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BabySeq Newborn Screening Project Aims For Increased Diversity in Second Phase

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This story has been updated to include additional comments from Robert Green.

NEW YORK – BabySeq, the next-generation sequencing-based universal screening program for newborns, is gearing up for a second, expanded study. The lead researchers said they want the four-year, $5.1 million grant to help address a lack of diversity in the first cohort.

The original BabySeq cohort was not diverse and thus the findings are not generalizable, according to the project's co-principal investigators Robert Green of Brigham and Women's Hospital and Ingrid Holm of Boston Children's Hospital.

"They were pretty overwhelmingly wealthier people and of European ancestries," Green said. Holm added that in phase two, they're hoping to recruit more than half of the participants from African American or Hispanic families.

The grant, funded mostly by the National Center for Advancing Translational Sciences (NCATS), part of the National Institutes of Health, will help sequence 500 babies and their families at three clinics in the Eastern US. Whereas the first phase of BabySeq was conducted in a hospital setting, phase two will move to enroll participants in community clinics in Boston, New York, and Birmingham, Alabama. The program has partnered with Mount Sinai and the University of Alabama-Birmingham to enroll participants and will work with researchers at Baylor University on surveys and outcomes analysis. The Laboratory for Molecular Medicine will perform sequencing.

The new project will feature two other changes. The children will be a little older, up to 6 months in age, and they will receive whole-genome sequencing, rather than whole-exome sequencing.

"Primarily, [WGS] means that we can look for copy number variants," Holm said.

While some bioethicists have been skeptical of universal newborn screening with NGS, Green and Holm suggested that the case for it is gaining strength.

"There is a whole revolution occurring in terms of gene targeted therapies," Green said, with a handful already and a hundred more in development. "These are rare diseases, most of which the risk can be detected with early sequencing."

"It's a really strong team," said Josephine Johnston, a bioethicist and director of research at the Hastings Center who was first author on a 2018 report critical of universal newborn sequencing. "If there is benefit to be had, if this project could be helpful to primary pediatric care, these people will find it because they are really enthusiastic about it and they're good researchers."

"My overall take on the first study was they had low enrollment and quite modest findings," she said. "But they still got another big grant, so they're going to try it in a different context."

Launched in 2013, BabySeq phase one wrapped up in 2019. The project produced more than 20 peer-reviewed papers and the researchers felt that their randomized controlled trial helped ease fears that newborn screening would have deleterious psychological effects on parents. In a paper published in September in *JAMA Pediatrics*, the BabySeq team suggested that there was no signal of increased anxiety or distress and no disruption in parent-child bonding, between the two arms of the study (the control group received a standard heel prick newborn screening test).

In other publications they revealed that 18 infants, or 11 percent of the sequenced newborns, harbored a variant associated with risk of a childhood-onset disorder. In some cases, these variants helped explain phenotypic observations already made. The original BabySeq study curated a list of approximately 1,000 disease-associated genes to return results for.

"Based on these exciting data, we wrote several follow-up grants that were not funded," Holm said. One was an application for a follow-up study, submitted to the Eunice Kennedy Shriver National Institute of Child Health and Human Development as part of an RFA. "It just wasn't innovative enough, for whatever reason," she said.

With their new funding, researchers are seeking to correct their earlier lapse by emphasizing community pediatric clinics. "This is a big issue in genomics, across every research domain and all over precision medicine," Green said. "It's partly access to care, which is exacerbated for all the reasons we're aware of: historical injustice, distrust, and failures of many research projects to make themselves culturally relevant. We are just trying our best to make sure BabySeq 2 does a better job of that."

They have also established a stakeholder board "that really represent perspectives from diverse sources that are helping with protocol design, education, and so forth," Holm said.

Moving to a community-based clinic may also help increase the participation rate, Johnston said. "BabySeq 1 did not get anything like the level of uptake that they were expecting," she said. "One of the possible explanations was because they were asking people who had just given birth. … My thought is that they're hoping they'll get much higher enrollment if they do it in a primary care context."

Using whole-genome sequencing could lead to finding more newborns with risk-associated genetic variants. "My guess is that we'll find some, but I don't think it's going to increase to 20 percent [from 11 percent]," Holm said. Many variants could be of unknown significance, which the study will not return to patients.

Another rationale for expanding BabySeq relates to newly available treatments for rare diseases. The recommended uniform screening panel (RUSP) — the list of conditions that the US Department of Health and Human Services recommends for states to screen for — is "not keeping up with treatable genetic conditions," Green said. According to him, there are more than 800 treatable childhood genetic conditions, while the RUSP currently has 35 (some states test for more conditions.)

Green said he believes that earlier critiques of the study's premise, including Johnston's were "written without appreciation of the flood of new treatments being developed, which completely changes the medical and ethical equation."

"There's just so much more going on now in ability to do genetic treatments that to put them all on the RUSP, you've got to have the exome. That's a big motivation, and that's why studies like this are timely," he said.

The researchers have not started recruiting yet but received conditional approval from their institutional review board late last month. "It's a big step," Green said. "It took us much, much longer the first time."

They're even looking toward bringing in partners with their own funding to increase the cohort size beyond what the new grant will support. "It would be nice to have several thousand [participants]," Holm said.

"The ultimate goal is to have a much larger group because we have a better chance of finding those n-of-ones," she said.

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