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BabySeq project explores impacts of genetic disease testing in newborns

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In the 1960s, doctors began screening newborns for a metabolic condition called phenylketonuria (PKU). Since then, dozens of other diseases have been added to the panel of tests given to newborns, most looking for inherited genetic disorders. (The exact number of tests varies by state.)

In the era of increasingly common genomic sequencing, an effort called the BabySeq Project aims to explore the medical, behavioral, economic, and ethical impacts of adding genetic testing to the roster of newborn screenings. Some of the first findings from the project are being reported January 3 in the *American Journal of Human Genetics*.

"Traditional newborn screening uses biochemical analysis on a small drop of blood to look for a small number of conditions that can benefit from early intervention," says senior author Alan Beggs, director of the Manton Center for Orphan Disease Research at Boston Children's Hospital and one of the principal investigators for BabySeq. "In contrast, genomic sequencing has the ability to simultaneously analyze thousands of genes that are known to cause disease.

"But the specificity and sensitivity of genetics tests are uncertain and relatively low, and not all of the diseases that we may find are treatable," he says. "This leads to a potentially complex package of information about a baby. It's important to look at how people view this information and what the outcomes of having it are."

The BabySeq study, led by Beggs and Robert C. Green, of Brigham and Women's Hospital, together with Amy L. McGuire and collaborators at the Baylor College of Medicine, included sequencing of 159 newborns; 127 were healthy, and 32 were being treated in neonatal intensive care units, although not necessarily for genetic conditions. Parents who consented to have their babies tested filled out questionnaires including questions related to family history.

The investigators report that 15 of the babies (9.4%) carried mutations that revealed a risk of diseases that could arise or be managed in childhood, including cardiomyopathy and hearing loss. The investigators say this number was surprising, because none of these results were anticipated based on the infant's clinical or family history.

"In this study, we focused on reporting gene variants that had substantive evidence to confer risk for disease" says first author Ozge Ceyhan-Birsoy, a clinical molecular geneticist, now at Memorial Sloan Kettering Cancer Center.

With additional parental consent, 85 babies were also tested for certain conditions that arise later in life but for which at-risk individuals could benefit from early screenings and other interventions. Three of them were found to carry gene variants that put them at a higher-than-average risk of adult-onset cancers. Two had

variants in BRCA2, and one tested positive for Lynch syndrome.

"This part of the testing was very different from the component that looked at childhood diseases," Beggs says. "In this case, it alerted the parents that they should also get tested because they were the ones who had more imminent risk. One of the aspects that's important to highlight with this kind of research is that genetic testing has implications for the whole family." This is in contrast to other medical testing, he notes, which only informs you about the health of the person having the test.

The BabySeq project aims to look at issues that arise with this kind of testing. The investigators are not proposing that it become part of standard newborn screening at this time. "There are many considerations with offering these tests to individuals," says co-author Casie Genetti, a genetic counselor at Boston Children's Hospital. "We plan to follow these babies, as well as their parents and their doctors, to look at how this information gets used and how it impacts health and well-being long term. It will help us to get a pulse on whether this kind of testing is feasible on a larger scale."

Another aspect to note is that, unlike other definitive screening tests, genetic results are rarely cut and dried. Genomic sequencing can reveal variants in disease-associated genes that confer higher levels of risk, but in some cases, this might lead only to unnecessary worry, as the absolute risk would still be small. In addition, many gene variants have unknown significance, making predictions of their eventual effects difficult. In the current study, the investigators only reported variants that were pathogenic or likely pathogenic if a child was healthy, but variant classifications may change over time as researchers continue to collect long-term data on people who carry them.

"This is one of the reasons it's important to continue to follow the participants in this study," Ceyhan-Birsoy concludes.

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The *American Journal of Human Genetics*, Ceyhan-Birsoy et al. "Interpretation of genomic sequencing results in healthy and ill newborns: Results from the BabySeq Project." https://www.cell.com/ajhg/fulltext/S0002-9297(18)30424-5

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