ASHG 2024 Abstract

Title: Impact of Gene-Disease Validity on Variant of Unknown Significance rates in hereditary cancer panels

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Gene-Disease Validity scores (GDV) measure the strength of evidence that exists to support the association of a particular gene with a particular condition. GDVs are utilized to make decisions about the context in which each gene should be offered, as well as how variants in the gene should be classified and reported. Here we review 3 iterations of an expanded-phenotype hereditary cancer panel (EX-P) to evaluate how rates of Variants of Unknown Significance (VUS) have changed with new knowledge, updated GDVs, and changes to panel content.

From September 2018 to June 2024 there have been 3 versions of EX-P (V1, V2, and V3). Seven genes found on V1 were once thought to have an association with heritable cancer but were eventually removed due to disputed evidence of pathogenicity and subsequently weakened GDV. These genes are *BLM*, *FANCC*, *GALNT12*, *MRE11A*, *NBN*, *RAD50*, and *XRCC2*. Similarly, *RECQL* was added to EX-P V2 and removed with the update to V3 based on evolving evidence and GDV, and so is included in our list of 8 eventually removed genes (RGs).

It is worth noting that changes beyond gene removal are made to panel contents with each update. Genes are also added for both previously indicated and new phenotypes. For example, the addition of *EGFR* for a new lung cancer indication on V2, as well as *MSH3* for the existing colorectal cancer indication. To account for these additions, as well as any laboratory changes, we compared each panel to a theoretical version of itself with RGs removed rather than comparing the VUS rate of V1 to V2 to V3.

V1 of EX-P included 7 of the 8 RGs and the VUS rate was 34.7%. Had RGs not been present, the VUS rate would have been 28.9%. *MRE11A* and *RAD50* were removed during the update to V2 while *RECQL* was added, and the VUS rate was 37.1%. This rate would have been 33.4% had RGs not been present. The latest update, V3, lacks all RGs and shows a VUS rate of 32.2%. The lower VUS rate of V3 when compared to V1 and V2 is particularly noteworthy as the population of patients being tested has shifted since 2018 with more clinically and ancestrally diverse patients undergoing hereditary cancer testing, including those who are unaffected. This change to the testing population is expected to contribute to an increase in VUS rates.

These perhaps seemingly small percentage differences equate to hundreds of patients each year who are not given a VUS result. VUS results are notoriously complicated for both patient understanding and provider counseling, and there is general agreement in the field that efforts should be made to reduce the volume of VUS results released. Utilizing GDV in the curation of panels is one way to help accomplish this and to maximize the clinical utility of panels.