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

Poster 27

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BACKGROUND

- The expansion of next-generation sequencing (NGS) technologies has significantly increased the rate of gene discovery in the last decade.
- Standardized gene-disease validity (GDV) curation is essential to inform multigene panel testing (MGPT) design, variant assessment, and the clinical utility of genetic testing.
- GDV curation is dynamic and must consider the continuous learning curve in interpreting genetic variation. Longer-term trends in GDV scores have not been analyzed in the context of clinical impact on a commercially offered hereditary cancer MGPT.
- Unique gene-variant combinations are frequently detected in individuals with common diseases like cancer. Characterizing these gene-disease relationships (GDR) requires multiple lines of evidence and large population datasets to avoid premature characterization.

METHODS

- We reviewed GDV curation in the setting of a hereditary cancer predisposition (HCP) MGPT over a 7-year period (2016-2023).
- 85 genes on HCP-MGPT were classified into five standardized GDV categories at time of panel addition.
- During this time frame, our GDV framework was revised to provide discrete scoring rules for evaluating gene-disease associations for common disease with heterogeneous etiologies.
- 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.

FIGURE 1: Changes in GDV scores over a 7-year period for genes on HCP-MGPT (n=85)

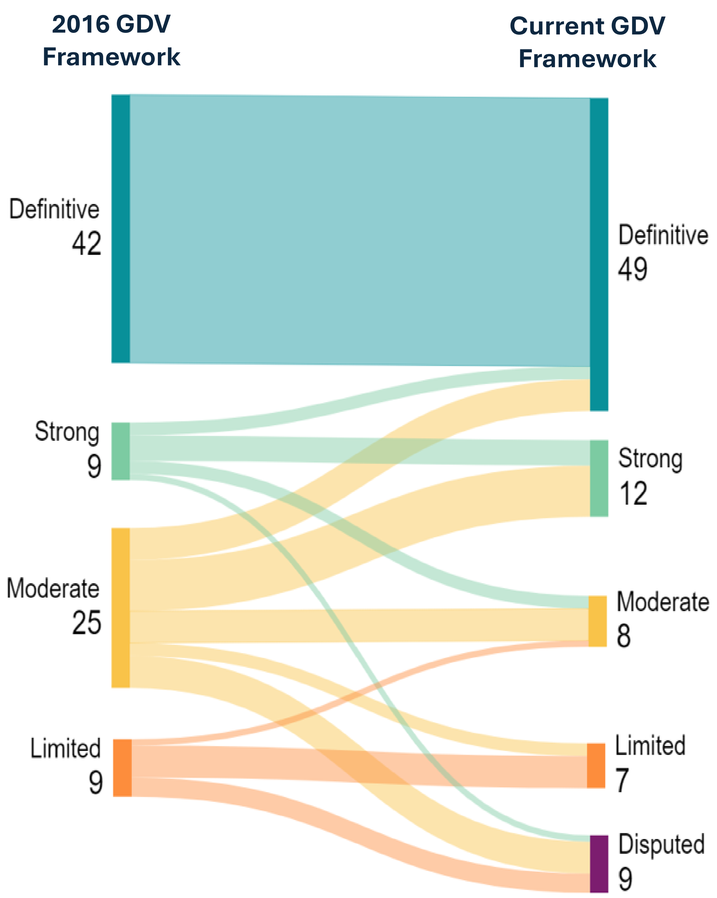


TABLE 1: GDV Comparison of Select Genes

Gene	Disease	2016 GDV Score	2016 GDV Classification	2023 GDV Score	2023 GDV Classification	Reason for Change*
BRCA2	HBOC	13+ and replicated over time	Definitive	17+	Definitive	N/A
CDH1	HDGC					
MLH1	Lynch syndrome					
RAD50	AD Breast cancer	13	Moderate	-4	Disputed	1, 2, 3
NBN	AD Breast cancer	10	Moderate	-7	Disputed	1, 2, 3
POT1	Melanoma	10	Moderate (2018)	17+	Definitive	1, 2, 4, 5, 6
NTHL1	AR Polyposis	8	Moderate (2018)	18	Definitive	4, 5, 6
PDGFRA	GIST	7	Limited (2018)	9.2	Moderate	2, 4, 5
RPS20	AD Colorectal cancer	6	Limited (2018)	4.4	Limited	2, 4

AD: autosomal dominant; AR: autosomal recessive; HBOC: hereditary breast and ovarian cancer; HDGC: hereditary diffuse gastric cancer; GIST: gastrointestinal stromal tumor

*1. Case control data 2. Calibrated proband scoring with new framework 3. Application of negative points 4. Additional case reports 5. Co-segregation data 6. New Functional/experimental data

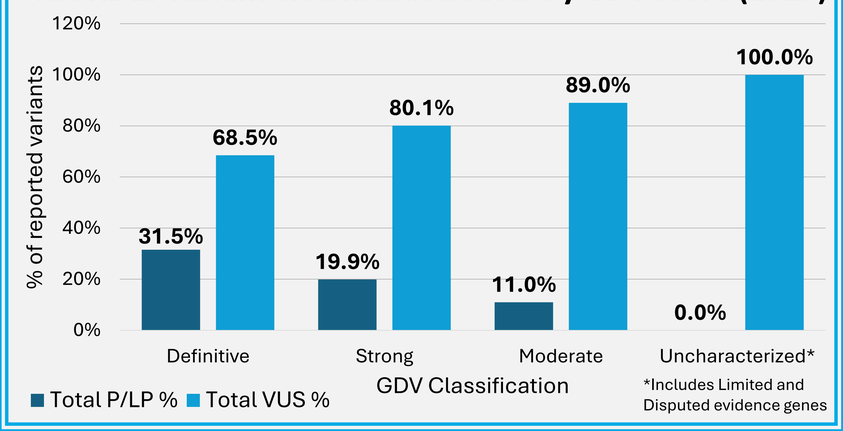
Table 2: Comparison of the 2016 and current GDV frameworks

2016 GDV Framework		Current GDV Framework	
Criteria	Points Available	Criteria	Points Available
Genetic Evidence		**Genetic Evidence**	
Number of unrelated patients	1 – 4	Number of unrelated patients with variants reported	0 – 18
Number of pathogenic variants	0 – 4		
Number of publications reported independent probands	0 – 3	Number of publications reported independent probands	0 – 3
N/A	--	Case-control studies	-18 – 18
Statistical Evidence	0 – 1	Statistical Evidence	0 – 1
Experimental Evidence		**Experimental Evidence**	
Gene function	0 – 2	Gene function	0 – 2
Gene disruption experiments	0 – 2	Gene disruption experiments	0 – 2
Model organism	0 – 2	Model organism	0 – 2
Total Points	**Gene-Disease Validity Score Category**		**Total Points**
"Canonical"	Definitive		17+ known mechanism
13+	Strong		13+
8 – 12	Moderate		8 – 12
2 – 9	Limited		>0 – 7
0 – 4	No Known Disease Relationship		0
--	Disputed		<0

RESULTS

- Genes with Definitive GDRs (n=42) were unchanged, while most genes with Strong (5/9, 55.6%) and Moderate (20/25, 80%) GDRs changed categories. **[Figure 1]**
- 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. **[Figure 2]**

FIGURE 2: Variant classification rates by GDV score (2023)



TAKE HOME POINTS

1. Limited evidence genes on hereditary cancer predisposition multigene panel testing (HCP-MGPT) do not increase clinical utility.
2. Upgrades for Limited evidence genes were rare over the 7-year reassessment period, with no breast or colon cancer predisposition genes upgraded.
3. GDV curation should account for phenotype frequency and heterogeneity to avoid premature characterization in the setting of common disease.

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