by choosing an assay with lower tartrate concentrations (2, 3).

Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

Authors’ Disclosures or Potential Conflicts of Interest: No authors declared any potential conflicts of interest.

References


News & Views

Genome Editing as a Tool toward Better Functional Understanding of Variants Identified by Next-Generation Sequencing

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Next-generation sequencing has revolutionized clinical laboratory diagnostics; however, it is not without its challenges. One of the main shortcomings of clinical laboratories using this technology is interpretation of the variants identified. International efforts are aimed at reclassification of variants of unknown significance (VUS)2 as deleterious or benign, based on available data such as allelic frequency in a control population, conservation of the amino acid, in silico predictors, and published functional assays. However, these efforts have their limitations. A recent article in Nature Medicine by Tsai et al. (1) discusses a recent technology called genome editing as a relatively quick, simple, and cost-effective way to reclassify VUS. Briefly, genome editing, via the Cas9 system, allows RNA-guided DNA nuclease enzyme to induce site-directed double-strand breaks in DNA sequences of interest followed by either nonhomologous end-joining (NHEJ) repair or homology-directed repair (HDR). NHEJ or HDR can lead to efficient introduction of insertion/deletion mutations of varying sizes or precise sequence changes using a donor template, respectively. This system allows genome editing to be performed in situ with a very high efficiency and without the need for drug selection markers.

The article by Tsai et al. proposes that this genome editing technology could be used to elucidate the pathogenicity of the variants detected in a clinical setting (1). First, genome editing could be useful in determining whether a variant is playing a causative role (pathogenic) or not (benign). For instance, a recent study using this technology introduced knockout mutations in Pten and Trp53 in vivo in adult mouse liver, which resulted in tumor formation. Second, drug resistance mutations could be studied with this technology. For example, genome editing in a human embryonic kidney cell line introduced specific mutations that allowed identification of those that result in resistance to triptolide, a drug being studied for the treatment of pancreatic cancer. A third way this technology could be useful is in studying combinatorial effects of multiple variants. An example of this has been performed by introducing mutations in multiple genes important in hematopoiesis in a mouse model, which led to mice developing acute myeloid leukemia.

Although genome editing technologies have their limitations (discussed in the article), Tsai et al. highlight...
their potential utility in laboratory diagnostics (1). They envision that a clinical laboratory and a basic science facility, which has expertise in genome editing, would be linked together to provide a high-throughput functional assessment of variants. The findings of the basic science facility would be communicated back to the clinical laboratory for prospective validation on patient specimens. Based on the outcome, variants of clinical importance (pathogenic) can be incorporated into reporting, and those without functional effects (benign) would decrease the number of VUS being reported out. This would not only have a huge impact on workflow of the clinical laboratory, but more importantly would provide a clear result to the patient.

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Authors’ Disclosures or Potential Conflicts of Interest: No authors declared any potential conflicts of interest.

Reference


New Guideline for the Reporting of Studies Developing, Validating, or Updating a Prediction Model

In medicine, patients and their care providers are confronted with making numerous decisions that are commonly, if not always, made on the basis of a probability—a probability that a specific disease or condition is present (diagnostic setting) or a specific event or outcome will occur in the future (prognostic setting). In the diagnostic setting, the probability that a particular disease is present is used, for example, to inform the referral of patients for further testing, initiate treatment directly, or reassure patients that a serious cause for their complaint is unlikely. In the prognostic setting, predictions are used for planning lifestyle or therapeutic decisions based on the probability of developing a particular outcome or health state within a specific time period. Prognostic probabilities can be estimated from ill or healthy individuals, and simply refer to the prediction of an outcome in the future in individuals at risk for that outcome.

In practice, diagnostic and prognostic probability estimations are rarely based on a single test result (or single predictor), since such information is often insufficient to provide reliable estimates. Hence, to guide practitioners and patients in these probability estimations, so-called multivariable prediction models are developed. Prediction models convert multiple (2 or more) pieces of information from the patient—e.g., a patient’s age, sex, symptoms, signs, and laboratory and imaging test results—into a diagnostic or prognostic probability.

Prediction models are becoming increasingly abundant in the medical literature, and policymakers are increasingly recommending their use in clinical practice guidelines. In virtually all medical domains, prediction models are being developed, evaluated (validated), and implemented. For some specific diseases, there are even an overwhelming number of competing prediction models for the same outcome or target population. It is therefore important that these clinical prediction models and the research done to develop or evaluate these models be transparently reported. However, the overwhelming evidence shows that the quality of reporting of prediction model studies is poor. Only with full and clear reporting of information on all aspects of a prediction model can risk of bias and potential usefulness of prediction models be adequately assessed.

The Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) initiative, which has included clini-