Evaluating the strength of evidence for gene-condition relationships: impact on multi-gene panel testing design

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Disclosure statement: All authors are employees and stockholders of Invitae Corporation.

Introduction
As multi-gene panels have become routine in evaluating patients for genetically heterogeneous conditions, growing inter-laboratory variability has occurred in the number of genes offered in panels for many disorders. Some of this variability can be attributed to the relationship between the timing of assay design and the rapid discovery of new gene-condition relationships; however understanding the clinical validity of the diverse multi-gene panels offered in today’s molecular diagnostic setting is becoming increasingly important. Establishing the clinical validity of a multi-gene panel depends on an accurate and detailed understanding of the validity of each included gene. We proposed a method for establishing the clinical validity of genes and evaluated that method with a set of 93 pediatric and neuromuscular gene-condition relationships.

Results
We categorized 85 genes as having a strong association with at least one neuromuscular condition (muscular dystrophy, myopathy, congenital myasthenic syndrome). Eight genes were categorized as having only a suggested association with a neuromuscular condition. Three of those genes (SCN4A, SYNE1 and TMEM43) have a strong association with a non-neuromuscular condition.

Conclusions
We created a framework for categorizing gene-condition relationships, that establishes a method for distinguishing between genes proven to cause a condition and genes for which only preliminary evidence suggests an association. Although testing a gene before its clinical validity is conclusively established has legitimate benefits, understanding the rationale for its inclusion on a panel is critical for clinicians. The clinical utility of the findings in any gene ultimately depends on the strength of the evidence linking that gene to disease.