Genomic sequencing as a standalone newborn screening tool falls short

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With the rise of genomic sequencing, health technology companies are promising parents they can detect rare metabolic disorders in newborns who, despite a healthy appearance, may need immediate treatment.

Now, scientists from UC San Francisco, UC Berkeley and Tata Consultancy Services are offering the first comprehensive assessment of how sequencing stacks up to the older screening technology, tandem mass spectrometry (MS/MS), that California uses to analyze the blood spots taken at birth for rare disorders, known as inborn errors of metabolism. They found that, when used alone, sequencing comes up short, missing some sick babies, while flagging many healthy ones for unnecessary follow-up testing. But sequencing can still be useful in cases that look suspicious but were not clearly identified by MS/MS.

"There has been a lot of publicity about universal sequencing for newborns," said Jennifer Puck, MD, professor of pediatrics at UC San Francisco and co-senior author of the study, published Aug. 10, 2020, in *Nature Medicine*. "But claims that sequencing is the key to health have been made without the support of rigorous studies."

Accuracy is essential when it comes to newborn screening. If cases are missed, seriously ill babies will go without prompt treatment for diseases that require urgent attention, such as phenylketonuria (PKU), which causes cognitive impairment when left untreated. But referring healthy babies for expert care is wasteful and puts families through unnecessary stress.

This study used a technique called whole-exome sequencing to look for mutations in 78 genes that are known to be involved in the 48 metabolic disorders for which every California newborn is screened. These diseases are rare, affecting about 150 of the estimated half a million babies born each year in California, and there are no signs when babies are born that they are going to get sick.

Since screening is meant for asymptomatic individuals, in this case newborns, it's very different from using sequencing as a diagnostic aid for patients with a medical problem that has already been detected.

"All of the prior studies of the utility of exome sequencing have started with a patient already in front of a doctor—in other words, a patient with a problem," Puck said. "You start with a clue in hand, a person with a particular difficulty, and you're trying to see if there's an underlying genetic reason for that. When you switch to screening mode, you don't have any clues. Most newborns look perfectly healthy."

Inborn metabolic disorders provided a unique opportunity to benchmark the performance of whole-exome sequencing, because it could be compared with California's well-established newborn screening program, which has been using MS/MS since 2005. These disorders have been well studied, and they are known to be caused by changes in a limited set of genes, most of which have been identified. So when they embarked on the study, the team had expected that sequencing technology might do better than the state's MS/MS screening method.

The state's current method looks for clues in babies' blood that something is wrong. The team found that the dried blood spots, which are taken at birth and then stored, could be used years later to analyze DNA. This provided a comprehensive view of nearly all the babies born in California with inborn errors of metabolism—about 1,334 of the nearly 4.5 million babies who were born in the period under study, from July of 2005 to December of 2013.

The team found that the standard MS/MS screening found 99 percent of babies with metabolic disorders, with a false positive rate of just 0.2 percent. But whole-exome sequencing would have found only 88 percent, missing about 160 of the 1,334 California babies who were ultimately diagnosed with metabolic disorders, while incorrectly identifying about 8,000 babies each year as being in need of urgent evaluation by a metabolic disease specialist.

The scientists said the shortcomings of the sequencing approach could

have several causes.

"These are well-studied single-gene conditions, but that does not mean we have found all the genes associated with them," said first author Aashish Adhikari, Ph.D., a member of UCSF's Institute for Human Genetics and UC Berkeley's Department of Plant and Microbial Biology. "Additional genes could be involved, as well as additional biological and environmental factors that may limit our ability to predict disease from DNA sequences alone."

Another problem is that these diseases are so rare that scientists haven't had many sequences to examine. Also, California's newborns are from highly diverse genetic backgrounds, with many variants that have never before been analyzed, since previous studies have emphasized people of Northern European ancestry. To analyze these new variants and predict their impact, the team had to develop a special computational pipeline.

But if whole-exome sequencing has limited use as a standalone primary screen, the study demonstrated that it still can be used to make a definitive diagnosis in cases where MS/MS showed something might be wrong, but doctors were unsure of what it was. And sequencing may yet prove useful in identifying newborns with treatable conditions that current screening methods cannot find.

"If the current mass spectrometry testing comes out unclear, sequencing could reveal a gene variant that solves the mystery," said Steven Brenner, Ph.D., professor at UC Berkeley, a member of UCSF's Institute for Human Genetics, and co-senior author of the study. "Sequencing to screen additional carefully vetted disorders could enable timely treatment of some children with conditions that presently go unrecognized until it's too late for optimal intervention."

More information: Adhikari, A.N., Gallagher, R.C., Wang, Y. et al.

The role of exome sequencing in newborn screening for inborn errors of metabolism. *Nat Med* (2020). doi.org/10.1038/s41591-020-0966-5