IN THIS ISSUE

Genome-first approach identifies novel disease link

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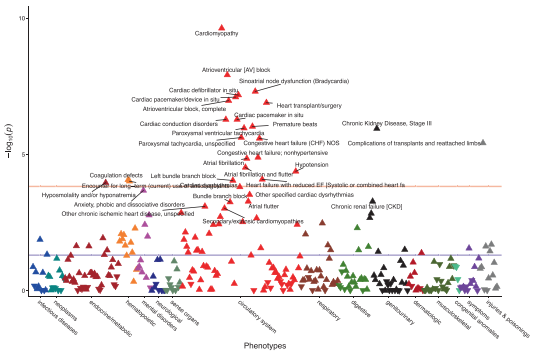

To determine the genetic basis of diseases, researchers and clinicians have traditionally used a "phenotype-first" approach, in which individuals with phenotypic disease traits are genotyped to identify gene variants that may be related to or responsible for a disease. Although this strategy has successfully identified new gene variants associated with human diseases, it often proves challenging to demonstrate pathogenic variants cause disease. In contrast, a "genome-first" approach, in which large, heterogeneous populations are sequenced and later associated with phenotypes, can uncover the clinical significance of specific gene variants. In this issue, Park and colleagues show the value of such an approach by revealing that pathogenic variants in the gene *LMNA*, a highly pleiotropic gene known to cause dilated cardiomyopathy and familial partial lipodystrophy type 2 among several other rare diseases, are an underdiagnosed cause of cardiomyopathy and renal disease. To conduct a phenome-wide association study (PheWAS) on pathogenic variants in *LMNA*, the researchers exome-sequenced DNA from nearly 11,000 individuals in the Penn Medicine Biobank and associated predicted loss-of-function and annotated deleterious missense variants with detailed phenotypes derived from linked electronic health records. Sequencing identified 72 individuals with predicted loss-of-function or deleterious missense variants in *LMNA*, and PheWAS showed a robust signal for primary cardiomyopathy and related diagnoses such as sinoatrial node dysfunction and congestive heart failure. The analysis additionally identified chronic kidney disease as a phenome-wide significant disease phenotype. Follow-up analyses revealed that *LMNA* carrier status associated significantly with decreased estimated glomerular filtration rate and serum albumin levels. The findings suggest that primary renal disease may be a novel laminopathy. Altogether, the findings provide a framework for discovering new gene–disease relationships via genome-first analyses. —*V. L. Dengler, News Editor*

New guide measures genetic tests' clinical utility

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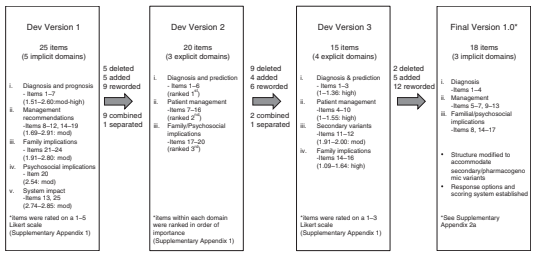

Genetic, genomic, and other "-omic" tests are gaining interest due to their anticipated benefits such as identifying disease risk before symptoms begin and allowing a precision medicine approach to management that improves quality of life. The impact a genetic test has on diagnostic or therapeutic management, prognosis, health, and psychological benefit to patients and families is known as its clinical utility. Although researchers and clinicians have been developing this concept for nearly 20 years, a single, validated measure that quantifies clinical utility does not yet exist. Now, Hayeems and colleagues present the Clinician-reported Genetic testing Utility InDEx (C-GUIDE), a measure designed to assess the impact of germline genetic testing results on a per-case basis. To generate the index, the researchers first conducted a scoping review of nearly 200 publications to select an initial set of 25 items to include in the index. Then they called on geneticists and genetic counselors as well as nongenetics stakeholders such as cardiologists and rheumatologists for feedback regarding each preliminary item's meaning, wording, and importance to the concept of "clinical utility." This round of assessment resulted in rewording of more than one-third of the items and reduced the overall number from 25 to 20. A second round of stakeholder evaluation, in which participants ranked the items by importance, further reduced the index to 15 items. Finally, the researchers gathered comments from an expert panel of clinical geneticists and genetic counselors. This analysis finalized the items, structure, and scoring of the index to 18 items under three domains—diagnosis, management, and familial/psychosocial implications—to provide a total clinical utility score. In future work, Hayeems and colleagues plan to assess C-GUIDE's reliability and construct validity in a range of settings. —*V. L. Dengler, News Editor*

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