Ambry Genetics

WHITE PAPER

Gene-Disease Validity Assessments in Hereditary Cancer Testing

Introduction

Gene-Disease Validity (GDV) is a scoring system used to evaluate the strength of the association between specific genes and diseases, providing an essential framework for genetic testing and clinical decision-making in healthcare. The GDV system categorizes gene-disease relationships into distinct tiers: Definitive, Strong, Moderate, Limited, No Known Disease Relationship, and Disputed, each reflecting a different level of scientific evidence and understanding of the gene-disease link. The accuracy of gene-disease associations determines the reliability and usefulness of genetic testing in assessing cancer risk and guiding patient care.

Clinical genetic testing has evolved extensively over the last decade with the advent of next generation sequencing (NGS) technologies, which have significantly changed the landscape of genetic testing. The use of multigene panel tests (MGPT) has revolutionized the risk assessment and counseling surrounding hereditary cancer predisposition for patients[1].

MGPT has considerably increased the diagnostic yield of genetic testing by detecting pathogenic variants that would not have been identified through single gene-by-gene testing[2]. However, including genes that do not have a well-defined association with disease poses a significant challenge for clinical management and interpretation of results. By including genes with limited GDV on MGPT it increases the likelihood of receiving a variant of uncertain significance (VUS). Genes with limited GDV can only yield a result of VUS since the causal relationship is not proven.

Currently, there are no established guidelines for determining which genes to include on expanded MGPT, and commercial testing laboratories differ in gene content and approach[3]. The Clinical Genome Resource (ClinGen) has developed a framework and guidelines for determining the GDV, with the intention of providing guidance for MGPT gene content and standardization of GDV scoring[4,5].

Accurate GDV is crucial for providing clinically meaningful results from diagnostic genetic testing. Despite the advancements, challenges remain, particularly in assessing genes implicated in common adult-onset diseases, as certain levels of evidence used for GDV scoring in rare diseases may be misinterpreted for these more common disorders. The inclusion of newly-discovered candidate genes with limited evidence does not increase diagnostic yield, and many genes added to expanded MGPT may confer only a small magnitude of cancer risk compared to historically highly-penetrant genes. Thus, it is vital that there is continued reassessment of newly-characterized genes and growing evidence of seemingly well-established gene-disease associations by expert teams familiar with the process and with access to large, evolving data sets[1].

In this overview, the concept of GDV in hereditary cancer genetic testing will be outlined, the importance of accurately assessing gene-disease associations will be defined, and the challenges in establishing validity and the implications for patient care will be explored. A case study will be used to illustrate key points, and we will discuss potential future developments in this field.

Understanding Gene-Disease Validity-Key Terms

Gene-disease validity refers to the assessment of the strength of a relationship between a gene and a specific disease or phenotype. (Figure 1)

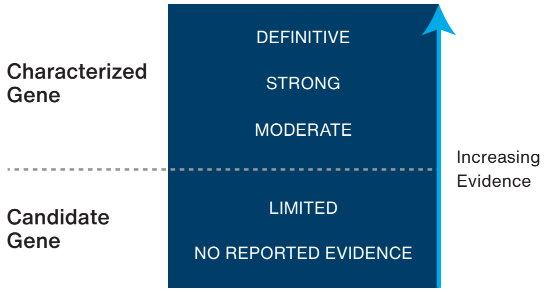

Figure 1. Clinical Validity of Gene Disease Association

Clinical validity assesses the relationship between the genetic variant being analyzed and the disease under consideration.

The **clinical utility** of a genetic test refers to its ability to provide helpful information about diagnosis, treatment, management, or prevention of a disease.

Gene-Disease Validity: A Reminder of the Firsts

To illustrate the concept of GDV, let's consider an example involving a genetic variant associated with breast cancer. Suppose researchers have identified a specific genetic variant in the *BRCA1* gene in individuals who have very early-onset breast cancer in multiple generations and aim to determine *BRCA1* gene-disease validity score in relation to breast cancer susceptibility.

They conduct extensive studies, over many years, involving diverse populations, analyzing the prevalence of this pathogenic variant in individuals with and without breast cancer.

The research findings reveal a statistically significant association between the presence of the *BRCA1* variant and an increased risk of developing breast cancer.

However, the strength of this association is further examined through various criteria such as the odds ratio, population attributable fraction, and replication across different studies. Additionally, functional studies might be conducted to understand the biological mechanisms through which this genetic variant contributes to cancer development.

If all the evidence consistently supports a strong and replicable link between the *BRCA1* pathogenic variant and breast cancer, the gene-disease validity of this association is considered high. This implies that individuals with this genetic variant are at an elevated risk of developing breast cancer compared to those without the pathogenic variant.

Clinical Validity Assessment of Genes for Inclusion In Multi-Gene Panel Testing

To visually demonstrate this concept, consider a study by Zion et al. (Figure 2) where they analyzed data from MGPTs associated with cardiovascular indications. The findings indicated that genes with higher GDV scores demonstrated an increased ability to classify pathogenic or likely pathogenic variants. In contrast, genes with lower CV scores displayed a higher prevalence of variants of uncertain significance (VUS). Importantly, only VUS were reported in genes with limited clinical validity[6]. Another way to put this is, if we cannot be sure a gene is related to a phenotype, by default the pathogenicity of any variant within that gene will also be uncertain.

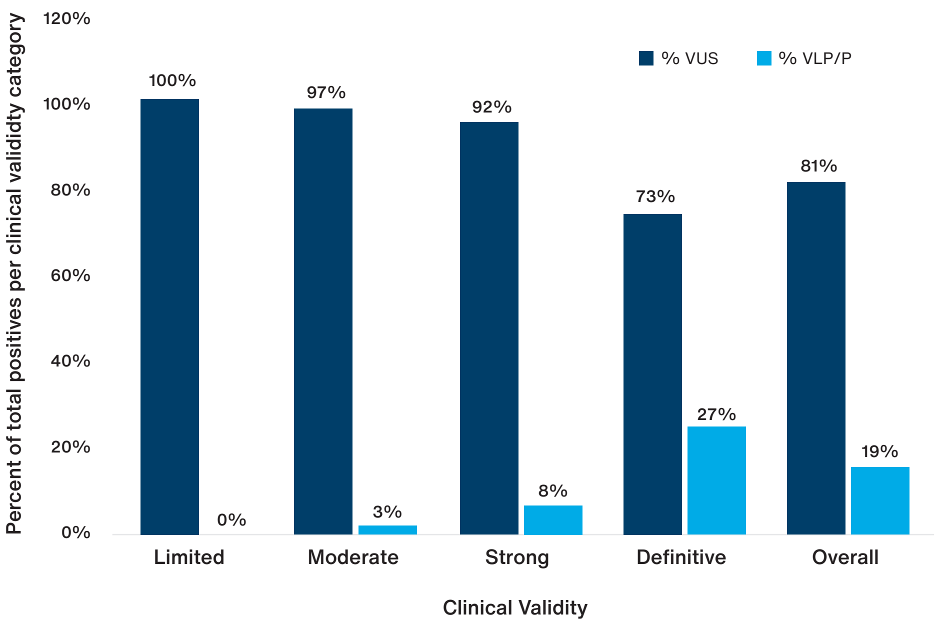

Figure 2. Clinical validity assessment of genes for inclusion in multi-gene panel testing.

Selecting genes for MGPT with established GDV increases the accuracy and clinical relevance of the results, thereby optimizing the effectiveness of genetic testing and enhancing the precision of medical interventions for patients undergoing MGPT for hereditary cancer.

Gene-Disease Validity: Emerging Cancer-Risk Genes

Now let's consider a hypothetical scenario where one research group initially identifies a genetic variant in a specific gene, *GeneX*, as a potential candidate associated with an increased risk of breast cancer.

They conduct an initial study that suggests a possible link, but subsequent investigations reveal challenges in establishing a strong and consistent gene-disease validity.

In this example case, the initial published study found a statistically significant association between the *GeneX* variants and breast cancer risk. However, as further research unfolds across independent researchers, collecting data from new sources and clinical testing laboratories, several factors emerge that limit the gene-disease validity of this association.

Conflicting Study Results: Subsequent studies, conducted by different research groups, in diverse populations, yield inconsistent results. Some studies fail to replicate the initial findings, while others show no significant association between the *GeneX* variants and breast cancer. The lack of agreement across studies raises doubts about the robustness of the observed relationship.

Small Effect Size: Even if a statistically significant association is found, the effect size (the magnitude of the association) might be small. A small effect size suggests that the *GeneX* variants have a limited impact on breast cancer risk, making it less clinically relevant. This diminishes the gene-disease validity because the practical significance of the association is now questioned.

Population-Specific Associations: The initial study focused on a specific population or subgroup, and subsequent research reveals that the association is not universally applicable to all ethnicities. Gene-disease validity is compromised when an association is only observed in certain populations but not consistently across diverse groups.

Publication Bias: There might be a tendency for studies with positive results to be published, while studies with negative findings may go unpublished. This publication bias can create a distorted view of the gene-disease association, and a comprehensive assessment of all available evidence is necessary to determine validity accurately.

Biological Plausibility Concerns: Further investigations into the biological mechanisms fail to provide a clear understanding of how the *GeneX* variants contribute to breast cancer risk. Without a well-established biological rationale, the gene-disease validity is undermined, as the observed association may be coincidental.

In this example scenario, due to the limitations mentioned, the gene-disease validity for the association between the *GeneX* variants and breast cancer would be considered limited, and all future clinical genetic testing performed would result in VUSs returned to patients.

This emphasizes the importance of rigorous and reproducible research and data sets to establish reliable genetic associations, the importance of ongoing and standardized GDV scoring/applications in clinical testing workflows, therefore ensuring that findings have meaningful implications for clinical practice and patient care.

Clinicians as Key Partners in Gene-Disease Validity Assessment

Providing comprehensive clinical information at the time of ordering plays a pivotal role in enhancing the accuracy and relevance of gene-disease variant scores, particularly when dealing with expanded panels. In instances where clinical data is not supplied to the laboratory responsible for variation curation, the risk of encountering potential pitfalls in the interpretation of genetic variants, especially in genes with limited evidence, becomes more pronounced. This lack of contextual information may contribute to the larger data set and continued classification of these as VUSs.

The importance of thorough clinical information cannot be overstated, as it serves as a critical guide for variant curation. Clinicians are uniquely positioned to furnish pertinent details about a patient's medical history, family background, and specific clinical manifestations, all of which contribute to a more nuanced understanding of the potential impact of identified genetic variants in the larger aggregate data sets that inform GDV.

Conclusion

Navigating the landscape of gene-disease relationships presents a multifaceted challenge, exacerbated by the rapid advancements in next-generation sequencing technologies and the ongoing surge in gene discovery rates. While the identification of new cancer susceptibility genes lags behind the rate for rare Mendelian diseases, addressing the intricacies of GDV in common diseases like cancer is imperative.

The advent of larger multi-gene panel tests (MGPTs) in diagnostic laboratories has significantly improved the diagnostic yield for hereditary cancer predisposition testing, surpassing the capabilities of traditional single-gene testing approaches. However, a careful balance must be found between expanding the size of MGPT to optimize diagnostic rates and excluding genes with insufficient evidence for clinical relevance to the targeted testing cohort.

In response to this challenge, meticulous curation of gene-disease validity becomes pivotal for both panel design and downstream variant curation. It is noteworthy that the inclusion of genes with limited evidence does not enhance diagnostic yield, as these genes lack the robust evidence required for clinically meaningful gene-disease relationships.

Key Takeaways

- **Crucial Role of Gene-Disease Validity:** Proactively curated, standardized GDV assessment is fundamental in hereditary cancer genetic testing to develop higher-quality products with increased clinical relevance and decreased frequency of ambiguous results.
- **Challenges with Expanded Panels:** While MGPTs offer enhanced diagnostic capabilities over single gene testing, the inclusion of genes with poorly defined disease associations poses challenges for clinical management and result interpretation, leading to an increase in variants of uncertain significance (VUS). If we cannot be sure a gene is related to a phenotype, by default the pathogenicity of any variant within that gene will also be uncertain.
- **Importance of Clinical Information:** Providing comprehensive clinical information during the ordering process is paramount for enhancing the accuracy and relevance of gene-disease data sets, particularly when dealing with expanded panels. The lack of contextual information increases the risk of encountering interpretation pitfalls, especially in genes with limited evidence.
- **Role of Clinicians in Variant Curation:** Clinicians play a crucial role in furnishing pertinent details about a patient's medical history, family background, and specific clinical manifestations. This information contributes to a nuanced understanding of the potential impact of identified genetic variants, ensuring a more accurate interpretation.
- **Ensuring Diagnostic Integrity:** Ongoing refinement and scrutiny in the assessment of gene-disease relationships are essential to ensure the integrity of diagnostic outcomes in the dynamic landscape of expanding genetic knowledge. Rigorous and reproducible research remains fundamental in establishing reliable genetic associations with meaningful implications for clinical practice and patient care.

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