Impact of Gene-Disease Validity on Variant of Unknown Significance Rates in Hereditary Cancer Panels

Elyse Ryan, MS, CGC[1,2]; Jessica Grzybowski, MS, CGC[1]; Devon Thrush, MS, CGC[1]; Daniel Kostecki, MS, MEng[1]; Carrie Horton, MS, CGC[1].

[1] *Ambry Genetics. 1 Enterprise, Aliso Viejo, CA 92656*
[2] *Author contact: eryan@ambrygen.com*

Introduction

Gene-Disease Validity (GDV) indicates the strength of evidence that exists to support an association between a gene and a specific condition. These scores guide genetic testing panel design, as well as how variants may be classified and reported. Over time, with new data, GDVs often change.

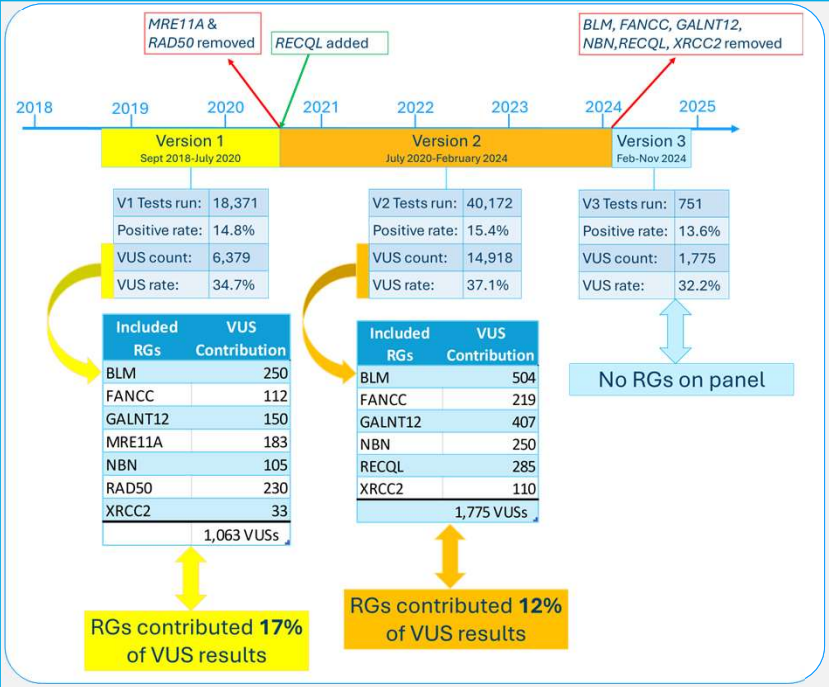
Here, we review three iterations of an expanded-phenotype hereditary cancer panel (EX-P) to evaluate how rates of Variants of Unknown Significance (VUS) change with new knowledge, updated GDVs, and changes to panel content. Over the time of this study, 8 genes had GDVs downgraded to "Disputed", indicating that there was enough evidence to refute previously believed cancer associations.

Methods

Theoretical versions of past EX-P iterations were generated using present day GDVs, excluding any gene now considered Disputed; These genes were referred to as Removed Genes (RGs).

Comparison approach: Analyses were made to theoretical versions of each EX-P iteration, not the current version, to account for changes in gene content and test methodologies which inherently have an impact on overall positive and VUS rates. The population of patients being tested for hereditary cancer predisposition is also known to have shifted over time, which has an impact positive and VUS rates.

Results & Discussion



↑ Figure 1. EX-P timeline with pertinent information regarding the differences in RG content, number of tests run, and positive/VUS rates for each iteration. **RGs contributed a significant proportion of VUS results for both V1 and V2.**

Gene:	BLM	FANCC	GALNT12	MRE11A	NBN	RAD50	RECQL	XRCC2
Disputed cancer association(s):	Breast Colorectal	Breast	Colorectal	Breast Prostate	Breast	Breast Ovarian	Breast	Breast

↑ Figure 2. Removed Genes (RGs) and their previously believed associations with cancer predisposition conditions.

EX-P Version	True VUS Rate	Theoretical VUS Rate with RGs Removed	Effect of RG Removal on Overall VUS Rate
Version 1	34.7%	28.9%	**-5.8%**
Version 2	37.1%	33.4%	**-3.7%**

← Table 1. **Lower theoretical overall VUS rates equate to thousands of patients who would have not received a VUS result, which are notoriously complicated for both patient understanding and provider counseling.**

Take Home Points

1. Individual genes require continuous evaluation to maintain accurate GDVs.
2. Hereditary cancer panels require continuous curation to maintain maximum clinical utility.
3. Removal of genes with disputed GDVs lowers overall VUS rates of hereditary cancer panels.

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