DNA sequencing in newborns reveals years of actionable findings for infants and families

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Researchers who lead the world's first comprehensive sequencing program for newborn infants have published the next chapter in the ongoing study of the BabySeq Project, with new findings on infants and families who have been followed for three to five years.

In a study published in the *American Journal of Human Genetics*, researchers from Mass General Brigham and Boston Children's Hospital reported that over 10% of the first 159 infants to undergo screening through DNA sequencing were discovered to have unanticipated mutations in disease-associated genes, all of which were medically actionable, meaning that the child would likely benefit from early treatment or surveillance.

When their families were followed over the next five years, these findings prompted genetic testing, specialty consultations and even procedures among infants' at-risk family members. Most striking, the at-risk mothers of three infants identified with previously unrecognized elevated risk for adult-onset cancer chose to undertake risk-reducing surgeries.

"By screening apparently healthy newborns, entire families were alerted for the first time that dangerous but treatable genetic variants were present," said corresponding author Robert C. Green, MD, MPH, a physician-scientist at Brigham and Women's Hospital and professor of genetics at Harvard Medical School, who co-leads the BabySeq Project. "We were stunned to see that with no specific guidance from the study, newborn sequencing prompted life-saving actions among several

mothers."

Babies born in U.S. hospitals currently undergo routine newborn screening, a laboratory test to identify the risk of up to 60 treatable conditions. But hundreds of additional genetic disorders, including a growing number of devastating childhood diseases, now have targeted treatments, including gene and cell therapies that can offer permanent prevention or cures. With these developments, the implementation of newborn DNA sequencing has taken on greater urgency.

The BabySeq Project is a first-of-its-kind randomized clinical trial begun as a collaboration between Brigham and Women's Hospital (BWH) and Boston Children's Hospital (BCH), and which expanded to include Massachusetts General Hospital (MGH). The trial was designed to examine how best to use genomics in clinical newborn medicine.

The first phase of the study enrolled 325 infants and families from well-baby nurseries and newborn nursery at BWH and neonatal intensive care units at BWH, BCH, and MGH between 2013 and 2018. Half of the newborns received genomic sequencing with comprehensive interpretation and return of results for nearly 1,000 genes. The sequencing looked for variants related to genetic risk for childhood-onset and childhood-actionable conditions, as well as several highly actionable adult-onset conditions that could only be inherited from one of the parents. The families have been followed for three to five years to understand medical, behavioral and economic outcomes.

Sequencing newborn DNA not only revealed the risk of future disease, but in some cases uncovered hidden conditions that were already present. For example, in one of the healthy newborns enrolled in the study, researchers detected a harmful change in the ELN gene, which can cause supravalvular aortic stenosis, a condition that if untreated, could lead to heart failure. On follow-up testing, a previously unsuspected narrowing

of the aorta was detected.

"Both our research team and the family were surprised that a DNA test led to the discovery of an anatomical abnormality in this baby," said co-lead author Nidhi Shah, MD, a medical geneticist at Dartmouth Health Children's, and collaborator with the Genomes2People Research Program. "This case highlights how genomic screening can uncover treatable genetic conditions that may not be apparent to healthcare providers during routine pediatric care."

"The results of this study indicate that conducting thorough genetic sequencing of newborns has the potential to significantly improve health outcomes for infants and their families," said Alan Beggs, Ph.D., Director of The Manton Center for Orphan Disease Research at Boston Children's Hospital, and co-leader of this BabySeq Project. Rare disease experts agree. In a separate study recently published by BabySeq investigators, a remarkable 88% of rare disease experts agreed that DNA sequencing to screen for treatable childhood disorders should be made available to all newborns.

The BabySeq Project has published extensively on the impact of newborn sequencing and, as part of BabySeq2, is currently enrolling newborns in multiple cities, prioritizing inclusion of a diverse, nationally representative cohort of families.

More information: Robert C. Green, Actionability of Unanticipated Monogenic Disease Risks in Newborn Genomic Screening: Findings from the BabySeq Project, *The American Journal of Human Genetics* (2023). DOI: 10.1016/j.ajhg.2023.05.007.
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