Study finds 41% of infant deaths associated with genetic diseases

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In a study appearing today in *JAMA Network Open*, Rady Children's Institute for Genomic Medicine (RCIGM) researchers found that the contribution of genetic diseases to infant deaths was higher than

previously recognized. Of 112 infant deaths evaluated, single-locus (Mendelian) genetic diseases were found to be the most common antecedent of infant mortality and associated with 41% of the deaths.

Researchers also found that treatments predicted to positively impact outcomes were available for 30% of these genetic diseases. The implication of the study is that strategies for neonatal diagnosis have substantial potential to decrease mortality during the first year of life.

"At least 500 genetic diseases have effective treatments that can improve outcomes, and it seems that undiagnosed genetic diseases are a frequent cause of preventable deaths," said Stephen Kingsmore, MD, President & CEO of RCIGM. "Broad use of genomic sequencing during the first year of life could have much greater impact on infant mortality than was recognized hitherto."

The cohort study was conducted at Rady Children's Hospital in San Diego and included 546 infants (112 infant deaths [20.5%] and 434 infants [79.5%] with acute illness who survived) who underwent diagnostic whole-genome sequencing (WGS) between Jan. 2015 and Dec. 2020. Infants underwent WGS either premortem or postmortem with semiautomated phenotyping and diagnostic interpretation.

Among the findings:

- Single-locus genetic disease were the most common identifiable cause of infant mortality, with 47 genetic diseases identified in 46 infants (41%).
- 39 (83%) of these diseases had been previously reported to be associated with childhood mortality.
- 28 death certificates (62%) for 45 of the 46 infants did not mention a genetic etiology.
- Treatments that can improve outcomes were available for 14

(30%) of genetic diseases.
- In five of seven infants in whom genetic diseases were identified postmortem, death might have been avoided had rapid, diagnostic WGS been performed at the time of symptom onset or intensive care unit admission.

"Prior etiologic studies of infant mortality are generally retrospective, based on electronic health record and death certificate review, and without genome information, leading to underdiagnosis of genetic diseases. In fact, prior studies show at least 30% of death certificates have inaccuracies," said Christina Chambers, Ph.D., MPH, who co-led the study. "By implementing broad use of genome sequencing in newborns we might substantially reduce infant mortality."

To that end, in June 2022, RCIGM announced a novel program to advance and evaluate scalability of a diagnostic and precision medicine guidance tool called BeginNGS (pronounced "beginnings") to screen newborns for approximately 500 genetic diseases that have known treatment options using rapid Whole Genome Sequencing (rWGS).

BeginNGS uses rWGS to diagnose and identify treatment options for genetic conditions before symptoms begin, an advancement over current pediatric uses of rWGS that focus mainly on children who are already critically ill.

Once a diagnosis is made, BeginNGS uses Genome-to-Treatment (GTRx), a tool that provides immediate treatment guidelines for physicians to help them understand genetic conditions and their available treatment options, which may include therapeutics, dietary changes, surgery, medical devices or other interventions.

More information: Reclassification of the Etiology of Infant Mortality With Whole-Genome Sequencing, *JAMA Network Open*

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