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By Monica Heger

Citing the success of non-invasive sequencing-based prenatal tests for fetal aneuploidies, several researchers at last week's American Society of Human Genetics conference in San Francisco reported that they are looking to expand the technique to screen for other genetic disorders, though they acknowledged that a number of ethical challenges must be addressed before the approach enters widespread practice.

Currently, a number of US and European companies are offering tests for fetal trisomies, including Sequenom, Verinata Health, Ariosa, and LifeCodexx. Additionally, Natera plans to launch a test this year.

Sequenom, Verinata, and LifeCodexx all use shotgun sequencing and chromosome counting to call fetal aneuploidies. Ariosa uses a targeted sequencing strategy to evaluate chromosomal copy number. Natera also uses a targeted sequencing protocol, but evaluates SNPs rather than copy number (*see story, this issue*).

These tests are being adopted so quickly in prenatal care that John Stuelpnagel, executive director at Ariosa, estimated during a roundtable discussion at the conference that they are currently among the fastest-adopted clinical tests in the US. Sequenom alone has forecast that it will run 50,000 of its MaterniT21 Plus tests this year.

Fetal sequencing "will move soon to sub-chromosomal aberrations, then single-gene disorders, and eventually whole-genome sequencing," said Diana Bianchi during a presentation at the

meeting. Bianchi is executive director of the Mother Infant Research Institute at Tufts Medical Center and a member of Verinata's scientific and clinical advisory board.

Technology Advances

The technology is advancing so quickly that many researchers think it could soon be used to screen for many more disorders aside from aneuploidies.

A likely next first step is to screen for sub-chromosomal duplications and deletions, according to Bianchi.

Speaking at the ASHG meeting, Bianchi noted that Verinata researchers have already demonstrated that they can detect fetal sub-chromosomal duplications and deletions through sequencing.

In a poster presentation, Verinata's Anu Srinivasan showed how the company used a binning method and deeper sequencing to detect a 20-megabase pair deletion on chromosome 7 and a 38-megabase pair duplication on chromosome 6 from two different samples.

In a departure from the chromosome-counting method that the company uses to detect trisomies via shotgun sequencing, it divides the DNA into 1-megabase pair sized bins, similar to binning approaches for whole-genome haplotyping. Additionally, the team sequences deeper — to around 8x coverage versus the 0.5x coverage that it uses to screen for trisomy.

The Verinata team first tested the method by creating a mixture of known samples from a mother's DNA and her son's DNA and found that the 20-megabase pair deletion in chromosome 7 could be detected in mixtures down to 5 percent concentration of the son's DNA.

Next, they applied the method to a known clinical sample from Verinata's validation study MELISSA, and were able to detect a 38-megabase pair duplication on chromosome 6 in the fetal genome. In this case, the fetal fraction of DNA was around 12 percent.

Srinivasan said that the technique is still in early research and would require much more validation before it could be used clinically.

Additionally, several research groups have demonstrated that it is possible to sequence an entire fetal genome from maternal plasma, including Dennis Lo's group at the Chinese University of Hong Kong and Jay Shendure's team at the University of Washington (*IS 12/14/2010* and *GWDN 6/6/2012*).

While most think that sequencing entire fetal genomes is still a long-term prospect, Tufts' Bianchi said that sequencing to detect sub-chromosomal aberrations and even single-gene disorders would be possible in the near future.

Allan Bombard, Sequenom's chief medical officer, also spoke at the ASHG meeting and agreed that "single-gene disorders are clearly the next opportunity for this emerging field."

Ethical Issues

Expanding sequencing-based prenatal testing beyond trisomies raises a number of ethical issues, however. For instance, the use of sequencing to screen even for a single serious disorder such as fragile X syndrome poses a host of challenges, Stanford's Norton said during a roundtable discussion on prenatal sequencing.

While fragile X could be a good target for screening, she said, "the phenotype in girls is very broad," so a positive result doesn't mean that a physician will be able to make a prediction about how the disorder will manifest itself.

This is the case for many disorders, even Mendelian ones, she added, and in the case of fetal sequencing, there is no phenotype to correlate with the genomic information to make better predictions and informed decisions.

Gregory Heath, senior vice president and director of Illumina's Diagnostics business unit, agreed that there is a danger in trying to predict "soft phenotypes" such as autism based on sequencing data gleaned from noninvasive testing. Even Mendelian disorders are hard to predict in a fetus, particularly if the disorder is rare enough, he said.

Expanding into whole-exome or whole-genome sequencing would pose even more challenges because there are so many variants of unknown significance. Even in kids with rare disorders where the phenotype is known, exome or whole-genome sequencing often does not uncover the causative variant.

In cases where there is no phenotype data, "interpreting sequencing results of a fetus of which you know very little is very difficult," Bianchi said.

Additionally, said Jaime King, an associate professor at the University of California Hastings College of Law, it will be difficult to adapt informed consent and genetic counseling to the requirements of broad noninvasive testing.

"Ethicists have expressed concern that women won't receive adequate counseling" about the capabilities of such tests and their predictive power, King said.

Nevertheless, both Bianchi and Norton noted that noninvasive prenatal sequencing tests for trisomy have been received favorably by their patients. Tufts currently offers the tests from Sequenom, Verinata, and Ariosa; while Stanford offers Ariosa's test.

Norton said in an email that in the six to eight months that Stanford has been offering Ariosa's test around 28 percent of the 961 women that have been offered it have decided to receive it.

Of women who test positive on state screening tests, 43 percent opt for the Ariosa test, compared to just 22 percent of women who are offered the test because of age or who are simply weighing all their options, she added.

Norton said that reasons for declining included cost, wanting the nuchal translucency ultrasound that is part of the state test, doctor preference for state screening, and a lack of published guidelines indicating the test is appropriate.

Bianchi said that introducing the noninvasive screening tests has already led to a "dramatic decline in invasive procedures." At Tufts, women who are classified as being at high risk for fetal aneuploidies are offered the option to receive a noninvasive sequencing test. If the screen is negative, women are advised to receive no further testing. If results are positive or uninformative or borderline, women are advised to receive a confirmatory diagnosis — either amniocentesis or chorionic villus sampling.

Similar models have been adopted at other institutions offering these screening tests, and a recent study in the *Journal of Managed Care Medicine* of the cost-effectiveness of Verinata's test found that it could reduce invasive tests by 72 percent (*CSN 5/2/2012*).

What has not yet been studied is how such tests could impact abortion. However, both Norton and Bianchi asserted that having access to the information does not necessarily mean a woman will terminate her pregnancy.

In fact, said Norton during the roundtable discussion, knowing "affects planning for consequences," and can enable women to choose a specific hospital for delivery where specialists may be on hand to provide appropriate care right away.

Bianchi added that she has seen many women who have no intention of ending their pregnancy be very enthusiastic for noninvasive testing. "Women want the information, and they want it noninvasively," she said.

Additionally, she said her lab has started research on prenatal treatment of Down syndrome and early results suggest it could be treated prenatally with antioxidants.

Noninvasive sequencing tests could also impact women's reproductive rights, said UC Hastings' King. In 2011, twice as many laws were passed putting restrictions on abortion than any other year, she said.

In some states the laws are so restrictive that if a woman were to go through the current protocol for prenatal screening, which involves a blood serum test, ultrasound, and an invasive diagnostic procedure if one or both of those tests are abnormal, by the time she found out for sure it may be too late to legally have an abortion.

Because sequencing-based tests can be done so early in pregnancy, at 10 weeks, they have the ability to afford a woman more time to get effective counseling and make an informed decision, she said.

Noninvasive prenatal tests could be "a valuable tool to help women retain their reproductive rights and options," King said.

Monica Heger tracks trends in next-generation sequencing for research and clinical applications for GenomeWeb's *In Sequence* and *Clinical Sequencing News*. E-mail Monica Heger or follow her GenomeWeb Twitter accounts at @InSequence and @ClinSeqNews.

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