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## Comprehensive mitochondrial disease diagnostic criteria still relevant in genomic era

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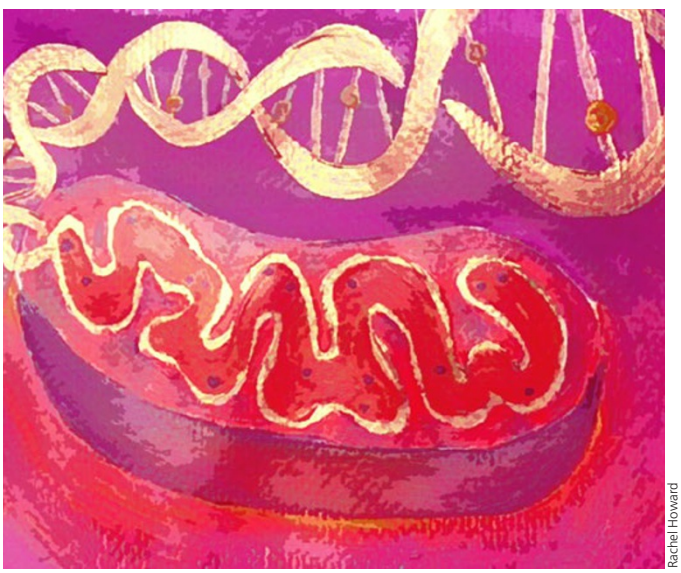
Mitochondrial syndromes remain among the most challenging disorders to diagnose accurately, even with the assistance of genomic testing. The sheer number of genes and intersecting pathways involved in mitochondrial metabolism makes tracing clinical symptoms to their source problematic, not to mention problems like heteroplasmy that arise from the unique physiology of these organelles. While genomic testing has assisted the diagnostic process, it remains unclear whether genomics can or will take the place of physiologic testing. In a study reported in this issue, Witters et al. evaluated the clinical route to diagnosis of 136 patients at seven clinical centers. The research team retrospectively collected data from both electronic medical records and genomic test results. Among clinicians, the use of direct sequencing of mitochondrial DNA, followed by genomic panels, has become standard. Some clinicians have questioned the need for muscle biopsy to establish a definitive diagnosis. In this study, researchers compared the use of genomic testing with use of the established comprehensive mitochondrial diagnostic criteria scoring system, which incorporates clinical features, imaging, and metabolic testing data. Patients with nuclear DNA mutations obtained a definitive diagnosis more often when diagnosed using the traditional disease criteria. Patients with mitochondrial DNA abnormalities received a definite diagnosis more often when analyzed by traditional Sanger sequencing than by gene panels. The results suggest that clinical phenotyping provides valuable support for whole-genome sequencing analysis and that it can assist in interpreting genomic testing results. The investigators conclude that comprehensive evaluation remains relevant in the era of genomic testing. *—Karyn Hede, News Editor*



Rachel Howard

## Genome-scale sequencing may supplant gene panels as a first-tier test in select clinical contexts

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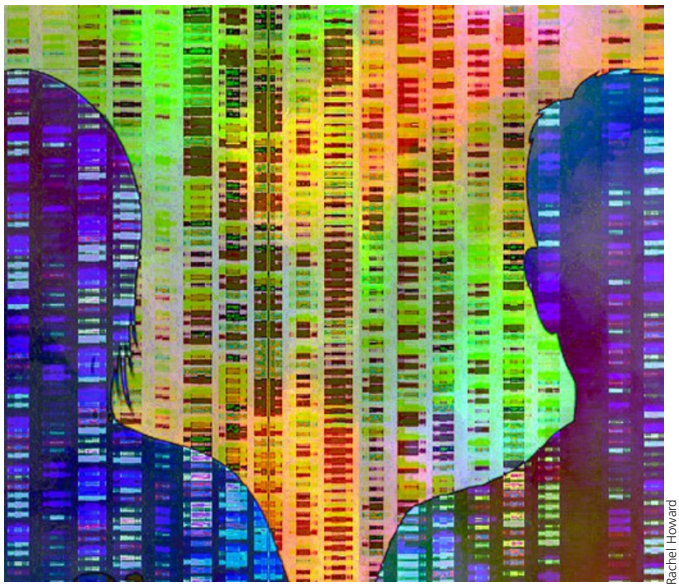

Rachel Howard

A new prospective head-to-head analysis suggests that the days of targeted genetic testing panels may be coming to an end in certain clinical settings. A research team based at the University of Toronto Hospital for Sick Children recruited 103 pediatric patients over a 2-year period from April 2013 to June 2015 and compared their diagnostic journeys. All patients received conventional testing by design. Twenty-five of the participants obtained a diagnosis, whereas whole-genome sequencing (WGS) identified variants in 42. The 17 patients whose diagnosis was due solely to WGS are described in detail. WGS detected not only all the variants seen in whole-exome sequencing (WES) but also many that would have been beyond the scope of WES. These included single-nucleotide variants, small copy-number variants, and noncoding variants. The authors suggest that in this setting the clinical practice of reserving WES and WGS for patients who fail multiple targeted diagnostic tests is wasteful of both time and money. The findings indicate that WGS may offer time savings and a more efficient route to diagnosis compared with WES. Moreover, while WGS remains more costly overall, when the high cost of iterative testing and the time cost are factored in, WGS, with its superior diagnostic yield, becomes competitive. The authors conclude that WGS will eventually become a first-tier diagnostic test in certain circumstances. However, in other settings, such as when evaluating patients with more clinically discrete presentations, a targeted approach will likely prevail. It's all about clinical context. *—Karyn Hede, News Editor*