# Newborn Sequencing Projects Demonstrate Successes, Challenges of Widespread Implementation

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***Premium***

NEW YORK (GenomeWeb) – Between rapid diagnoses of critically ill infants and unwieldy general population screening tests, four National Institutes of Health-funded projects are illustrating both the promise and challenges of sequencing the genomes of newborns.

At Cambridge Healthtech Institute's Molecular Medicine Tri-Conference in San Francisco last month, researchers from the four Newborn Sequencing in Genomic Medicine and Public Health (NISGHT) study sites described progress their institutions have made, challenges, and future plans.

The four projects are all addressing various aspects of one broad question, whether or not "we are ready for prime time," Stephen Kingsmore, president and CEO at Rady Children's Institute for Genomic Medicine and principal investigator of the STAT-seq NSIGHT project, said in a presentation.

Thus far, according to the researchers who presented at the conference, it seems that while sequencing has utility for diagnosing sick infants, it may not yet be ready to replace standard tests for broad population screening. In addition, researchers from two NSIGHT projects at the Brigham and Women's Hospital and the University of North Carolina, Chapel Hill described challenges beyond the technical aspects of testing, including recruiting participants, dealing with unexpected findings, and returning information about carrier status.

Kingsmore, who developed the STAT-seq protocol while at Children's Mercy Hospital, has since implemented the protocol at Rady. The group is conducting a randomized controlled study to compare whole-genome sequencing with standard testing for babies admitted to level 4 neonatal and prenatal intensive care units. Kingsmore said that about one-third of babies enrolled in the NICU are suspected of having a genetic disease.

Due to the success of diagnosing critically ill infants and in many cases being able to guide their treatment and likely save lives, Kingsmore's group is in the process of implementing STAT-seq at pediatric hospitals that are part of the Sanford Children's Genomic Medicine Consortium, a network of six pediatric hospitals.

At least initially, those hospitals will send samples to Rady for testing, Kingsmore said. Rady's clinical genome center has both Illumina HiSeq 2500 and HiSeq 4000 instruments, but it also sends samples for testing to Envision Genomics, the HudsonAlpha Institute spinout launched by Howard Jacob.

Ultimately though, "we'd like to do this in every NICU and PICU in North America," Kingsmore said. "We feel it's time to generalize this technology."

Kingsmore described several case examples, including one three-day-old infant who had been suffering from seizures since birth. Sequencing yielded a provisional diagnosis in 68 hours, Kingsmore said, which pointed to an effective treatment and enabled the baby to be discharged from the hospital.

Kingsmore said this is important because previously an infant with the same syndrome was hospitalized for two months, racking up $165,000 in hospital charges compared to $14,000 for the baby who underwent STAT-seq. In addition, Kingsmore said, reducing the amount of time that the baby suffered from seizures could have important longer-term clinical consequences. "Seizures are bad for a developing baby's brain," he said, and can cause developmental disability. The quicker the seizures can be treated, the less severe the baby will be affected.

Two of the other NSIGHT projects — BabySeq and NC Nexus — have not come to such clear-cut conclusions about the benefits of newborn sequencing. Study leaders from those projects have previously reported on the challenges of enrolling participants into the study, despite families initially indicating interest.

Joel Krier, clinical chief of the Division of Genetics at the Brigham and Women's Hospital, said in a Tri-Con presentation that patient recruitment has been a "surprising lesson." The BabySeq study includes two cohorts — healthy newborns and babies who have been admitted to the NICU — and the rate of enrollment is low for both groups. For babies admitted to the NICU, overall enrollment rate is 7 percent and for healthy babies it is 8.3 percent, Krier said.

Parents decline for numerous reasons, Krier said, with logistics being the most commonly cited reason. Others have concerns about confidentiality, insurance discrimination, and getting unfavorable results.

Already, he said, the team has had to grapple with difficult questions. For instance, he said, in one case, the researchers uncovered a pathogenic variant in the BRCA2 gene of an infant. The group did not have IRB approval to return results for adult-onset conditions, but felt that they could not ignore the finding.

Currently, the group returns results related only to pediatric onset diseases, including carrier status results for pediatric diseases and pharmacogenomic results for pediatric drugs.

In this case though, Krier said the team contacted the IRB and received permission to discuss the BRCA2 finding with the family. Before discussing with the family, they first collected additional family history and found out that there was some history of breast, ovarian, and prostate cancer. Ultimately, Krier said, they did discuss the BRCA2 finding with the family, who was surprised but grateful to have the information. That experience spurred the group to rethink its return of results protocol, and it is now considering seeking IRB approval to return those types of findings. Krier said the team is still working out the details of what types of results would be returned.

Another unexpected result of the work so far has been how time consuming returning carrier results has been, Krier said. "A lot of the counseling ends up focusing on what the carrier results mean," he said. Returning those findings is "challenging for physicians and challenging for patients to wrap their heads around what the risk means for them," he said.

Don Bailey, who is spearheading the ethical portion of the NSIGHT project at UNC, said that one reason for low recruitment may be the burden of joining the study itself. Like the BabySeq research group, UNC's NC Nexus study has also seen surprisingly low rates of enrollment despite a high initial interest. Bailey said that from an initial survey of 117 pregnant women, 88 expressed interest in joining. Ultimately though, only seven have completed the enrollment and given samples from their baby. An additional three women have completed all the steps but have not yet had their babies and given samples. The "burden" of joining is too great, he said, with "too many forms and questionnaires."

The University of California, San Francisco NSIGHT researchers are approaching the project from a different angle. For their project, dubbed NBSeq, they have IRB approval to analyze archived, de-identified dried blood spot samples from newborns. The group is seeking to determine whether exome sequencing can potentially augment or replace standard newborn screening for metabolic disorders.

In California, newborns are screened for around 50 metabolic disorders, Jennifer Puck, professor at UCSF and a principal investigator of the NBSeq project, said in an interview. Many of those disorders are tricky to diagnose via standard methods, she said, so one goal was to see whether exome sequencing could potentially replace those other methods. Although the study is still ongoing, preliminary results from 600 analyzed samples suggest that exome sequencing cannot serve as a first-line screening test, Puck said.

Because the goal of the study was to evaluate the use of sequencing as a first-line test for all newborns, the researchers decided to use exome sequencing to keep the costs down and also wanted to design a bioinformatics pipeline that would automatically sort through and call variants in order to minimize the amount of manual variant calling, which would not be practical for population screening, Puck said.

In addition, she noted that many of the metabolic conditions currently screened for are difficult to diagnose by any method, not just sequencing. During a presentation at TriCon, Aashish Adhikari, a postdoc at the University of California, Berkeley, gave an example of the type of cases missed by exome sequencing. Two cases were positive by standard tests for isovaleric acidemia, a condition that causes problems breaking down the amino acid leucine. The researchers' automated exome pipeline did not

flag any pathogenic variants, but going back through the data manually, they observed hemizygous variants in the IVD gene and decided to perform whole-genome sequencing on the sample. In both cases, they identified deletions in the IVD gene.

However, she said, despite not being suitable as a first-tier test, it could serve as a second-line test. There were "cases where exome sequencing was able to answer questions that had puzzled the doctor," she said.

In addition, the team is continuing to analyze the remaining 1,100 or so dried blood spot samples. The samples include self-reported ethnicity data, Puck said, so sequencing and analyzing the samples could help build up the knowledgebase of population-specific genetic variation in many of the diseases. "Most of what we know about the genetics of metabolic disorders is from white European populations," Puck said. But because California is so diverse, the researchers now have the chance to increase their knowledge about other populations. Even with well-understood disorders like phenylketonuria, little is known about population-specific variation, she said.

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