MIT Technology Review

Prenatal DNA Sequencing

Reading the DNA of fetuses is the next frontier of the genome revolution. Do you really want to know the genetic destiny of your unborn child?

By Antonio Regalado on April 23, 2013

Earlier this year Illumina, the maker of the world's most widely used DNA sequencing machines, agreed to pay nearly half a billion dollars for Verinata, a startup in Redwood City, California, that has hardly any revenues. What Verinata does have is technology that can do something as ethically fraught as it is inevitable: sequence the DNA of a human fetus before birth.

Verinata is one of four U.S. companies already involved in a rapidly expanding market for prenatal DNA testing using Illumina's sequencers. Their existing tests, all launched in the last 18 months, can detect Down syndrome from traces of fetal DNA found in a syringeful of the mother's blood. Until now, detecting Down syndrome has meant grabbing fetal cells from the placenta or the amniotic fluid, procedures that carry a small risk of miscarriage.

The noninvasive screen is so much safer and easier that it's become one of the most quickly adopted tests ever and an important new medical application for Illumina's DNA sequencing instruments, which have so far been used mainly in research labs. In January, Illumina's CEO, Jay Flatley, told investors that he expects the tests will eventually be offered to as many as two million women a year in the United States, representing half of all pregnancies – up from around 250,000 mothers, mostly older, who now undergo the invasive tests. "It's unprecedented in medical testing how fast this has gone from lab research to acceptance," says Diana Bianchi, executive director of the Mother Infant Research Institute at Tufts University and the chief clinical advisor to Verinata. "It's a huge impact for any technology in its first year."

But this is likely to be just the start for prenatal DNA sequencing. The same labs and companies that launched the Down syndrome tests, like Verinata, have also figured out how they can get much more information from a mother's bloodstream, including the complete genome sequence of her fetus. That's a technical breakthrough, and maybe a commercial one, too. Pregnancy, with its hopes, anxieties, and frequent doctor's visits, could be where genome sequencing finally finds a major consumer application.

"I think that we are going to sequence the genome of everyone – of every fetus – in the first trimester, at least in part," says Arthur Beaudet, a pediatrician and head of human genetics at the Baylor College of Medicine, in Houston. Today some patients have their genomes sequenced to shed light on genetic diseases or illnesses like cancer, but one day people won't wait until they're sick. "We are already going to know the data at birth," he says.

That won't happen right away. For one thing, sorting out a fetus's exact DNA code via its mother's blood requires a huge amount of repeated sequencing, making it too expensive for routine use. (Illumina currently charges $9,500 to sequence the genome of an adult, and so far attempts to sequence fetal

DNA have cost much more.) And there are still technical problems: the fetal genome results are still not accurate enough for making diagnoses. Ethically, too, the technology is a minefield. If we learn the genetic destiny of our children while they are still in the womb, what kinds of choices might we make?

"Technically, all this is possible before we've figured out whether we should be doing it," says Jay Shendure, a genome scientist at the University of Washington. "You've got the whole genome – then what do you do with that? There are a lot of things that will have to get ironed out." Shendure works with Ariosa, one of Verinata's competitors. Last summer, his was one of two U.S. labs to demonstrate how the fetal genome might be revealed from a pregnant woman's blood. He says the studies conducted so far on fetuses, including his own study, have been retrospective – they studied blood samples stored by hospitals. But Shendure says he is now working with doctors at Stanford to implement the technology during an actual pregnancy. In other words, as early as this year the first human whose complete genetic code is known in advance could be born.

Full Genome

In 1997, a Hong Kong scientist named Dennis Lo showed that a pregnant woman's blood contains trillions of bits of DNA from her baby. The DNA comes from cells in the placenta that have died and ruptured. By Lo's estimate, as much as 15 percent of the free-floating DNA in a mother's bloodstream is the fetus's. High-speed DNA sequencing can turn those fragments into a wealth of information.

Sequencing the DNA in the blood of a pregnant woman could reveal the full genetic code of a fetus.

To detect Down syndrome, which causes cognitive and physical impairments, geneticists have typically looked through a microscope to count the number of chromosomes in fetal cells captured in a procedure called amniocentesis. An extra copy of chromosome 21 means the fetus is affected, and about 65 percent of U.S. women confronted with that diagnosis choose an abortion.

To get the same information from a few milliliters of blood, scientists use a trick first suggested by Lo. They randomly sequence millions of those circulating DNA fragments, often only 50 to 500 DNA letters long. Then, using a computer program, they line up the sequences against a map of human chromosomes. After that, it's a counting exercise: if more bits than expected match up with chromosome 21, that's evidence of an extra copy somewhere, and the fetus probably has Down syndrome. The method is clever because it doesn't matter that the mother's DNA and that of the fetus are mixed together and are, in fact, partly identical. The same approach can find extra copies, or trisomies, of chromosomes 18 and 13, as well as missing or duplicate X chromosomes – all causes of birth defects in infants.

Last July, the scientific founder of Verinata, Stanford University biophysicist Stephen Quake, showed how in addition to detecting extra chromosomes, sequencing the DNA in the blood of a pregnant woman could reveal the full genetic code of a fetus, letter for letter. Shendure's lab did something similar, as have two teams in China.

Reconstructing the six billion chemical letters of a fetal genome from those DNA fragments isn't easy. It requires lots of extra sequencing to see past the mother's genes. Shendure says the bill came to $50,000, and Quake's lab cut its experiment short after running up similar expenses. Yet the work showed that a genome readout might act as a kind of universal test not only for extra chromosomes but for common congenital diseases, too. Those are conditions, like cystic fibrosis or beta-thalassemia, that are caused when a person inherits two defective versions of a particular gene, one from each parent. There are about 3,000 such diseases whose precise genetic cause is known.

Some 200 other maladies, including some cases of autism, are caused by known duplications or deletions of larger swaths of DNA. A genome test would show all of them.

Quake says proving that a full genome readout is possible was the "logical extension" of the underlying technology. Yet what's much less clear to Quake and others is whether a universal DNA test will ever

become important or routine in medicine, as the more targeted test for Down syndrome has become.

"We did it as an academic exercise, just for the hell of it," he says. "But if you ask me, 'Are we going to know the genomes of children at birth?' I'd ask you, 'Why?' I get stuck on the why." Quake says he's now refining the technology so that it could be used to inexpensively pull out information on just the most medically important genes.

The problem is that it's simply not clear whether doctors, or parents, really want so much information. That's a challenge Illumina has already encountered in its Individual Genome Sequencing service, with which it first offered genome sequencing to medical patients in 2009. Yet the service hasn't exactly taken off. Illumina now decodes about one genome a day for medical reasons (mostly of adults with cancer or young children with mystery ailments). What's clear is that the ability to gather DNA data has outstripped the ability to understand that information, which means it has also outstripped the medical demand for it. "Showing the utility of the genome is the main challenge going forward," says Mostafa Ronaghi, Illumina's chief technical officer.

Why Worry?

Illumina's Jay Flatley is the person who engineered the Verinata takeover. The 60-year-old chief executive has led his company to $1.15 billion in revenue by besting other makers of sequencing machines and last year also resisted a hostile takeover offer of $6.7 billion from Roche, the world's largest diagnostics firm. Flatley convinced shareholders not to accept the deal, promising to make genomics a "routine" part of people's lives, increasing Illumina's profits.

Flatley has predicted for years that genome sequencing will become a reality in medicine – specifically, that every child will get its genome sequenced "at birth." So does he now think it could happen even earlier, during pregnancy? In a field with a reputation for wild, unfulfilled promises, Flatley is known as a cool realist whose predictions often come true. "It's not the technology that is limiting. It will be clearly possible to do this in two years," he says. But a commercial market is much further away than that. "Most people would have an inherently negative reaction, and for good reason."

While adults can decide whether to undergo genome sequencing, an unborn child can't consent to knowing its genes.

The problem is that having more information about a fetus's traits could present doctors and parents with a deluge of information they aren't able to understand or act on. And if they do act, that could be controversial, too. "Whole-genome sequencing could open Pandora's box," says Henry Greely, a law professor who studies bioethics at Stanford. "You'd have the whole sequence, so you might be able to look for straight nose, curly hair. How many parents are going to abort a fetus because of male pattern baldness? I don't think many. But it's probably more than zero." Greely says that because fetal DNA is detectable in the bloodstream so early in pregnancy – as early as six or eight weeks – the pregnancy could be ended relatively easily.

One doesn't have to look far for a case that could stir concerns about eugenics. This year, with its chromosome-counting test, Verinata began offering a screen for Klinefelter syndrome, in which males have an extra X chromosome. The condition – which causes reduced testosterone, feminine features, and often infertility – affects 1 in 1,000 men, so about as many American men have it as live in Pittsburgh. What's more, the symptoms can be so mild that some of those affected don't even realize it. Even so, about half of women choose to end a Klinefelter pregnancy. If Verinata's test is widely applied, many more women will have to decide whether to make that choice.

Dennis Lo believes that as fetal DNA sequencing advances, test makers should restrict themselves to reporting just the 20 or so most common serious diseases. "We are going to face the challenge of what do you look for and how do you counsel women," he says. "I think we must use the technology in an ethical fashion and should refrain from analyzing things that are not life-threatening. Like predisposition to diabetes when someone is 40 years old. We don't even know what medicine would be in 40 years, so why worry the mother about that?"

Morris Foster, an anthropologist at the University of Oklahoma who heads a panel of ethics advisors that Illumina has hired, says he and Flatley have discussed whole-genome sequencing of the unborn. "It's clearly something that is on the horizon," he says. "My advice to Illumina is, 'You are a lab receiving a physician order. You don't second-guess the physician.' The ethical advice I would give to a physician is much more complex and nuanced."

Medical groups are still struggling to formulate rules for handling genomic data for adults. And Foster says prenatal tests would make the legal and ethical obligations facing a doctor that much more complicated. For one thing, he says, while adults can decide whether to undergo genome sequencing, an unborn child can't consent to knowing its genes. And that knowledge could affect a person's entire life. "The whole sequence invariably tells you more information than you can act on," he says. "Yet because you can generate that data, it's likely that we will. Instead of stopping people from knowing things about themselves, you'd want to use it in a way that doesn't create anxiety or strain families and medical resources."

Foster fears that, if anything, people will put too much stock in genes. "I think the greatest risk is the overinterpretation of genetic findings. That doctors will think a variant associated with diabetes means you are going to get diabetes. Or that the absence of it means you are not," he says. For parents, such probabilities might seem like certainties, even if they aren't really. "If they bring a child to term with a genetic-based risk, would it cause the parents to treat the child otherwise?"

Right now, Illumina's medical genome lab takes orders only for adult DNA data, or for sick children. And its new subsidiary Verinata carries out only an improved version of fetal chromosome tests that are familiar to doctors. Even so, given the quick advance of prenatal DNA technology in the lab, Flatley thinks society may need some new laws. "What would help a lot is legislation that says you can't do certain things," he says. Partly, that argument is self-serving: a messy social debate is going to slow down genome sequencing. On the wall of the company cafeteria, next to a towering row of framed patents Illumina has won, hangs a newspaper article from 2009, in which Flatley is quoted as predicting that all newborns will have their genomes sequenced by 2019, six years from now. In it, the CEO struck a by now familiar note. The limits to the technology of DNA sequencing, and to his company's prospects, "are sociological," he said. The only constraints are "when and where people think it can be applied."

Credits: Frank Rogozienski | Wonderful Machine, Max Whittaker, Shane Brown

Tagged: Biomedicine, Illumina, DNA sequencing, 10 Breakthrough Technologies, Down Syndrome