IN THIS ISSUE

Early sequencing use may provide timelier diagnosis

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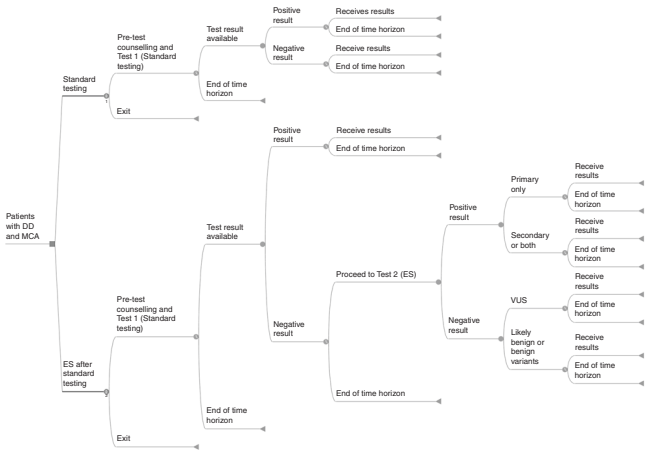

Guidelines for identifying a genetic diagnosis for multiple congenital anomalies (MCA) and developmental disabilities (DD) recommend a tiered approach. However, the standard testing pathway can be both expensive and time consuming, with diagnostic yield remaining low. As reported in this issue, Li and colleagues constructed an economic model to assess the cost-effectiveness of using genome (GS) or exome sequencing (ES) throughout the diagnostic pathway for individuals with unexplained DD and MCA. The researchers constructed a discrete-event simulation model, representing a hypothetical cohort of 1,000 patients with unexplained DD and/or MCA. A series of sequential events represented the diagnostic pathway in the model, which compared seven testing strategies. The model showed that, as compared with standard testing, early use of GS not only improved diagnostic yield but also cost less. The least costly strategy was ES as a second-tier test, when first-tier chromosomal microarray analysis failed to yield a diagnosis. ES alone as first-tier was the second least costly strategy, followed by ES with chromosomal microarray (CMA) as first-tier and, finally, GS as first-tier. In contrast, using either ES or GS after standard testing was the costliest strategy. The researchers determined that ES with CMA as first-tier dominated the other six strategies the team analyzed because it was less costly and more effective. This strategy led to the highest number of molecular diagnoses within the model's 3-year time horizon. In contrast, standard testing resulted in the lowest number of molecular diagnoses. The findings show that early use of ES yielded more diagnoses at a lower cost compared with late use or standard testing. The researchers conclude that the early use of ES or GS could benefit patients with unexplained DD or CMA by providing a timelier diagnosis. —*V. L. Dengler, News Editor.*

Virtual patient reveals reporting discrepancies

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Despite the existence of classification guidelines, variant analysis, interpretation, and reporting vary across laboratories. Vears and colleagues found that these differences significantly impact whether laboratories identify causative variants. The researchers created a virtual patient by inserting eight disease-causing variants from actual patients into an existing "genome-in-a-bottle" sequence. Only four variants—one each in *HDAC8*, *BICD2*, *MYBPC3*, and *PLN*—related to the virtual patient's phenotype. The other four variants encompassed a heterozygous variant in a recessive gene, a pathogenic variant, a variant of uncertain significance, and a variant that could be considered an unsolicited finding. The team then invited laboratories to analyze the patient's sequencing data and issue a report to the "referring clinician," i.e., the research team. Participating labs also completed a questionnaire on their reporting rationale and policies. About two-thirds to three-quarters of participating labs reported either one of the two variants in *HDAC8* and *BICD2* that were responsible for the patient's primary phenotypes, while less than half of labs reported both variants. Whereas more than three-quarters of labs reported the *MYBPC3* variant, less than half reported the *PLN* variant. A follow-up analysis revealed that laboratories utilizing input from a clinical geneticist for their analysis were more likely to report the *MYBPC3* variant. Labs often indicated that they did not report a variant because they had used a filter or gene panel that excluded it. At least two-thirds of labs did not report the other four variants, often due to reporting policies. Altogether, the data show that reporting practices vary substantially across laboratories, and that a significant number of laboratories did not identify variants responsible for a virtual patient's phenotype. The authors conclude that the findings carry serious implications for patient care. —*V. L. Dengler, News Editor.*

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