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Do candidate genes increase clinical utility of hereditary cancer panels? When less is more

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Next generation sequencing has spurred new gene discovery for hereditary cancer predisposition (HCP) and allowed the development of multigene panel tests (MGPT). While the inclusion of more genes on HCP-MGPT increases diagnostic yield compared to single gene testing, data is lacking on how including new candidate genes on HCP-MGPT impacts diagnostic yield and variant of uncertain significance (VUS) rates. We assessed the frequency of variant classifications by gene-disease validity (GDV) scoring categories of genes on HCP-MGPT.

Reported variants in genes on HCP-MGPTs offered at a commercial laboratory from 2014-2021 were retrospectively reviewed. The frequency of pathogenic (P), likely pathogenic (LP) variants, and VUS were recorded and categorized according to four different GDV categories: uncharacterized (genes with limited/disputed GDV), moderate, strong, and definitive based on evaluation of published clinical and experimental evidence in accordance with the ClinGen GDV framework. Frequencies were determined by reviewing cases with a reported relevant variant (>240,000 cases). Genes uncharacterized for HCP but characterized for an autosomal recessive disorder were excluded from this analysis (*FANCC, RAD50, MRE11, XRCC2, BLM, NBN*). Genes with moderate or limited GDV for HCP at the start of the time frame (n=20) were reviewed for changes to GDV category. Variants were classified in accordance with ACMG guidelines.

Of >240,000 cases reported, the frequency of P/LP variants was 31.5%, 19.9%, 11.0%, and 0% among genes in the definitive, strong, moderate, and limited/disputed categories, respectively. VUS rates were inversely proportional to positive rate and increased as GDV scores decreased (68.5%, 80.1%, 89.0%, 100% for the definitive, strong, moderate, and uncharacterized categories, respectively). Among 20 genes with moderate/limited GDV at time of addition to MGPT, only 1 (5%) became characterized to a definitive GDV. Instead, the majority (55%) were downgraded to limited or disputed, and the remainder were unchanged limited (25%) or moderate (15%).

Rates of clinically actionable variants (P/LP) are correlated with higher GDV scores, and the rate of VUS is inversely related to GDV scores. Most genes with limited or moderate GDV at the time of panel addition were downgraded to limited/disputed categories or remained uncharacterized. The inclusion of newer candidate genes on HCP-MGPT did not affect the diagnostic yield, but substantially increased the VUS rate on HCP-MGPT. These results emphasize the importance of standardized GDV scoring to inform variant classification and gene inclusion criteria on MGPT to optimize clinical utility.

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