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A Brave New World of Prenatal DNA Sequencing

Companies count DNA sequences in the blood of high-risk moms to test for Down syndrome and other large-scale disruptions, but they could do more.

By Susan Young on January 30, 2013

Prenatal testing could become safer and more informative in the coming years thanks to technologies developed to survey a fetus's genome from the mom's blood.

Illumina, the world's leading manufacturer DNA sequencing machines, is now moving aggressively into the field of prenatal sequencing. Earlier this month, the company announced that it would purchase startup Verinata, which launched its prenatal chromosome counting system last spring. The acquisition follows a string of moves by Illumina to increase its presence in prenatal medical diagnostics (see "DNA Sequencing Leader Buys into Prenatal Testing").

Conventional methods for checking a fetus's genome for abnormalities require invasive procedures, such as using a needle to withdraw some amniotic fluid surrounding the fetus or some cells from the placenta, methods that can sometimes cause a miscarriage.

These tests mainly focus on abnormal numbers of certain chromosomes (such as the condition that causes Down syndrome) and are offered only to women with high-risk pregnancies. But much more could be gleaned from the fetal DNA floating in mom's blood, and some believe that such tests will soon be available to many women.

The first company to offer prenatal screening from a mother's blood was Sequenom, which made its MaterniT21 test available in October 2011. Last year, doctors used Sequenom's test to screen more than 60,000 pregnancies for abnormal numbers of chromosomes.

To search for these chromosome disorders starting from 10 weeks of gestation on, the companies sequence the bits of DNA floating in a sample of the mother's blood.

Around 12 percent of the DNA in her blood belongs to her fetus. The tests do not distinguish which sequences belong to mom or the unborn baby. Instead, counting algorithms are used to search for small but significant changes in the amount of one chromosome to another. DNA sequencing machines read out strings of DNA letters a few dozen base pairs long, and the mix of mom's and baby's sequences are

then sorted by chromosome. If there are more sequences than expected belonging to a particular chromosome, then the fetus probably carries an extra copy.

In a normal blood sample, around 1.36 percent of the cell-free DNA should belong to chromosome 21, says Alan Bombard, chief medical officer of Sequenom. When a fetus has Down syndrome, the test usually finds 1.4 percent. “That’s not much difference, but you are counting it 10 million times,” says Bombard.

Medical experts are also taking note of the burgeoning field. In November, two medical societies released a joint opinion that the noninvasive DNA tests could be used to screen high-risk pregnancies, which include cases where the mother is over 35 or has had previous pregnancies with chromosome abnormalities (see “Medical Society Approval for Noninvasive Prenatal Testing”).

The technology stands to change the whole of prenatal medicine, says Nancy Rose, a clinical geneticist who chaired the joint-opinion committee. “This is a very early use of the technology and it will only get better,” says Rose. Still, the committee recommends the tests be offered only to women with high-risk pregnancies, not to those with average or low-risk situations: “There just isn’t any data on low-risk patients,” says Rose. “We don’t have good information to give these women without having large prospective trials. It’s a reasonable stance to be cautious.”

Another reason for caution for using the tests for pregnancies of low or average risk is that any indication of a chromosome disorder would need to be confirmed with an invasive procedure such as an amniocentesis, which can cause a miscarriage. “Many folks’ biggest concern is a false positive,” says Bombard.

Still, Illumina sees a much bigger market in the future. “With these noninvasive approaches, eventually we will be able to test everyone,” says Greg Heath, who manages Illumina’s diagnostics division. And one day, the tests could screen for a much greater number of disorders.

While the noninvasive prenatal testing companies are currently offering tests for whole chromosome errors, they are looking to a future where they can get a much more detailed view of the fetal genome and perhaps even tell parents about whether their unborn baby carries particular gene mutations.

“We are just getting started with [abnormal numbers of five specific chromosomes], but we will be expanding this to single gene disorders,” says Bombard. “This is just the first step in what we hope to be a long road to help patients,” he says.

Illumina and Verinata say they will also pursue more refined fetal genetic analysis. “The limit is the cost of sequencing, not something fundamental about the approach,” says Rich Rava, chief scientific officer of Verinata. “We’ve always looked at it as whole-genome technology,” he says.

“As sequencing gets cheaper and cheaper, if you wanted to look at a particular mutation, say, in the cystic fibrosis gene, you may be able to do that in the future,” says Heath.

As the technical advances come, the ethical issues remain to be addressed. “Tackling just that single

gene gets into different issues." says Heath. With a whole-genome sequence from a fetus, how do families handle knowing that their unborn child carries a genetic risk that may cause problems only late in life compared to mutations that will likely cause an early death?

"If there is the probability that a baby is going to die within the first six months of a short and painful life, you might make a different decision," says Heath. "We think any choices should be informed choices."

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