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CLINICAL GENETICS

Baby sequencing steps

The accurate diagnosis of a genetic condition at birth can benefit a child by giving access to tailored surveillance, treatment and management as well as information and support, such as adequate genetic counselling, for the individual and their families. The BabySeq project, a pilot randomized clinical trial exploring the value of routine genomic sequencing of neonates compared with standard newborn screening, now reports initial results in the *American Journal of Human Genetics*.

Although genomic sequencing can potentially shorten the diagnostic odyssey for patients with rare paediatric diseases, the analysis and interpretation of identified variants remains highly challenging, which has meant that the use of whole-exome sequencing (WES) and whole-genome sequencing as a diagnostic tool at birth remains far from routine. The BabySeq study enrolled 316 participants, including 251 healthy neonates and 65 neonates who had been admitted to newborn intensive care units (NICUs). A total of 157 neonates were randomly assigned to standard newborn screening, whereas the remaining 159 (127 healthy babies and 32 in NICUs) underwent WES in addition to standard newborn screening tests.

Only results for genes strongly associated with childhood-onset conditions were shared with parents. Of the sequenced study participants, 15 (9.4%) — 10 healthy neonates and 5 admitted to the NICU — were found to harbour genetic variants that increase the risk of a childhood-onset disease or condition for which early treatment would be beneficial, such as cardiomyopathy, congenital adrenal hyperplasia or hearing loss. The results could not have been predicted on the basis of clinical or family history of these neonates.

A total of 88% of sequenced neonates had carrier status for one or more rare genetic variants known to be associated with recessive diseases, that is, they were not at risk of the disease themselves but could pass disease-causing genetic variants on to their offspring. Carrier status for pharmacogenomic variants, that is, variants that influence the response to drugs used in the paediatric patient population, were identified in 5% of study participants undergoing WES. About half of the parents agreed to receive WES results about actionable adult-onset conditions, such as breast or colon cancer, which were found in three babies (3.5%), prompting referral for counselling and potential surveillance for the parent who had passed on these variants.

The BabySeq Project will continue to follow up the sequenced study participants to determine the economic, medical and behavioural impact of WES on the families over time.

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ORIGINAL ARTICLE Ceyhan-Birsoy, O. et al. Interpretation of genomic sequencing results in healthy and ill newborns: results from the BabySeq Project. *Am. J. Hum. Genet.* **104**, 76–93 (2019)
FURTHER READING Wright, C. F. et al. Paediatric genomics: diagnosing rare disease in children. *Nat. Rev. Genet.* **19**, 253–268 (2018)