Pushing the Limit(ed)s: Modifications to a Gene-Validity Framework for Common Diseases and the Impact on Clinical Utility of Genetic Testing

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Abstract

Purpose: Defining gene-disease relationships (GDRs) is critical for multigene panel testing (MGPT) design, variant interpretation, and clinical management and is particularly challenging for common diseases with heterogeneous etiologies such as hereditary cancer predisposition (HCP). We present a revised gene-disease validity (GDV) framework adapted to both common and rare disease-associated genes.

Methods: 85 genes on HCP-MGPT were classified into five standardized GDV categories at time of panel addition. Reassessment of GDRs was performed, and changes in classifications due to GDV framework adaptations and/or new evidence were curated. VUS and positive rates were evaluated by GDV score.

Results: Genes with Definitive GDRs (n=42) were unchanged, while most genes with Strong (6/10, 60%) and Moderate (19/24, 80%) GDRs changed categories. Notably, 23.5% (n=8) of genes received a clinically significant downgrade. GDRs associated with breast cancer were significantly more likely to be downgraded (OR 25.5; 95% CI [3.42-317.4]; p-value=0.00015). No variants in genes with Limited GDRs were classified as pathogenic/likely pathogenic.

Conclusions: GDRs are influenced by disease prevalence, penetrance, and genetic heterogeneity. Calibration of a GDV framework accounting for these variables improves accuracy of MGPT. Limited evidence genes did not increase diagnostic yield and were rarely upgraded, indicating that including these genes on HCP-MGPT provides limited clinical utility.