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NIH Newborn Sequencing Projects' Lessons, Next Steps Highlighted at Meeting

Jun 26, 2019 | Monica Heger

SAN FRANCISCO – As researchers wrap up four projects funded by the National Institute's of Health in 2013 to investigate the use of sequencing in newborns, there seems to be clarity that sequencing is a great tool for helping to quickly diagnose acutely ill newborns but that it might not be quite ready to replace standard newborn screening tests implemented by states.

And, while researchers have demonstrated that newborn sequencing can identify disease risks early in life without causing families undue stress, there is still some debate about how to implement such testing.

During a National Institutes of Health public session this week, which was webcast, researchers who led the NIH's newborn sequencing program, called NSIGHT, discussed findings from the study, next steps, and what they saw as sequencing's role in screening and diagnosing acute disease in newborns.

Already, several researchers are expanding on their studies, including a push by Rady Children's Hospital to expand the use of sequencing to diagnose acutely ill infants to other hospitals in California; and the launch of a Preventive Genomics Clinic at Brigham and Women's Hospital to use sequencing to screen healthy adults.

One area where sequencing has already proven itself is for newborns and infants admitted to the neonatal intensive care unit. Stephen Kingsmore, president and CEO of Rady Children's Institute for Genomic Medicine, said that initial results in 2015, when his team first began the NSIGHT project at Children's Mercy Hospital "flabbergasted us." Of 35 babies to receive whole-genome sequencing, 20 received a diagnosis, 11 had a change in management, four had improved outcomes, and one life was saved, he said.

Since then, Kingsmore has continued to expand the trial and also moved to Rady Children's. He noted that the team finished its NSIGHT 2 study in October, which enrolled 213 infants who were randomized to either rapid whole-genome or rapid exome sequencing, unless the infants were

extremely ill and then they received ultra-rapid whole-genome sequencing. The main goal of that study was to determine the physicians' perceived clinical utility and benefit of sequencing, to compare diagnostic rates between whole-genome and exome sequencing, and to determine how the parents felt about the sequencing process.

The researchers are still analyzing results, but overall, both clinicians and parents felt that both whole-genome and exome sequencing were useful, Kingsmore said. Clinicians of the kids who were the sickest and received ultra rapid whole-genome sequencing were the most likely to say the test had clinical utility. The parents of those kids felt the same way, Kingsmore said. That showed that even when parents got a negative report, they still felt the test was useful, he said.

Kingsmore added that the group is continuing to analyze the data and is doing a cost-effectiveness study. From a previous study of 42 infants, the team found that sequencing resulted in a net healthcare savings of $128,544.

The Rady team last year received $2 million from California for a pilot dubbed Project Baby Bear to provide rapid WGS as a first-line diagnostic test for newborns in the NICU at six participating hospitals. To date, Kingsmore said that about 97 infants have enrolled, and so far there has been a 52 percent diagnostic rate and a change in management for 41 percent of the babies.

To move beyond California, Kingsmore said that Rady last year partnered with Vermont Oxford Network and launched the Vermont Oxford Rady Children's Genomic Network to provide educational resources to multidisciplinary neonatal teams in other states and around the world to learn about genomics. Kingsmore said that so far, groups from 29 US states and nine different countries have joined. Resources include webinars, conferences, workshops, and online resources.

A major challenge in implementing the protocol outside of the NSIGHT setting is that neonatologists have to deal with much fewer resources. "During NSIGHT we had medical geneticists, genetic counselors, program managers, nurses," Kingsmore said. "But now, suddenly we're confronted with real medicine, where you don't have the support staff and a busy neonatologist trying to decide what to do and whether the baby will benefit."

While sequencing acutely ill newborns has demonstrated its utility and is moving toward routine use in some NICUs, sequencing as a standard newborn screening test is not ready for prime time, according to Jennifer Puck, one of the principal investigators of the NBSeq project and professor at the University of California, San Francisco.

Newborn screening "focuses on urgent, infant-onset, and treatable disorders that are only detected by newborn screening," and the "significant public health benefits have allowed screening to be performed without explicit parental consent," Puck said. As such, the bar is necessarily high for testing. "Medical need, not technology, should be the driver of population-based screening," she said.

The NBSeq researchers decided to use exome sequencing, but they analyzed just 78 genes associated with inherited metabolic disorders, which are typically screened for in newborns in California using mass spectrometry from dried blood spots. Screening by mass spec is "extremely effective," Puck said with greater than 99 percent sensitivity and specificity.

The researchers sequenced 1,190 samples, 178 of which served as a validation set to develop an automated screening analysis pipeline. From the test set of 1,012 samples, 674 were known to have an inborn error of metabolism. The sequencing pipeline detected 571 and missed 103. In 53 of the missed cases, the sequencing pipeline found only one pathogenic variant — the researchers required two to be identified in order to make a positive call.

Some of the missed variants included deletions, which were not detectable by exome sequencing. In another case, a potential variant was found in an intronic region just upstream a relevant disease. The prediction programs did not predict that it would impact the gene, but upon further testing, the researchers discovered that it likely would impact splicing.

Overall, Puck said that sequencing had about 88 percent sensitivity, but said that performance was variable across the genes screened. As such, "exome sequencing alone is not a good replacement for mass spec screening," she said. However, "sequencing could be [a] helpful second tier test following a positive screen to reduce false positives in some conditions with a high false-positive rate."

In addition, Puck noted that around one-third of the variants the team identified "had not been seen before, so it was hard to predict their effect." She attributed the large number of variants of unknown significance to California's diverse population and the fact that less is known about populations that are not of European descent since fewer genomic studies have been done in those populations.

Two other NSIGHT studies: BabySeq, led by researchers at Harvard University and Brigham and Women's Hospital, and NC Nexus, led by researchers at the University of North Carolina, Chapel Hill and RTI International, evaluated the use of sequencing in both healthy and sick newborns.

The NC Nexus study evaluated sequencing for three different categories of disease: childhood-onset and medically actionable, adult-onset and medically actionable, and childhood-onset but not medically actionable.

They included 466 conditions in the childhood-onset medically actionable group and returned positive results found in this category to any family who enrolled in the study. Families from two cohorts — those with healthy newborns and those with sick newborns — were then randomized into a group where they only received those results or to another group where they had the choice of receiving the additional categories of results.

The goal was to evaluate how NGS could extend the utility of newborn screening and to evaluate what information should be included, what information parents wanted, and how they make those decisions, according to Cynthia Powell, co-principal investigator of NC Nexus and an associate professor of pediatrics and genetics at UNC-Chapel Hill.

A major component of the study included designing a decision support tool to walk families through the decision-making process. Ryan Pacquin, a public health research analyst at RTI, said that of the 190 couples and 14 single moms who enrolled in the study, the majority of those given a choice opted to receive additional results. In addition, he said, the researchers found that couples tended to report making the decision together and those who did opt for more results did not regret their decision or feel extra stress about the decision or concern for their child.

Robert Green, codirector of BabySeq at Brigham and Women's Hospital, similarly reported that his team found that returning genetic risk information about newborns did not cause undue stress on families.

Green said that of 163 babies sequenced, the researchers found a "surprisingly high percentage of unanticipated results." Eighteen, or 11 percent, harbored a variant that indicated a risk for developing a childhood-onset disorder, including several cases where the finding explained phenotypic observations that had already been made.

Of the 18 infants with disease-related findings, four were diagnostic findings that either explained an observed phenotype or prompted the discovery of a previously unrecognized phenotype. Eight variants were found that were consistent with a family history of disease, including cancer-related variants. And, there were six cases where a variant indicated a disease for which there was no family history. Green noted that in some cases, the finding of a pathogenic variant prompted a more extensive dive into a family's history. For instance, he said, finding a BRCA2 variant in one newborn prompted the family to go back through their history and they discovered several instances of breast, ovarian, and pancreatic cancer on the mother's side of the family, leading her to get tested for the mutation as well and make more informed health decisions, Green said.

There were also a "tremendous number of carrier findings," Green said. Around 88 percent of babies were heterozygous for one or more recessive allele. He cited one family who after getting carrier results from their child decided to get tested themselves before having another child and found that they were both carriers for the same very rare disease, a "crazy coincidence," Green said. But as a result of that finding, they opted to use reproductive technology to avoid having a child with the condition.

As previously reported, the BabySeq study investigators faced significant hurdles in enrolling families. Follow-up surveys with those families found that many declined due to logistical hurdles. Green said that many declined because they had literally just had a baby, and thinking about anything else was overwhelming. However, he also cited the "gauntlet" of oversight by both the US Food and Drug Administration and the institutional review board. "There's a certain kind of bias that gets injected into clinical trials when you have to overelaborate the risks in an overly elaborate consent process," he said.

The team found that among those who did participate in the study, including both the families with sick and healthy newborns, getting back sequencing results did not change their perceptions of their child's vulnerability or disrupt the bond between the child and parents.

Green, who was also a principal investigator of the MedSeq study, which evaluated the impact of sequencing healthy adults, said that since these studies, Brigham and Woman's Hospital has launched a Preventive Genomics Clinic where adults can receive comprehensive genomic sequencing with in-depth interpretation "without any limitations due to our perceptions of actionability." The researchers also plan to study outcomes of people who get sequencing.

Despite finding that sequencing healthy newborns can sometimes be beneficial by prompting families to have a better understanding of their risk for certain diseases, and did not cause undue distress, the NSIGHT Ethics and Policy Advisory Board last year developed a report published by bioethics think tank The Hastings Center that advised against sequencing healthy newborns.

And indeed, during the NIH meeting, while researchers agreed about the utility of it for diagnosing acutely ill infants where speed is urgent, they did not all agree on the broader use of sequencing as a population screen for diseases that cannot afford to be missed.

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