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Genomic sequencing to screen newborns raises more false alarms than routine blood tests, study finds

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With advanced technology, clinicians can now sequence the genomes of apparently healthy newborn babies, seeking to turn up hidden inherited

diseases that aren't caught by routine blood testing. But new research sharpens questions about whether these DNA tests are sufficiently accurate.

In the largest study of its kind, published Monday in the journal Nature Medicine[5], a team led by researchers at the University of California, San Francisco, compared sequencing data to the results from standard blood testing conducted in newborns. They found that whole exome sequencing — a sequencing technique that reads all the chemical letters in the regions of the genome that code for proteins — turned up more false positives and more false negatives for inherited metabolic disorders.

Robert Green, a medical geneticist at Harvard and Brigham and Women's Hospital who was not involved in the research, called the study "really rigorous." Its findings, he said, are "a reminder that what we bring to sequencing at this moment in time is not as comprehensive as we sometimes imagine."

For their new study, the researchers analyzed de-identified data from newborn babies in California. Almost all of the 4.4 million babies born in the state between 2005 and 2013 were screened for inherited disorders using standard blood-based biomarker testing in which blood samples drawn from a newborn's heel are analyzed. (The process does not involve DNA testing.) When that technology, known as tandem mass spectrometry, was used, a total of 1,334 of those babies were ultimately diagnosed with an inherited metabolic disorder.

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The UCSF researchers and their colleagues conducted whole exome sequencing on blood spots stored in a biobank to try to assess the results that method would have yielded had it been used in standard practice.

They found that whole exome sequencing would have missed 12% of babies who indeed have metabolic disorders and incorrectly flagged 1.6% as having metabolic disorders that they did not actually have. By comparison, when the tandem mass spectrometry technology was used in routine care, it missed only 1% of babies who had metabolic disorders and incorrectly flagged only 0.2%

Had whole exome sequencing been used as a standalone screen in the clinic, the study suggests, about 160 California babies would have gotten false negatives and 8,000 would have gotten false positives.

The findings may add new fuel to longstanding criticisms of newborn sequencing. Critics worry that routine sequencing of newborns is too expensive, may create unnecessary stress for families, and rarely adds value over standard screening.

“Whether or not you think this is a good idea from an ethics point of view, which I think there are lots of reservations about, it actually is not as helpful as you might think it’s going to be,” said one of the senior authors of the study, Jennifer Puck, a UCSF physician whose research focuses on inherited immune disorders.

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The problem with the sequencing method, Puck said, appeared to lie in the

genome's complexity, an issue that was exacerbated by the diversity of California's population. The researchers turned up many variants that they didn't know how to interpret, including genetic changes that had never been reported in the literature, and in other cases didn't find variants they'd been expecting.

"The genome is a lot more complicated than people give it credit for, so we can't just use it as a screening test," Puck said.

The research did not completely dismiss the utility of genomic sequencing in newborns. The researchers found that it would have been a helpful second-line test for newborns whose standard biomarker screens were abnormal. "It could resolve many of those cases and shorten the diagnostic odysseys of the families and help achieve a result in those cases," Puck said.

The study was funded by a National Institutes of Health grant and as well as from Tata Consultancy Services, an India-based company that offers genetic sequencing services. A number of the study authors have affiliations with genetic testing companies, including the paper's first author, who is an employee of Illumina.

Outside of research, deep genetic sequencing is almost never conducted in apparently healthy newborns, in large part because of the expense. But some companies and health officials hope that will change.

Francis Collins, the director of the NIH, has repeatedly expressed hope that someday all newborns will have their genomes sequenced at birth. And in the U.K., a health minister last fall announced plans to offer sequencing to babies born in the country, starting with a pilot program of 20,000 newborns.

In 2017, the Boston-based company Veritas Genetics launched a $1,500

genome sequencing service in China called myBabyGenome. (Veritas last December ceased its U.S. operations and did not immediately return STAT's request for comment on Monday morning on the status of the myBabyGenome offering in China.)

The Chinese genetics company BGI markets a genetic test for newborns, aimed at "parents who want a comprehensive genetic screen for their baby." (BGI's website notes that the test has not been cleared or approved by the U.S. Food and Drug Administration and is not available in the U.S.)

While the new research suggests that sequencing falls short as a standalone screening method, no serious researchers and clinicians are suggesting that it be used that way, said Green, who has been a cautious proponent of preventive sequencing of apparently healthy people.

Green — the co-leader of a clinical trial known as the BabySeq Project[10] that sequenced the genomes of more than 150 babies born in two Boston hospitals — said he thinks there will be cases in which sequencing catches inherited diseases missed by routine biochemical screening, and vice versa.

"I think it speaks to the possibility," Green said, "that the most comprehensive screening for newborns will be some combination of conventional newborn screening and a future where we are able to quickly, safely, efficiently sequence all newborns."

About the Author Reprints[4]

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