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IN THIS ISSUE

How do we quantify the clinical value of genomic sequencing?

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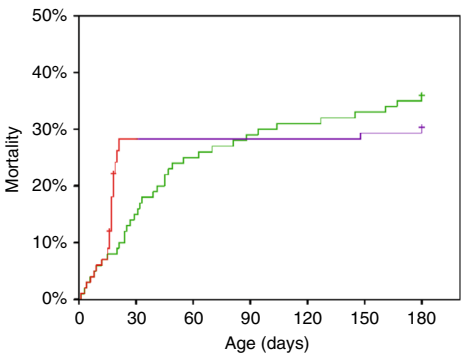

The diagnostic utility of genomic sequencing—exome and genome sequencing—has been documented in a variety of patient populations; but quantifying the clinical value, which is needed for widespread adoption, is more challenging. In this issue, Friedman et al. contemplate how the clinical value of genomic sequencing might be estimated in acutely ill infants in neonatal and pediatric intensive care units. The authors assert that investigations of clinical value must consider the effects of genomic sequencing that extend beyond simply making a diagnosis. They delineate the information they believe will be required and discuss the benefits and limitations of various measures including the ACCE (analytical validity, clinical validity, clinical utility, and associated ethical, legal, and social implications) framework, mortality, length of stay, and quality- and disability-adjusted life years (QALYs and DALYs), considering each in the context of current standards of care. The authors conclude that explorations of clinical value should frame genomic sequencing as a comprehensive scan for disease as opposed to a large panel of single-gene tests and suggest that genomic sequencing should be compared with chromosomal microarray, per case of serious disease diagnosed. In an associated comment also in this issue, Grosse and Farnaes discuss the recommendations of Friedman et al. and emphasize the importance of evaluating whether genomic sequencing explains patient phenotypes and whether test results impact patient management and outcomes. In comparison with standard of care, Grosse and Farnaes make a case for calculating the reduction in hospital days for nonfatal outcomes rather than assessing mortality. They also note that the perceived and actual value of a diagnosis and costs and benefits to relatives and families are also important metrics and argue that real-world observations may remain the main source of data, with compilation of information from multiple sites providing optimal data for analysis. *—Raye Alford, News Editor*

Validation of a complementation assay for estimating pathogenicity of *BRCA2* VUS

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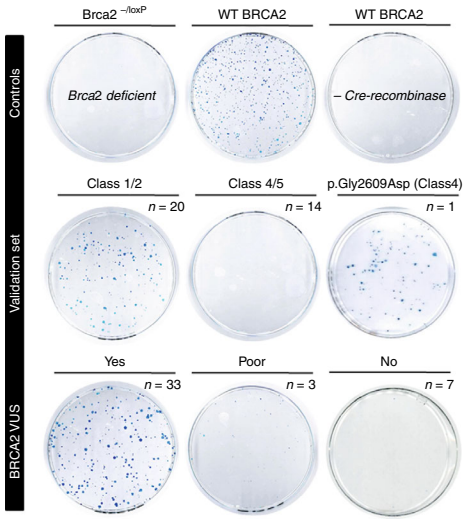

Variants of uncertain significance (VUS) pose a substantial challenge to the diagnosis and management of patients. In silico tools and clinical information support predictions of pathogenicity, but even with these data uncertainty about clinical risk often remains. Mesman et al. describe performance of a complementation assay for functional analysis of *BRCA2* VUS. The assay is based on mouse embryonic stem (ES) cells with one disrupted *Brca2* allele and one conditional *Brca2* allele. Cre-mediated deletion of the conditional *Brca2* allele results in nonviable ES cells that can be rescued by functional *BRCA2*. In this study, the research team transfected constructs carrying variant *BRCA2* alleles into ES cells to assay rescue of the lethal phenotype and homology-directed repair (HDR). Using 35 *BRCA2* variants of known pathogenicity, the authors validated the assay, distinguishing between class 1/2 variants and class 4/5 variants with 100% sensitivity and specificity: class 1/2 variants rescued the ES cells and demonstrated ≥50% of wild-type (WT) HDR activity; class 4/5 variants failed to rescue the ES cells or demonstrated <30% of WT HDR activity. Forty-three class 3 VUS were then tested: 36 variants rescued the ES cells, 4 of which demonstrated 31–46% of WT HDR activity and 3 of which demonstrated <30% of WT HDR activity. The authors conclude that this assay can reliably assess the functional impact of *BRCA2* variants but suggest that further investigation is needed to derive estimations of cancer risk from assay results. They caution, however, that this assay only tests HDR, and variants that compromise other functions of *BRCA2* might still be associated with elevated cancer risk. *—Raye Alford, News Editor*

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