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Brigham and Women's, Boston Children's to Evaluate Benefits and Risks of Infant Clinical Sequencing

By Molika Ashford

This is the first in a series of profiles of centers awarded grants this year by the NIH under the Genomic Sequencing and Newborn Screening Disorders research program.

A team from Brigham and Women's Hospital and Boston Children's Hospital plans to use an initial $6 million grant from the National Institutes of Health in a randomized trial beginning next year to explore the benefits and risks of genome sequencing in newborn babies.

The effort is one of four projects funded to a total of $25 million over 5 years by the NIH's National Human Genome Research Institute and National Institute of Child Health and Human Development this month to explore the potential for genome sequencing to improve newborn healthcare.

Led by Brigham and Women's Hospital's Robert Green, and Boston Children's Hospital's Alan Beggs, the study will enroll 480 newborns and their families. The researchers will use sequencing to assess the infants' risk of future diseases and how such information affects medical care and the relationship between parents, children, and their doctors by comparing randomized groups who receive sequencing to those who don't.

Green told *Clinical Sequencing News* this week that the group's interest in looking at infant sequencing began to develop soon after Brigham and Women's began another large-scale clinical sequencing study called MedSeq, funded under another NHGRI effort, the Clinical Sequencing Exploratory Research program (*CSN 1/4/2012*).

Unlike MedSeq, the new infant study, called BabySeq, will be a joint effort — led equally by Brigham and Women's and Boston Children's Hospital.

"We worked intensely developing our protocols pipeline for reporting results back to both specialists and non-specialists in the MedSeq project," Green said. "And we had also already been collecting some preliminary data — surveying more than 500 parents on a newborn unit and asking if this is something they would want."

"So with that preliminary data and collaboration with Boston Children's we started brainstorming and we came up with the idea of this randomized trial of newborn sequencing in two different populations: in sick babies in the neonatal intensive care unit and in healthy babies."

The study protocol has not been finalized yet, nor has it been approved by the group's institutional review board. But assuming that the team's initial plans are approved, the researchers will start next year recruiting about 480 newborns and their families — half from Boston Children's NICU and half from well babies born at Brigham and Women's.

Each group will be randomized to receive either conventional state mandated newborn screening, or additional whole-exome or whole-genome sequencing to look for alterations associated with things like birth defects, predispositions to future medical conditions, and predictions about responses to certain drugs.

Based on finalized protocols approved by the projects' IRB, researchers will then return such information to parents and pediatricians.

According to Green, the group intends to eventually move the project to whole-genome sequencing, but may initially start with exome sequencing.

Beggs told *Clinical Sequencing News* this week that the team is hoping to work with newly-formed Claritas Genomics — a Life Technologies and Boston Children's Hospital joint venture focused on developing diagnostic tests for inherited pediatric diseases (*CSN 1/8/2013*) — to perform sequencing in the study.

Both Beggs and Green said that decisions about whether participants will be able to choose what types of results to receive, as well as overall limits in terms of what types of information will be returned to families in the study, are yet to be determined.

According to Green, the team hopes to use protocols developed over years of genomics research to track a wide range of outcomes including health outcomes; behavioral outcomes, such as how people respond to learning about their child's genomic information; and social outcomes, like buying insurance, taking more vitamins, or investigating on the web.

"If our protocol is to share information with pediatricians," Green said, "we would also track what pediatricians think about the information, how well they understand or misunderstand, whether they act on it, and what the downstream consequences — even economic consequences — are of those actions."

"The idea is to try to take as broad a view as possible of benefits and risks."

Beggs said that from his perspective, the hope is that the study will help tease out where things stand in the balance between costs and overall clinical benefits of sequencing in this population.

"We all know at this point that some worthwhile findings will result from something like this and that there will also be a lot of instances where we don't find anything worthwhile and some where we find things of unknown significance, and we worry and wonder, of course, if we could find anything that would be harmful," Beggs said.

"We also know there is a cost and a benefit to this," he said, and we know cost is rapidly dropping and at some point it's pretty clear that the balance is going to be tipped in favor of the benefits."

"I don't think we are there yet, but this is a five-year project … and I think the main thing we hope to get out of this is to find out how close we are to that tipping point and how we are going to do things, mechanically, when we get there," he said.

As with NHGRI's CSER grantees, the projects in the new Genomic Sequencing and Newborn Screening Disorders research program will each be divided into three sections — a first section focusing on sequencing and analysis, a second section dealing with research related to patient care, and a third looking specifically at the ethical, legal, and social implications of using genomic information in the newborn period.

While Green said the four funded groups will also be somewhat integrated, it's not yet clear whether there will be as strong a mandate for collaboration among the projects as there has been in the CSER program. The teams have their first organizing call in a few weeks.

"I think it's important that when NIH announced these grants they described them as pilot studies," Green said. "No one is cavalier here and we all recognize this is a new area and there are great sensitivities in giving information about a child to their parent that the child himself or herself might not wish to know once they reach the age of maturity."

"That uncertainty means this is a good thing that NIH is leading in terms of carefully exploring the benefits and risks and looking at it from different angles and emphases in the different projects."

Green said that the project may yield less in terms of hard medical outcome data than it does in information about the process of sequencing newborns in the clinical realm. "This isn't like a clinical trial where at the end of five years we are going to have 'the answer'," he said. "These numbers are still relatively small and most genomes will be relatively uninteresting.

"It will be the exceptions that really push this in the direction of benefit or harm and having to grapple with this in these pilots — with what it means to analyze a clinical genome in a child, give a report, fit it into an EMR, field questions from a physician who is looking at a genomic report maybe for the first time in his or her career — we are going to learn about and report on quite a number of things that can facilitate genomic medicine beyond just the outcomes of these 480 people."