Brigham and Women's Hospital
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DNA Sequencing in Newborns Reveals Years of Actionable Findings for Infants and Families

- 1 in 10 infants who had unanticipated and medically actionable results were followed for up to 5 years.
- In two-thirds of these infants, genomic results prompted medical surveillance, evaluations, and procedures among family members, yielding additional benefits.
- Elevated genetic risk for cancer found in three infants prompted risk-reducing surgeries in their at-risk mothers

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 3-5 years. In a study published today in the *American Journal of Human Genetics*, researchers from Mass General Brigham and Boston Children's Hospital reported that over 10 percent 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 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 3-5 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, PhD, 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.

Paper cited: Green et al**. "**Actionability and Medical Evaluation of Unanticipated Monogenic Disease Risks in Newborn Genomic Screening: Findings from the BabySeq Project," *American Journal of Human Genetics*, DOI: 10.1016/j.ajhg.2023.05.007.

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Disclosures: Dr. Green has received compensation for advising Allelica, Atria, Fabric, Genome Web and Genomic Life and is co-founder of Genome Medical and Nurture Genomics. Additional disclosures for co-authors can be found in the AJHG paper.

About Genomes2People, BabySeq Project and Precision Population Health at Ariadne Labs: Mass General Brigham is an integrated academic health care system, one of the nation's leading biomedical research organizations and a principal teaching affiliate of Harvard Medical School, uniting great minds in medicine to make life-changing impact for patients in our communities and people around the world. The Genomes2People Research Program at Brigham and Women's Hospital, the Broad Institute, Ariadne Labs and Harvard Medical School explores the medical, behavioral and economic outcomes of integrating genomic information into medicine and society. The NIH-funded BabySeq Project is the world's first project to introduce comprehensive DNA sequencing for apparently healthy infants and has published extensively on medical benefits, psychosocial outcomes and medical costs associated with newborn sequencing. Precision Population Health is a collaboration between Genomes2People and Ariadne Labs that aims to bring the power of genomic medicine to primary care settings, in order to prevent diseases before they occur. Follow us on social media at Twitter (@robertcgreen, @genomes2people, @francafund) and Instagram (@genomes2people, @francafund).

About Mass General Brigham: Mass General Brigham is an integrated academic health care system, uniting great minds to solve the hardest problems in medicine for our communities and the world. Mass General Brigham connects a full continuum of care across a system of academic medical centers, community and specialty hospitals, a health insurance plan, physician networks, community health centers, home care, and long-term care services. Mass General Brigham is a nonprofit organization committed to patient care, research, teaching, and service to the community. In addition, Mass General Brigham is one of the nation's leading biomedical research organizations with several Harvard Medical School teaching hospitals. For more information, please visit massgeneralbrigham.org.

About Boston Children's Hospital: Boston Children's Hospital is ranked the #1 children's hospital in the nation by U.S. News & World Report and is a pediatric teaching affiliate of Harvard Medical School. Home to the world's largest research enterprise based at a pediatric medical center, its discoveries have benefited both children and adults since 1869. Today, 3,000 researchers and scientific staff, including 11 members of the National Academy of Sciences, 24 members of the National Academy of Medicine and 9 Howard Hughes Medical Investigators comprise Boston Children's research community. Founded as a 20-bed hospital for children, Boston Children's is now a 485-bed comprehensive center for pediatric and adolescent health care. For more, visit our Answers blog, and follow us on social media: @BostonChildrens, @BCH_Innovation, Facebook, YouTube and Instagram.