NIH Initiative Pilots Genome Sequencing in Newborns

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—By Jen Uscher, special to the *Reporter*

Questions about how best to use genomic data are taking on greater urgency as gene sequencing becomes faster and less expensive, leading to increasingly widespread adoption in clinical settings. As genomics continues to advance, key challenges include ethical use of genomic information and helping families understand test results. With funding from the National Institutes of Health (NIH), researchers at several medical schools and teaching hospitals are investigating whether genomic sequencing can improve health care for newborns and potentially help answer some of those questions.

"The privacy and ethical issues surrounding participation in genomic research are already complex for individual, autonomous adults," said Stephen J. Heinig, AAMC director of science policy. "When you're sharing information with parents about their infant children, the issues become even more daunting."

As part of the Genomic Sequencing and Newborn Screening Disorders program, research teams at four sites each will receive approximately $6 million over five years to look at the technical, clinical, and ethical implications of using whole genome sequencing or whole exome sequencing—or sequencing parts of the genome that are known to code for proteins—in newborns. The researchers, who launched their projects last September, will collect DNA samples from newborns using a sponge inside the mouth, a traditional blood test, or a heel prick. All newborns will receive the standard test that screens for about 30 genetic, endocrine, and metabolic disorders and is routinely performed on almost all infants in the United States. Until now, DNA-based testing has been used primarily as a second-tier screening method—to confirm, for example, cases of cystic fibrosis.

"One of the things we're interested in exploring is how genome sequencing could be applied in a public health screening-type paradigm," said Anastasia Wise, Ph.D., an epidemiologist in the National Human Genome Research Institute Division of Genomic Medicine and project scientist for the initiative. "For instance, could it replicate or augment current newborn screening testing?"

The NIH wants to find out how genome sequencing could affect the clinical care of newborns. "If you're screening for more disorders, how do you use that information to inform treatment?" asked Tiina Urv, Ph.D., a program director in the Intellectual and Developmental Disabilities Branch of the Eunice Kennedy Shriver National Institute of Child Health and Human Development and program officer for the project.

At the University of North Carolina at Chapel Hill (UNC), a research group is sequencing the genomes of 200 healthy infants and 200 infants and young children with suspected or diagnosed genetic disorders. The children's parents will be randomized into two groups. One group will receive only results pertaining to conditions that already are included in standard newborn screening tests and genetic conditions that can develop during childhood for which treatment is available. A second randomized group will receive this information, as well as the option of learning about results pertaining to other conditions that can develop during childhood but are not treatable in the traditional sense and conditions that would not appear until adulthood—for example, BRCA-1 and BRCA-2 gene mutations that increase the risk of breast cancer. The researchers also will create a decision tool that can be accessed online or as software downloaded to a mobile tablet to help parents understand what the test results mean.

Some parents could receive test results that have implications for other family members, said Cynthia M. Powell, M.D., professor of pediatrics and genetics, chief of the Division of Pediatric Genetics and Metabolism at UNC School of Medicine, and the co-principal investigator of this study. If a test shows a baby carries a BRCA-1 or BRCA-2 gene mutation, for example, the parent may wind up finding out that he or she carries it, too, and may seek treatments that reduce the risk of developing cancer.

When clinicians report test results related to adult-onset conditions to the parents, however, they are potentially taking away the child's right not to know that information. "A lot of people have thought long and hard about the

December 2013 Home

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ethical issues involved in this, as have we, which is why we are doing it as part of a research study," Powell said. "We're not saying that whole genome sequencing is ready for broad use on a clinical basis, but it will be fascinating to find out what parents who participate in the study think about it."

A research team at Children's Mercy Hospital in Kansas City, Mo., will study the benefits and risks of rapid whole genomic sequencing technology in acutely ill newborns in the neonatal intensive care unit (NICU). Using a genome sequencing approach called STAT-Seq, the hospital can perform the test and receive the results in two days instead of weeks or months. Speeding up the turnaround time for these tests is important because it could lead to a diagnosis and appropriate treatment, which could save a baby's life, according to Stephen Kingsmore, M.B., Ch.B., D.Sc., director of the institution's Center for Pediatric Genomic Medicine and the principal investigator for the study. In some cases, genome sequencing makes it possible to provide diagnoses for babies with previously undiagnosable conditions.

Kingsmore and his team will sequence the genomes of 500 infants in the NICU and examine whether their methods increase the number of diagnoses and decrease the time it takes to reach a diagnosis. They also will look at whether the diagnosis changes the clinical treatment of the newborns. Kingsmore noted that in one recent case his team was able to find the gene defect that was causing a baby's liver failure. The infant received treatment, which cured the condition.

While incorporating sequencing tests into newborn care has benefits—particularly for children who receive a diagnosis through the initiative— a key challenge is determining how to protect and track genomic data over time, said Ross McKinney Jr., M.D., director of the Trent Center for Bioethics, Humanities, and History of Medicine at Duke University School of Medicine and a member of the steering committee for the AAMC's Forum on Conflict of Interest in Academe.

"As we gain a better understanding of the genetic variants that play a role in various diseases and conditions, do we go back periodically and review the sequences in the light of our improving understanding of what they mean? And if that's an obligation, who will carry it out?" McKinney said. "We will want to define pretty tightly who owns the data and has the right to access it and how it is stored."

In addition to UNC School of Medicine and Children's Mercy Hospital, Brigham and Women's Hospital in Boston and University of California, San Francisco, also are participating in the initiative.