NSIGHT Steering Committee Public Session

June 24th, 2019 1:30-5:00 PM

6700B Rockledge Drive, Bethesda, MD

The Newborn Sequencing in Genomic Medicine and Public Health (NSIGHT) program held their final Steering Committee Meeting on June 24-25, 2019 at the National Human Genome Research Institute in Bethesda, MD. NSIGHT is made up of four clinical sites: Brigham and Women's Hospital/Boston Children's Hospital/Baylor College of Medicine, Rady Children's/Children's Mercy, University of California, San Francisco, and University of North Carolina, Chapel Hill. The sites were awarded grants in September 2013, and the project concludes in August 2019. The public session began with an introduction to the program from Anastasia Wise (NHGRI) who gave an overview of DNA Sequencing and the differences between exome and genome sequencing. She also reviewed the three components required of all NSIGHT projects: that they involved genome or exome sequencing, that they advanced understanding of disorders in the newborn period, and that they included ELSI studies of possible implementation of genomic sequencing of newborns.

The first talk, *Is Sequencing Helpful in Population Screening for Metabolic Disorders?,* was given by Dr. Jennifer Puck of UCSF. Dr. Puck asked whether exome sequencing could replace mass spectrometry, which is currently used in newborn screening (NBS). NBS focuses on urgent, infant-onset, treatable disorders, and it happens without explicit parental consent in many states. She discussed how the California Biobank is an invaluable resource that stores dried blood spots from all babies born in the state. Her site elected to use an exome slice of 78 genes known to be involved in inherited metabolic disorders. Overall, the exome sensitivity was found to be 88%, but some genes did better than others. Dr. Puck concluded that exome sequencing would not be a good replacement for mass spectrometry right now, but that it could be a useful tool in cases where there is no mass spectrometry screen or as a second-tier test to help reduce false positives. To date, this was the largest whole exome sequencing study of unbiased inborn errors of metabolism and will serve as a benchmark for the capabilities of whole exome sequencing in the context of NBS.

The second talk, given by Cynthia Powell of UNC-Chapel Hill and Ryan Paquin of RTI International, was titled *Introduction to NC Nexus, the Decision Aid and Parental Decision Making about Whole Exome Sequencing.* Every infant in the US receives NBS, and the Recommended Uniform Screening Panel (RUSP) includes 35 core conditions that are recommended for states to test at birth. NC Nexus was interested in how Next Generation Sequencing (NGS) could extend the utility of current NBS, devising and evaluating a clinically oriented framework for analysis, and developing the best practices for incorporating NGS-NBS into clinical care. They were also interested in parental decision making. NC Nexus returned NGS-NBS results to two cohorts: an affected cohort with an NBS diagnosis of a metabolic condition or hearing loss, and a healthy newborn cohort recruited during pregnancy. Molecular analysts reviewing sequencing results were blinded to whether the baby came from the diagnostic or the healthy cohort. Overall, exome sequencing had 88% sensitivity for making molecular diagnoses.

To better understand how parents make decisions, NC Nexus created an interactive web-based decision aid that provided information about options and potential outcomes, promoted active deliberation, and facilitated families' choices about sequencing without swaying them in a particular direction. A subset of parents was also randomized into a "decision group" that could elect to receive results other than childhood-onset, medically actionable variants. 90% of couples decided to view the additional results. The decision aid showed that parents with a healthy newborn did not differ in their decision from those with a diagnosed genetic condition, and they tended to make their minds up about NGS-NBS early on in the decision-making process.

The third talk, *The Case for Preventive Genomics*, was given by Robert Green of Brigham and Women's Hospital. He argued that preventative genomics is not routinely in use because of barriers to its implementation. There is concern that people will not understand their results or that there will be unwarranted costs. Contrary to this perception, the Risk Evaluation and Education for Alzheimer's Disease (REVEAL) study, as well as sequencing studies MedSeq and BabySeq, showed that people who requested and then received their genomic results were typically happier and more empowered.

Dr. Green discussed how 20% of adults who were comprehensively sequenced were found to have a Mendelian disease variant and 92% of people have a recessive carrier variant. He stated that if sequencing is going to reveal health risks at any point in life, there may be benefit in testing earlier. In BabySeq, with a slightly more limited panel of genes, 11% of participants had a monogenic finding, most of which were child and adolescent adult onset conditions. There was an average of 2 carrier findings per infant.

The talk then shifted into BabySeq's experience with recruitment. Dr. Green talked about the bias that is injected into clinical trials in which the study must overemphasize the risks during the consent process. Parents who declined to participate in the study had different reasons for declining including study logistics, insurance or privacy concerns, and unfavorable results.

Dr. Green argued that society should be moving more rapidly towards preconception screening in the entire population, a process that was very successful with conditions like Tay-Sachs Disease. Genomic information can be thought of as a risk stratification tool and the benefits aggregate over time as more genes are analyzed.

The fourth talk was given by Stephen Kingsmore from Rady Children's Institute for Genomic Medicine, titled, *What has NSIGHT taught us about genomic medicine for infants in intensive care units?* Sequencing results can now be returned in as little as 36 hours through rapid whole genome sequencing (rWGS). Rady's NSIGHT program focused on seriously ill infants in Neonatal Intensive Care Units (NICUs) and Pediatric Intensive Care Units (PICUs), where over half of babies have an unknown disease etiology at the time of admission. Children were randomized to either the standard of care or rWGS. In a study at Children's Mercy Hospital, 57% of the rWGS group received a genetic diagnosis, as opposed to only 6% of the control group. Of the rWGS group, 31% had a change in management, 11% had a favorable change in outcome, and 1 (3%) had their life saved. Similar results were found at Rady, where the genetic disease diagnosis rate by rWGS was 43%. The majority of parents and physicians felt that this genomic testing was useful.

Other research in the US, England, Canada, and Australia has echoed these findings, demonstrating the utility of genomic medicine in infants. Ongoing barriers to adoption of these techniques include capital and labor intensity of rapid genomic medicine, a lack of training, insufficient evidence of cost effectiveness to drive reimbursement, and a lack of effective treatments for genetic diseases. Rady's NSIGHT project demonstrated that rapid genome sequencing could be successfully implemented in the care of seriously ill infants, and that rapid turnaround leads to timely medical interventions in ICUs and better outcomes. The project also demonstrated that the potential utility of rWGS remains understudied in many groups of infants.

Panel Discussion

Melissa Parisi (NICHD), moderated the panel discussion which started off with investigators taking a step back to consider whether they had answered the questions initially proposed in the request for applications. The three questions were:

1) For disorders currently screened, how can NBS be replicated or augmented?
2) What knowledge about conditions not currently screened for in newborns could genomic sequencing provide?
3) What additional clinical information could be learned from genomic sequencing relevant to clinical care of newborns?

Investigators agreed that sequencing does not replicate NBS program results with sequencing having lower sensitivity and specificity. Sequencing, however, could be used to gather information about prognosis or specific therapies. It could also help to solve more complicated cases in newborns with unclear screening results. To find a role for sequencing in the context of NBS, there would need to be a similarly stringent process for nominating and reviewing conditions that could be reported from sequencing and personnel would need to be trained throughout the system. Even still, there would be uncertainty with expansion of NBS to new conditions. The downside of this cautious approach to screening is that children would be missed that have conditions that could be detected from sequencing today. When NSIGHT began, it was not known if whole exome or genome sequencing from a dried blood spot was feasible. Now this platform is available, and the question is the best way to use it. It is important to consider the goals and context when sequencing because it can produce results outside of the reportable, treatable realm.

Some NBS tests are already using sequencing to help solidify a final diagnosis. This may present an opportunity for expanding sequencing as an NBS test. The group was divided about whether to include tests like Familial Hypercholesterolemia in NBS, which may not be directly relevant in childhood but could have implications for parental health. There is also additional clinical information that can be learned from the genome, such as secondary findings and PGx data. The group discussed whether it makes more sense to try to expand a component of the existing NBS system, or to set up a different system that electively sequences children for other potential benefits. The group agreed that it is critical that this sequencing remain within the current NBS system to ensure that appropriate follow-up is achieved. Additionally, many states do not support genetic testing for Medicaid patients.

The group discussed potential ways to integrate sequencing into screening programs. Children are required to get hemoglobin and lead testing near their first birthday. This is nearly universally done and is an opportunity to target families for screening when they will be thinking about consent in a calmer environment. However, this approach would also miss disorders that are critical to know about in the first weeks or months of life. Another option is to obtain sequence data at birth and keep that data tied to the child over time.

Sequencing tests often cause a trade-off between sensitivity and specificity, and there are not clear cutoffs for useful levels of sensitivity and specificity. The field needs to set limits for the number of false positives/missed cases they are willing to accept. Sequencing tests can be useful even if they miss some cases, as they identify some cases that wouldn't be found at all otherwise. There are concerns that parents will not be able to tell vital testing from non-vital testing. If too many tests are added, there is the risk that parents will stop screening altogether. Public trust in NBS programs must be preserved in order for these programs to remain universal. There are also concerns that wealthy families will be more likely to take advantage of sequencing and get better follow-up, worsening health disparities.

Cystic Fibrosis (CF) was mentioned as an example NBS test where sequencing is utilized. Massachusetts started DNA screening for CF in 1999. Each parent could choose whether to get the pilot test done on their newborn. This ended up being a successful model. Over time, data was generated to demonstrate the test's usefulness and eventually led to a mandate. Piloting sequencing as a test in a couple states could help researchers learn what might go wrong and whether this testing is beneficial on a statewide level.