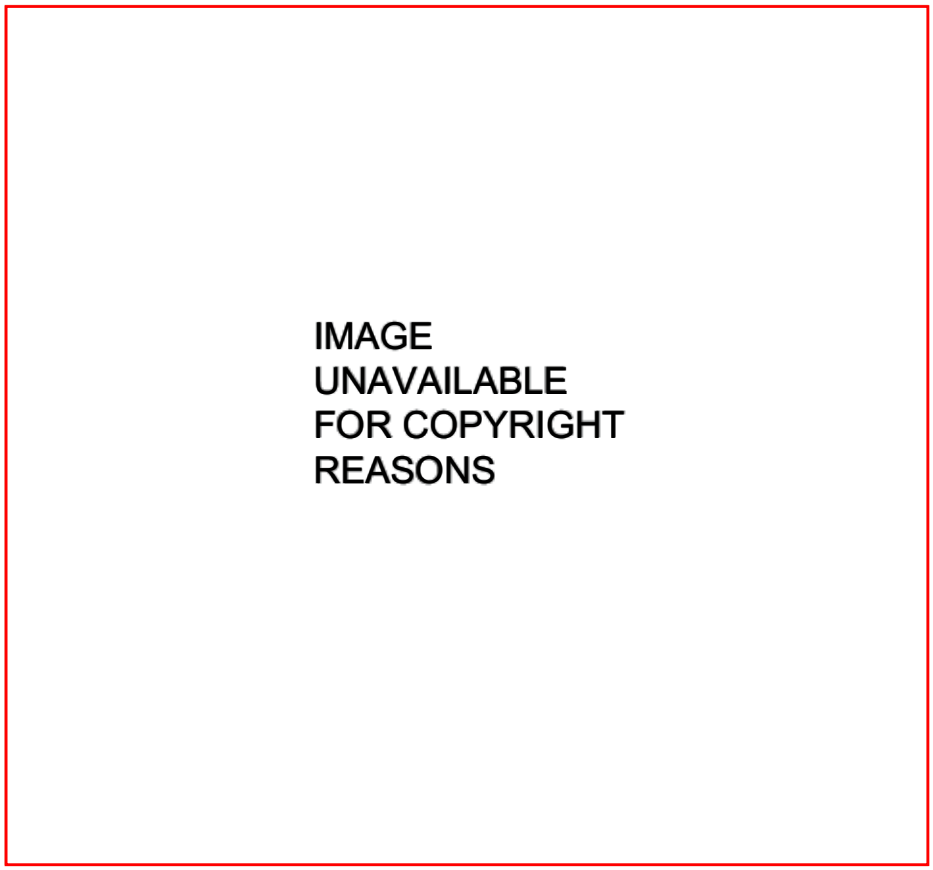
Screen test

A new technique could allow doctors to spot hundreds of potential genetic problems in unborn babies. But is it too soon to put it to use? Erika Check finds out.



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Hard to spot: current tests for genetic defects in fetuses rely on doctors anticipating what they might find.

Three years ago, a doctor told Debbie Sukin that her son had a rare and serious genetic disease called Angelman's syndrome. The diagnosis meant that her son, then just one year old, would face tremendous physical and mental challenges for the rest of his life. After the diagnosis, Sukin went to see Arthur Beaudet, a leading expert on the syndrome. Beaudet tested Sukin and her husband, and found that neither of them was carrying the genetic fault that had caused her son's disease — the condition had arisen spontaneously in the unborn child. Because there was no reason to suspect a problem, Sukin did not have any genetic tests performed during her pregnancy.

Beaudet, a geneticist at the Baylor College of Medicine in Houston, Texas, felt that Sukin's story represented a broader problem in medicine. He could see a widening gap between geneticists' growing understanding of the roots of disease and their inability to detect those diseases in the womb. The main problem is that prenatal tests can only catch genetic problems if doctors know to look for them. For Beaudet, this was simply not good enough.

To tackle the problem, Beaudet's lab has developed a way to test for more than 150 chromosomal abnormalities using a single package that costs just under US$2,000 a go. Over the past year, Beaudet has tested the technique in an unpublished clinical trial in 98 women who were at high risk of having babies with genetic problems. He was so convinced by the results that this August his clinic became the first in the world to offer the prenatal test. Beaudet predicts that the test will change the face of medicine. "This is going to cause a world revolution in prenatal and perinatal care," he claims. Beaudet's claims are perhaps optimistic — for now, the test will only be used by women who can already afford genetic screening.

Other doctors and scientists agree that the technique has huge potential, but they worry that it is too soon to use it in unborn children. They say it could pick up genetic features that are difficult to interpret, causing extra anxiety for parents-to-be. In some cases, the results mean that additional tests must be done to examine DNA from both parents, which could reveal instances of what geneticists delicately call 'non-paternity'. And others fear that the test will give parents more opportunities to terminate fetuses with undesirable traits.

Beaudet's technique is the latest development in a long line of tests that examine chromosomes in the fetus. Until recently, doctors could detect only large deletions, copies or rearrangements of chromosomes, such as an extra copy of chromosome 21, which causes Down's syndrome. Now, modern techniques such as fluorescence *in situ* hybridization, or FISH, can pick up much smaller changes.

A wider net

Beaudet's test has two powerful advantages. It picks up even smaller changes than the FISH test, and unlike FISH it simultaneously screens hundreds of chromosome areas that have been linked to disease. Doctors don't usually check for mutations in all of these areas because most of the mutations are extremely rare accidents that occur during development. Any abnormalities that show up can then be investigated further. "Our system allows you to do every known FISH test in the world at once," says Beaudet.

> "The big question is, where are we going to go with all of this?"
> — Dorothy Mitchell-Leef

The new test uses microarray-based comparative genomic hybridization, or array CGH. This is based on the principle that every cell should have two full copies of its DNA — one from the mother and one from the father. The test scans for regions of fetal DNA that deviate from this pattern because they contain too much or too little DNA. These aberrant patterns correspond to regions of the genome that are either copied or deleted, and could therefore cause disease.

Although array CGH is still very new, a few labs in Europe and the United States are already using it in the clinic. But in most instances, they use it only to look for genetic problems in children or adults who have unexplained mental retardation[1–3]. And, unlike Baylor, these labs believe that it is too early to use the test as a prenatal screening tool.

Their hesitation stems from a new understanding of human genetic diversity[4]. Researchers are finding that individuals who seem perfectly healthy often carry deletions and duplications of certain genes. The Baylor test looks for mutations across long stretches of DNA, and it could be difficult to predict the consequences of deletions and duplications of these regions in a fetus. "Until we have a much better understanding of what normal variation is, it is dangerous to launch into clinical testing in the prenatal context," says Martin Bobrow, a medical geneticist who is working with a group at the Wellcome Trust Sanger Institute near

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Informed choice: Arthur Beaudet discusses his prenatal genetic screening test with an expectant mother.

Cambridge, UK, on developing pre- and post-natal diagnostic tests based on array CGH.

Bobrow and others are also concerned about the test's power to uncover ever more detailed information about a developing baby. For instance, an old version of one genetic testing device scanned regions of the Y chromosome that allow a man to make sperm. If found in a fetus, defects in this part of the chromosome might signal that a baby boy is destined to grow into an infertile adult, perhaps leading some parents to think twice about keeping the baby. But, as Bobrow says: "Very few doctors would want to be involved in terminating a pregnancy on the basis of male infertility."

"The big question is, where are we going to go with all of this?" asks Dorothy Mitchell-Leef, a fertility doctor at Reproductive Biology Associates in Atlanta, Georgia. "I doubt if there's anyone alive today who is a perfect example of a healthy individual and has absolutely no disease." That makes it difficult to know what genetic changes really mark a fetus as abnormal, she notes.

Baby steps

Beaudet is aware of these pitfalls. But he argues that genetic counsellors have been dealing with these issues since the 1970s, when prenatal testing began. "We have always faced findings of uncertain significance in prenatal diagnosis," he says.

He adds that the results of Baylor's year-long preliminary study, described at the American Society of Human Genetics meeting on 26 October in Salt Lake City, Utah, have been reassuring. The test turned up no abnormal findings in the vast majority of pregnancies. In five of the 98 women taking part in the trial, the test uncovered obvious abnormalities — four were the tell-tale signature of Down's syndrome. In nine other cases, the test detected a genetic hiccough that wasn't known to be associated with any disease, but the variation was also found in one of the baby's healthy parents, so doctors assumed it was not dangerous.

Only once did the test turn up a variant that was not associated with disease and was also not found in either of the baby's parents. In future cases, Beaudet says, the group would like to perform a paternity test in these situations, to be sure it is looking at the right parental DNA. He admits that this raises issues of its own. "It's relatively new territory for prenatal diagnostics to have to look at data from both parents to interpret data on the fetus," he says.

But, he adds, the Baylor group will refine its methods as it learns which DNA variations are harmless to the fetus. And both Beaudet's team and other groups have performed studies to prove that the technology actually detects genetic changes that lead to disease[5,6].

Beaudet's prenatal work has followed strict ethical guidelines. But there is a legitimate worry that less scrupulous operators could develop the test to screen for genetic variations associated with desirable traits, such as height or IQ. Although more rigorous than in most other parts of the world, US regulation of genetic tests is still somewhat patchy. So some doctors are calling for self-regulation. Mitchell-Leef believes that medical societies should set policies now on what sorts of conditions should be tested in embryos and fetuses.

A. SEGALL & F. ROHWER

For Anca Segall, taking a full prenatal screening test was important for her pregnancy.

Beaudet and his group agree that such issues are important. But just as important, they say, are the voices of the pregnant women who have requested the test so far. This January, for instance, Anca Segall, a biologist at San Diego State University, had her unborn child tested. At 44, she was anxious to know upfront if her child had any major problems. "You really have to think about whether this knowledge is important for you, and it was for us," Segall says. Her test raised no red flags, and she gave birth this October to a healthy baby girl.

Sukin is not sure what she would have done had she found out five years ago that she was carrying a child who might have Angelman's syndrome. But she is sure she would have wanted to know. "We have a responsibility to share whatever knowledge is available," Sukin says. "The majority of people will have a healthy child. But when you're the statistic, your one kid is the most important thing." ■

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