STAT

A deep dive into newborns' DNA can reveal potential disease risks — but is the testing worth it?

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January 3, 2019

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When babies are born, clinicians draw a drop of blood from their heels[1][1] and analyze it for signs of dozens of diseases. But with the rise of sequencing technology, researchers have been investigating whether a deep dive into newborns' DNA could uncover more diseases — and whether making such an endeavor routine would be worth it.

On Thursday, researchers reported[2][2] some of their first results from the project, finding that newborn sequencing revealed genetic variants that raised the risk of certain childhood conditions in 9.4 percent of the babies tested. The mutations most often pointed to an elevated likelihood of heart conditions or hearing loss — traits that were not picked up by standard newborn screening.

Debate about newborn genomic sequencing continues[3][3], but to the project's leaders, their early results suggest that there is value in testing babies' DNA. At least some of the children with the flagged variants

will likely go on to develop those conditions, and now their families — and the specialists they have been referred to — can prepare or even try to head them off.

“My personal opinion is that probably in the not too distant future, most individuals will get sequenced at a really early point in their life,” said Alan Beggs, director of the Manton Center for Orphan Disease Research at Boston Children’s Hospital and a senior author of the study, which was published in the American Journal of Human Genetics.

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Beggs is one of the leaders of the BabySeq Project[66], a clinical trial comparing standard newborn screening and genomic sequencing to determine the medical, economic, and ethical effects of the latter. It is one of four federally funded studies[77] investigating such questions.

Newborn DNA testing offers several potential benefits. Mainly, it could expand the number of conditions clinicians can test for before a child starts showing symptoms, giving them and patients a head start in handling the diseases.

But there are downsides as well. Sequencing the DNA of newborns would be costly. False positives and false negatives can occur. Plus, most of the variants identified do not guarantee that the children with them will develop these conditions; rather, they raise the likelihood. This means that families could be exposed to unnecessary stress about the health of their children and to costly tests and doctors’ visits they didn’t need. Some experts argue that instead of casting such a wide net over healthy babies, doctors should target sequencing to children suspected of having a genetic disease or with a family history.

“This is a very nonspecific test for children who don’t have any indication for being concerned about their health,” said Dr. Jeffrey Botkin, a pediatrician and ethicist at the University of Utah, who was not involved in the study. “It just yields a ton of confusing information that I think is not going to prove to be valuable on balance.”

Experts said the finding that 9.4 percent of children in the study had a genetic variant associated with disease risk was high based on rates of genetic disease and on other sequencing studies. To Botkin, that indicated that many of these children would not ultimately develop these diseases.

“Giving people uncertain information about the health of their baby — that’s a serious concern,” he said.

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The BabySeq researchers reported to families only genetic variants that they know raise the risk of a disease that could affect someone during childhood or that could be addressed during childhood. If scientists don’t understand the influence a certain variant has — it could be for good, for bad, or do nothing — then the researchers excluded it.

For Lauren Stetson's daughter Cora, sequencing provided certainty that the heel prick didn't. Cora's initial blood draw indicated she might have biotinidase deficiency[99], which would have left her body unable to recycle the vitamin biotin and caused rashes and hair loss and possibly cognitive problems. But a follow-up test suggested Cora was fine, Stetson said.

Cora Stetson and her brother Cody. Cora has partial biotinidase deficiency, which was picked up with genomic sequencing. Cody does not have it.
Courtesy Stetson Family

The sequencing, however, showed Cora had partial biotinidase deficiency. (Her levels are close enough to normal that that could explain the discrepancy between the other tests, Stetson said.) Now 2, Cora takes a nightly supplement of biotin and has never had any symptoms of her condition.

"We are still playing defense," Stetson said about how medicine is normally practiced. "Why do we have symptoms first and then try to figure out what it might be?"

Still, Stetson acknowledged that families need to decide whether sequencing is right for them, given the uncertainty and fear it can inject into people's lives.

For the study, researchers sequenced the protein-coding portions of the genomes of 159 newborns, 127 who were healthy and 32 who were in the neonatal intensive care unit. The sequencing revealed that 15 children had a genetic risk of a childhood disease or a disease that could be managed during childhood.

Dr. Cynthia Powell, a geneticist and pediatrician at the University of North Carolina, who is working on one of the other newborn genomic sequencing projects, said that while the results reported by the Boston researchers were higher than many experts expected, the study demonstrated that serious conditions can be detected through sequencing. The main question now is about "penetrance": Just how many children with these variants will go on to display those conditions?

"When you're dealing with a healthy baby, and you find something that's likely pathogenic, are they really going to ever develop the condition?" Powell said.

Looking for diseases in newborns' DNA that could arise during adulthood is more ethically fraught than focusing on childhood conditions. Some experts argue that individuals should decide for themselves when they turn 18 whether they want to have their genomes examined. But in this study, 85 families agreed to have the researchers search their babies' genomes for variants tied to adult-onset diseases, and the researchers found three such cases.

Two were mutations in a BRCA gene that increase the chances of certain cancers, and the third was tied to Lynch syndrome, which also raises cancer risks. The parents who passed those variants onto the babies were unaware that they themselves had those cancer-risk genes, and they were referred to specialists, Beggs said.

Though Beggs said he thinks most people will ultimately undergo sequencing, he said in most cases it wouldn't need to occur when someone is a newborn.

It's a challenge[1212] the BabySeq researchers ran into when enrolling participants: Only 7 percent of families approached about enrolling agreed. Beggs said one reason was that parents were asked soon after their baby was delivered, and they were already overwhelmed enough without having to think about a clinical trial.

Beggs and his colleagues will continue to follow the families in BabySeq to track how having this genetic information plays out over time. Do they have regular visits with specialists even if their children aren't showing symptoms? Do these children develop any health conditions? And what kind of emotional baggage comes with knowing this information?

"Now the question is, how does this impact people over time?" Beggs said. "And do the benefits of having access to this information outweigh the costs?"

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