Babies' Genomes Identify Risks Overlooked by Newborn Screens

A trial called BabySeq, in which researchers performed genomic sequencing on 159 newborns, identified children susceptible to diseases that regular screening doesn't look for.

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The majority of babies born in the US undergo a hearing screening as well as a blood test to detect certain diseases that can be fatal if they go untreated, such as cystic fibrosis and phenylketonuria. Other diseases that don't have an appropriate biochemical test can go unidentified. Sequencing the genomes of newborns would be one way to determine a child's risk of developing one of these untested-for diseases, so researchers decided to try it out.

In a study published today (January 3) in *The American Journal of Human Genetics*, a team of researchers describes its findings from the exome sequences of 127 healthy newborns and 32 ill newborns. The group found that 15 of the babies had genomic variants that put them at risk for a childhood-onset disease and 140 of them were carriers for one of those diseases—risks that could not have been detected through traditional screening.

"None of these findings were anticipated based on what we knew about the infants—either clinical features or their family history," study coauthor Ozge Cehan-Birsoy, a clinical molecular geneticist at Partners Healthcare Personalized Medicine and Memorial Sloan Kettering Cancer Center, tells *The Scientist*.

Cehan-Birsoy's work is part of the BabySeq study, one of four projects funded by the National Institutes of Health (NIH) five years ago to explore the use of genome sequencing in a newborn screening setting.

See "Q&A: Sequencing Newborns"

Boston Children's Hospital geneticist Alan Beggs, bioethicist Amy McGuire of Baylor College of Medicine, and geneticist Robert Green of Brigham and Women's Hospital started the BabySeq project, Beggs says, in part because they thought genomic sequencing might give them insight into why sick newborns were sick. But their main research question was, "how does having the genomic information

impact [babies] in general?" Beggs adds.

BabySeq was designed as a randomized, controlled trial. All of the 268 families in the study met with a genetic counselor in order to discuss general family history. Slightly more than half of the infants had their whole exomes sequenced and any variants verified by Sanger sequencing, while the remaining participants did not. Cehan-Birsoy and her team then reviewed the sequencing information and wrote a clinical report, which was returned to the babies' families, put into their medical records, and made available to their pediatricians.

In the report, the team included information that indicated any risk for developing childhood-onset diseases—that could range from having a dominant, disease-causing variant to carrying an allele for a recessive disease—along with gene variants associated with adverse reactions to medications often given to children. Later on, the researchers also gave parents the option of consenting to receive information about risks for gene variants that can cause adult-onset illnesses, namely, those that predispose an individual to develop cancer, including *BRCA1* and *BRCA2*.

Of the 159 babies included in the sequencing arm of the trial, Beggs and colleagues identified 15 babies with variants tied to a risk for developing a childhood-onset disease. Ten of these infants were from the well-baby nursery, and five were from the neonatal intensive care unit. The variants were linked to a variety of diseases, including several heart conditions, a deficiency in the enzyme that metabolizes the vitamin biotin, and hearing loss. Two of these babies' genomes carried cancer-linked variants in *BRCA2,* and the mother of one baby also had a family history of breast cancer.

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"It's a heroic effort and a meticulously researched study. It's quite impressive in terms of the depth of what they did," says Stephen Kingsmore, a physician and CEO of Rady Children's Institute for Genomic Medicine in San Diego. He leads one of the other four programs funded by the NIH, in which he and his team evaluate the effects of genome sequencing in sick babies.

A whopping 140 of the 159 babies were carriers for childhood-onset orders, including cystic fibrosis and the developmental disorder Smith-Lemli-Opitz syndrome. Eight of the 159 infants were found to have variants associated with adverse reactions to medications.

"Most of these changes that we found are not related to any disease that they currently have," says Beggs. "The question is, how does this impact them? This kind of genetic information may have some predictive value, but it's not definitive and it's very possible all of these kids might not develop anything in the foreseeable future," he adds.

"When we're testing healthy babies and there's no family history of anything, we don't know whether a variant found in a gene is really going to lead to disease ultimately," agrees Cynthia Powell, a pediatrician and geneticist at the University of North Carolina, Chapel Hill. Powell was not involved in the BabySeq project, but she is part of a newborn sequencing project funded under the same umbrella. "Hopefully, they'll be able to follow these children long term to see if they do develop evidence of these conditions," she says, adding that the study "certainly gives quite compelling proof that [genomic sequencing] can be helpful."

Although sequencing is informative, there are more considerations before it should be implemented across the board. Cehan-Birsoy estimates that clinical exome sequencing would probably cost several thousand dollars per person. Newborn screening via a heel prick and blood test, on the other hand, costs a couple of hundred dollars at most, and it remains to be seen whether the exome sequencing will result in better outcomes for the infants.

The issue of cost should certainly be considered, agrees Barbara Koenig, a bioethicist at the University of California, San Francisco, who is involved in a newborn genomics project there. One related consideration is how genomic testing could change the landscape of newborn screening, which is one of the few advantages available to all babies in the US regardless of economics or social status, she says. Koenig coauthored a report published in August 2018 calling for nuance and attention to context when moving forward with genome sequencing in newborns.

"Another piece of the puzzle is how fast you need to do this," Kingsmore tells *The Scientist*. "It's not just a matter of [whether] genomic sequencing is going to be valuable in babies. The context is quite different for an ill baby versus a healthy baby, and in an ill baby speed is really important."

See "Exome Sequencing Helps Crack Rare Disease Diagnosis"

O. Ceyhan-Birsoy et al., "Interpretation of genomic sequencing results in healthy and ill newborns: results from the BabySeq Project," *The American Journal of Human Genetics*, doi:10.1016/j.ajhg.2018.11.016, 2019.

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