New Carrier Screening Test and Fetal Genome Discovery Could Impact Preconception, Prenatal Genetic Counseling

A new preconception carrier-screening test, described in the Jan. 12 issue of *Science Translational Medicine*, accurately identifies a couple’s risk of conceiving a child with any one of 448 catastrophic childhood genetic diseases. The test, developed by the National Center for Genome Resources (NCGR; Santa Fe, N.M.), could significantly alter how preconception genetic counseling is performed.

Current carrier testing recommendations apply to only five diseases in selected populations. But the present study assessed the ability to detect mutations on 437 genes that cause 448 severe, recessive childhood diseases. The developers included severe and highly penetrant diseases on the panel for which clinical utility of testing was clear in that testing results would change family planning or affect antenatal, perinatal, or neonatal care. Milder recessive disorders such as deafness, adult-onset diseases, and conditions lacking evidence of causal mutations were omitted.

Using 104 unrelated DNA samples, the researchers found the average genomic carrier burden was 2.8, with a range from zero to seven. The test had 95 percent sensitivity and 100 percent specificity.

“We are at an inflection point. The practice of genetic medicine is pretty ill-equipped to deal with a test like this,” says lead author Callum Bell, Ph.D., director of human genomics at NCGR and a co-developer of the test. “We expect the patient to be negative with general population screening. . . . But, with a test like ours we expect people to be positive to at least one. We are changing the expected outcome.”

The test is expected to become commercially available on a research basis through a CLIA lab established at Children’s Mercy Hospital (Kansas City, Mo.) in the third quarter of 2011. There are no current plans to submit the test for approval from the Food and Drug Administration. Final pricing is a “moving target,” says test co-developer Stephen Kingsmore, M.D., director of the Center for Pediatric Genomic Medicine, Children’s Mercy Hospital, but is expected to be less than $1 per tested condition. He expects the price to drop post-launch, while the scope of the test panel will increase. The panel currently tests for 568 diseases and could reach 750 in a couple years, Kingsmore tells *DTTR*. 

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– Callum Bell
While analytical costs will decrease with next-generation sequencing improvements, test interpretation, reporting, and genetic counseling will add additional costs.

“Technically we can provide much more information than we can digest,” says Bell. “When we counsel a family for one disease it may take 30 minutes to one hour. But, with hundreds of diseases the whole model has to be changed. It is not possible to talk about every disease.”

The authors encourage discussion of ethical, legal, and social implications of comprehensive carrier testing and say the discourse will influence the scope and setting of clinical adoption.

“Testing of donors for the in vitro environment is expected to happen fairly quickly and easily. Special populations will also be early adopters—testing of special populations with a family history of inherited diseases or in populations with higher rates of diseases,” says Kingsmore. “Each market will be a limited launch and then we will broaden to general populations through health care providers.”

Kingsmore describes the testing as “scalable,” processing 192 sample batches at a time. He says the short-term goal is 20,000 tests per year in the next two to three years.

While the test developers are only interested in preconception testing, the discovery that the entire fetal genome is present in maternal plasma leads some to speculate about a broad array of noninvasive prenatal genetic testing.

**Fetal Genome Discovery Could Alter Prenatal Diagnostics**

Researcher Dennis Lo, FRCPS, in a proof of concept study published in the Dec. 8 issue of *Science Translational Medicine*, sequenced maternal plasma DNA and discovered the entire fetal and maternal genomes were represented in maternal plasma at a constant relative proportion of 10 percent.

The discovery opens the door for using genome wide scanning to noninvasively diagnose fetal genetic disorders prenatally. Unlike conventional procedures, including amniocentesis and chorionic villus sampling, testing using maternal plasma DNA poses no threat to the fetus, and it could simultaneously test for multiple diseases. But it also raises ethical, legal, and social issues including how to provide genetic counseling for such a complex test and the appropriate spectrum of fetal genetic characteristics or abnormalities that can be ethically tested.

The authors speculate one direction for future development would be to apply the approach specifically to multiple disease-related genomic regions by targeted sequencing approaches, which would both reduce the cost and target counseling to a focused group of disorders.

While Lo’s discovery is not immediately applicable in clinical practice, researchers acknowledge that broad access to powerful genetic tests, such as those reported in both of these recent papers, reopens public debate.
“The two new studies in *Science Translational Medicine* expose the need for cautious application of rapidly emerging genome sequencing technologies to preconception carrier testing and prenatal genetic diagnosis,” wrote Laird Jackson, M.D., Drexel University College of Medicine, in an accompanying perspective piece. “Broad indiscriminate implementation of evolving genomic technologies, especially for preconception (carrier) and prenatal (fetal) testing for genetic disorders, raises concerns of unintended consequences of our technological triumphs that might undermine their purpose of improving human health.”

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