Novel screening approach improves diagnosis of metabolic disorders in newborns

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A team led by researchers at Baylor College of Medicine found that a screening method known as untargeted metabolomics profiling can improve the diagnostic rate for inborn errors of metabolism, a group of rare genetic conditions, by about seven-fold when compared to the traditional metabolic screening approach.

The study, published in *JAMA Network Open*, shows that untargeted metabolomics identifies many more disorders of greater variety as compared to traditional methods, including disorders for which there was not a clinically available biochemical test. The researchers hope that adoption of metabolomics to screen for inborn errors of metabolism will result in a more rapid, more efficient and less expensive diagnostic journey for individuals and families with rare metabolic disorders.

"Currently, newborn screening is conducted in every infant born in the U.S. to check for serious but rare health conditions at birth. Screening includes blood, hearing and heart tests," said corresponding author Dr. Sarah Elsea, professor of molecular and human genetics at Baylor and senior director of biochemical genetics at Baylor Genetics. "While newborn screening in general has improved in the last 10 years, clinically screening for inborn errors of metabolism has not changed substantially in the last 40 to 50 years."

Inborn errors of metabolism include conditions that disrupt the normal processes the body uses to transform food into energy and can result in serious conditions. Having an early diagnosis can lead to early treatment, when available. For instance, newborn screening looks for signs of conditions such as phenylketonuria, the body's inability to break down the amino acid phenylalanine, which results in its accumulation. Buildup of phenylalanine can irreparably harm the nervous system, but early intervention may help manage the condition.

"We developed a clinical test—untargeted metabolomics profiling—that looks at a broader range of metabolic compounds in the blood, therefore screening for many more disorders than the currently used approach," said Elsea, a member of Baylor's Dan L Duncan Comprehensive Cancer Center and Center for Drug Discovery. "In the current study, we compared the standard approach and untargeted metabolomics on their effectiveness identifying metabolic conditions."

The researchers compared the results of applying the two approaches to 4,464 clinical samples received from 1,483 unrelated families. They found that the traditional standard analysis has a positive rate of diagnosis of about 1%. However, using the untargeted metabolomics analysis the researchers were able to confirm a positive rate of diagnosis of 7%.

"This is a substantial increase in the ability to diagnose these conditions," Elsea said. "We are now able to identify in one blood sample more conditions than ever before."

"In addition, our analysis of many metabolic compounds in a single blood sample reduces the need of having to take more samples to do further testing looking for specific conditions. This includes taking samples of cerebrospinal fluid, which involves a more invasive procedure than drawing a blood sample," said co-author Dr. V. Reid Sutton, professor of molecular and human genetics at Baylor, medical director of the biochemical genetics laboratory at Baylor Genetics and director of the Inborn Errors of Metabolism Service at Texas Children's Hospital.

This screening approach offers the critical advantages of reducing the time to having a diagnosis and starting treatment, if available.

Using untargeted metabolomics in combination with genetic screening enables researchers and physicians not only to confirm a diagnosis with high degree of confidence, but also to rule out potential conditions. The novel, broader screening approach identifies severe forms of diseases and also mild forms that may not quite fit the characteristics observed in the more severe cases.

"We are finding individuals with milder forms of a disease are more common in our populations than those with severe forms," Elsea said.

"Our approach has been quite successful identifying seizure disorders, movement disorders and autism spectrum disorders. Our analyses have taught us to open our minds to a much greater spectrum of disease, allowing us to improve early diagnosis."

More information: Ning Liu et al, Comparison of Untargeted Metabolomic Profiling vs Traditional Metabolic Screening to Identify Inborn Errors of Metabolism, *JAMA Network Open* (2021). DOI: 10.1001/jamanetworkopen.2021.14155

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