeding problems since birth and developed a sleep disorder — and Bennie quickly grew concerned. "I had friends who had children around the same time," she says. "He

really was a very, very different baby in all regards."

Bennie took Marc to see a doctor but did not come home with a clear diagnosis. And when she got pregnant again when Marc was 17 months old, it didn't cross her mind that the child she was carrying might face similar challenges. Marc's autism diagnosis was confirmed when he was almost 3. His baby sister, Julia, was diagnosed about a year later at 23 months. "You just can't believe it's happening the second time around. You think: what are the chances?" says Bennie, who later founded the **Autism Awareness Centre Inc**, a company based in Canada.

Bennie wasn't aware then that autism frequently recurs in families: **Baby siblings** of autistic children are about 20 times more likely than the general population to be diagnosed with the condition. Bennie's children were born in the 1990s, and it wasn't until the following decade that scientists learned about baby siblings' high odds. Had Bennie known that Marc has autism before her second pregnancy, she says, she might have avoided getting pregnant again.

These days, with easy access to the facts about autism's recurrence and, increasingly, to tests that can detect some mutations associated with autism in fetuses, parents like Bennie are facing difficult decisions. Some parents see any knowledge about their unborn child as a bonus, and they welcome the opportunity to prepare for a child on the spectrum — and perhaps to begin therapies early. But others may worry they are ill-equipped to take on the responsibility of raising a child with developmental challenges. They may decide to have fewer children after having a child with autism or even to terminate a pregnancy based on the results of a prenatal test. In surveys, women **describe these decisions as "tortured"** and talk about a "frenzied search" for more information.

For now, though, the decisions are not based on solid facts: The information prenatal screens such as ultrasounds provide about autism is incomplete and can only hint at a heightened risk. One 2016 study, for example, linked kidney abnormalities on an ultrasound to the possible presence of **microdeletions in 17q12**, a chromosomal region linked to autism. Another study, published earlier this year, found links between excess brain fluid and mutations in **SCN2A**, a leading autism gene. Neither of these associations has been proven, however, so these parents should seek confirmation with tests that detect mutations, says **Ronald Wapner**, director of reproductive genetics at Columbia University's Institute for Genomic Medicine, who led the brain-fluid study. "Nobody should make a decision based on just a screening test; they should all have the diagnostic test," he says.

Diagnostic tests too, though, are less than definitive because researchers are still trying to understand how any given mutation might lead to autism. "Most autism is probably polygenic, meaning there are many, many genes contributing to it," says **Neil Risch**, a genetic epidemiologist at the University of California, San Francisco. Even if two people carry the same genetic variant, "one may have a very severe syndrome and the other much milder — or no syndrome at all," he says. Some parents **report feeling "even more uninformed"** after chromosomal microarray testing, which can detect some variants linked to autism, he says.

Expectant parents can opt to sequence the whole genome of the fetus, obtained through invasive procedures such as amniocentesis or chorionic villus sampling, or via noninvasive prenatal testing. Most invasive procedures require doctors to insert long needles into a pregnant woman's abdomen to obtain genetic material from the fetus — and so they raise the risk of miscarriage. By contrast, nonivastive tests need only a simple blood draw from the mother and pose no risk to the fetus.

For now, the question of which technique to use to sample fetal DNA is moot because the American College of Obstetricians and Gynecologists does not recommend whole-genome sequencing for prenatal diagnoses, other than for research purposes. Plus, "it's expensive and it takes time, and specialized people are needed for interpretation," says **Diana Bianchi**, director of the Eunice Kennedy Shriver National Institute of Child Health and Human Development. However, genome sequencing is likely to become more common as its cost drops and more people gain access to noninvasive tests.

When that happens, experts warn, it is likely to bring with it a host of thorny issues. Some say the tests may lead to more terminations — to the detriment of a society's neurodiversity. In Iceland, for example, only about two children with Down syndrome have been born each year since the introduction of prenatal tests for the syndrome in the early 2000s.

The more sensitive prenatal tests for autism become, the more likely they are to present families with increasingly challenging dilemmas. "What should we test for? What should we not test for?" Wapner says. "As our tools get better, these questions become more important; that's all worthy of a very difficult discussion."

Sensitive tests:

Before the introduction of noninvasive tests in 2011, many pregnant women skipped prenatal DNA testing because of the risks involved — unless they were older than 35 or had a family history of certain genetic conditions. Noninvasive tests analyze the mother's blood to isolate fragments of placental DNA, which is usually identical to the fetal DNA. Since the tests were introduced eight years ago, use of the invasive screening methods has dropped — **by more than 40 percent** from 2013 to 2017 in New York City, for example.

A noninvasive test for Down syndrome is highly accurate: Its sensitivity and specificity are both above 99 percent. But the usefulness of noninvasive prenatal testing for autism is limited. Some commercial labs offering the tests claim they can screen for mutations in a range of genes, including some related to autism. But only "a very small percentage of cases of autism" could be identified this way, Wapner warns.

These noninvasive tests entered the market in an unusual manner — one that Bianchi calls “upside down.” Genetic testing previously came from academic labs, and the results would then be “translated to patient care with the aid of professional society recommendations,” she says. Noninvasive tests were instead largely developed by commercial companies. Each lab screens for its own set of autism genes and makes its own decisions about which ones might be relevant. “It’s like the Wild West,” Wapner says.

Paired with sequencing of whole genomes or at least of the protein-coding portions, these tests would be more powerful. They could detect chromosomal microdeletions linked to autism, for instance, which are too small to be picked up by microarray analyses. But they might also produce more incidental and ambiguous results.

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Consider a 2017 case report of a 37-year-old woman who opted for a noninvasive test in her 12th week of pregnancy. The results were worrisome, suggesting **problems on chromosomes 13, 18, 21 and X**. Six weeks later, she had an amniocentesis and a microarray analysis — to test for fetal chromosomal abnormalities — and both came back normal. To be safe, though, the lab followed up with whole-genome sequencing of what they presumed to be fetal DNA collected during the noninvasive test. They found **a ‘saw-tooth’ pattern suggestive of cancer**. The doctors shifted their concern from her baby to her and advised her to get a body scan, which revealed lesions on her liver. The child turned out to be fine, but the mother was diagnosed with stage-four colon cancer.

“We are increasingly recognizing that the mother is sometimes the source of abnormal DNA patterns,” Bianchi says. The DNA obtained for the test isn’t always from the fetus or placenta, but rather from the mother. Yet a pregnant woman about to undergo a test is unlikely to be informed that she might get unwelcome news about her own health. In one survey of more than 300 genetic counselors, fewer than one in three **regularly warned women** of this possibility. And in a study of Dutch midwives who routinely counsel pregnant women about the tests, only 59 percent **correctly answered basic questions** about the technology.

Prenatal genetic test results can be confusing even apart from these sorts of incidental findings. For instance, it’s difficult to predict during pregnancy the effect of certain microdeletions on a child. “We may detect genetic variants which look suspicious,” Risch says, but without seeing the child later on, “we can’t really declare it as causal.” In other words, the chances of a ‘false positive’

are higher before birth. For this reason, many labs are more conservative in how they report genetic variants found before birth versus after.

For families that have older children with autism, Bianchi suggests a safer alternative: Test the couple and older children before turning the spotlight on the fetus. “You would focus your prenatal testing for the next child based on what you’ve found,” she says. If the older child has no discernible genetic involvement, it makes no sense to test the fetus. If the older child has a clear genetic condition, such as **fragile X syndrome**, however, it would make sense to test the fetus too.

Ethical challenges:

Given the lack of certainty around prenatal genetic testing for autism — and the intense emotional responses to ambiguous results — some couples **see little point in it**, research suggests. Studies also show that few couples — only 15.9 percent in one survey — would terminate a pregnancy if a prenatal test indicated their child was at risk for a severe form of autism. In that same survey, that number was almost 43 percent for Down syndrome.

Ambiguous results for autism also appear to have limited long-term impact. In a 2018 survey, Wapner and his colleagues found that parents who received ambiguous prenatal testing results **rated their babies as less skilled** at 12 months old than did parents who went home with normal results. Yet that view disappeared by the time the children turned 3 — at which point many of the parents said they had started to regret the decision to test in the first place.

Some parents who want prenatal autism tests say it’s because they would like to be prepared to start interventions as early as possible. **Jonathan Green**, a child psychiatrist at the University of Manchester in the United Kingdom, has developed a social-communication therapy that parents and clinicians can apply in babies as young as 9 months. He and his team tested the approach in 28 infants who have an older sibling with autism. They first recorded the parents interacting with their infants at home. Then a therapist sat down with the parents to go over the videos and offer feedback. “What we are aiming to do in this treatment is to alter the way that the parent is able to read and respond to the child’s communication,” Green says. The research is in an early stage, but it **seems to benefit communication skills** in both autistic and typical children, he says.

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Another early therapy under investigation targets oxytocin — a hormone involved in social bonding. Rat models of autism treated intranasally with oxytocin soon after birth show fewer autism-like behaviors than untreated rats do. There might even be ways to treat some forms of autism prenatally. In mice, researchers have used the gene-editing tool CRISPR to **correct harmful genetic mutations** responsible for Angelman syndrome. And dosing pregnant mother rats with the blood pressure drug bumetanide just before they go into labor seems to regulate the oxytocin system and mitigate autism traits in their pups.

For now, the most concrete benefit of prenatal genetic testing may simply be to help parents better understand the likelihood of autism recurring in another child in the family — something many are unaware of. The errors in understanding among parents vary depending on where they live. In one survey in the United States, more than 14 percent of parents who have one autistic child said they thought the risk of having a second child on the spectrum would be between 75 and 99 percent. In Spain, about a third of parents said the risk is exactly 50-50; in Taiwan, where there is greater stigma against disabled people, parents put the risk even lower, at about 33 percent.

The proportion of parents who decide not to have more children after one is diagnosed with autism also differs by region. In California, roughly one in three makes this decision, **according to one study**. By contrast, a study in Denmark pegged that number at just 6 percent. The researchers who led this study point out that access to free healthcare in Denmark could make having an autistic child less of a financial hardship.

Maureen Bennie now says she wouldn’t have it any other way. Had she known about Marc’s autism earlier and decided against having more children, it would have been a terrible mistake. “[Marc and Julia] really support each other. I think if I didn’t have two of them with autism, it would be a much more lonely and isolated life for them,” she says. Both of her children are doing well as adults, she adds: “A test will never tell you how well that child is going to do in life.”