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WHITE PAPER

The Role of Gene-Disease Validity in High Quality Test Design

Introduction

In recent years, multi-gene panel tests (MGPT) have emerged as a transformative tool in the field of genomics and personalized medicine. As applications and interest in genomics has advanced, so have the technological capabilities of these multi-gene panels, leading to more precise, comprehensive, and actionable insights.

Advancements in next-generation sequencing (NGS) technologies and bioinformatics tools have played a pivotal role in this evolution. Some panels now include hundreds of genes, with the intent of evaluating genes across a broad spectrum of conditions and enabling more detailed analysis. However, genes included on panels do not contribute to clinical utility uniformly.[1]

The ongoing refinement of MGPT is driven by several factors, including the characterization of gene-disease relationships that can change as new evidence develops. Based on available evidence, genes with established disease relationships and existing management guidelines will make up the backbone of a test, while genes lacking guidelines or consistent evidence of disease association may fluctuate over time and may be considered optional.

Positive and VUS Rates Differ by Gene

All genes have a distinct spectrum of variation, as some genes have highly conserved sequences that do not tolerate variability and the presence of any variant is strong evidence of pathogenicity while others exhibit high levels of variability that do not appear to be associated with disease (Table 1).[2,3] However, much of the difference between positive and VUS rates among genes is due to availability of evidence. Genes that are well-studied and have a robust repository of clinical and functional data generally exhibit lower inconclusive rates. In contrast, newly discovered or less well-characterized genes often have higher inconclusive rates due to limited information

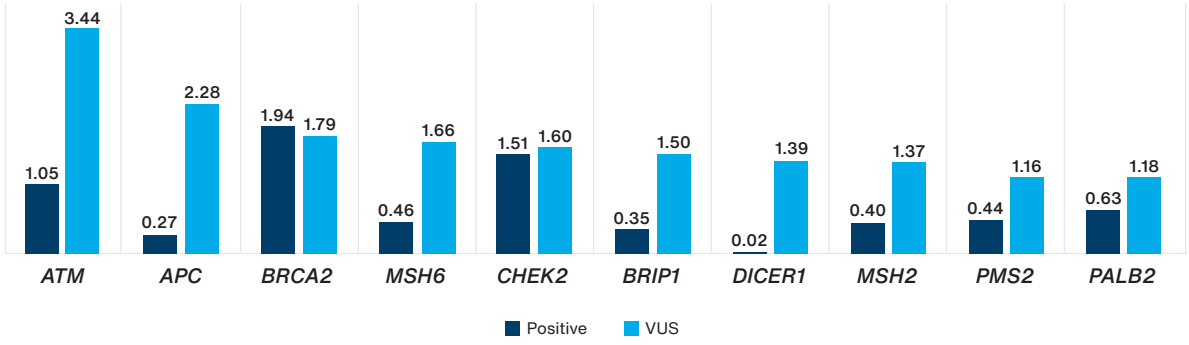

Table 1. Positive and VUS Rates Differ By Gene

about their clinical significance and mechanism of disease. In fact, in some genes (e.g., *GALNT12*, *RPS20*), every single reported variant will be classified as a VUS.

Limited Evidence Genes Do Not Contribute to Clinical Utility

Genes with limited or disputed evidence towards a disease association are both considered to be uncharacterized, and variants identified in these genes cannot be classified as pathogenic or likely pathogenic. Therefore, including genes in either of these categories on a panel can only increase the number of variants of uncertain significance (VUS) without contributing to diagnostic yield.[4]

There is some consensus that genes with disputed gene disease validity should be excluded from test panels since there is sufficient evidence to contradict their association with a given phenotype.[5] If laboratories decide to offer testing for genes with limited gene-disease validity in which supporting or conflicting evidence may yet develop, it is important to foster transparency about the lack of clinical utility these genes provide. For example, inclusion of limited evidence genes on a broad pan-cancer panel increases the VUS rate by nearly 14% while having no impact on positive rate (Figure 2) (internal data).

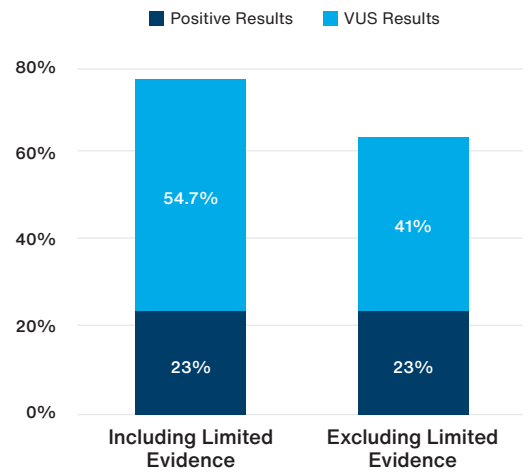

Figure 2. Impact of Limited Evidence Genes on Positive and VUS Rates

Multi-Gene Panel Design Must Evolve Over Time

As the field of genomics continues to advance, genetic testing laboratories bear the responsibility ensuring that their test offerings are current, accurate, and clinically relevant. This extends beyond the initial development of a test and requires ongoing research, integration, and validation of new technologies and clinical evidence.

For multi-gene panel tests to provide the highest level of scientific accuracy, labs must commit to monitoring new publications, clinical studies, and other emerging data on gene-disease associations. When a novel gene is linked to a hereditary condition, laboratories have an obligation to evaluate its potential inclusion in their panels (Figure 3).

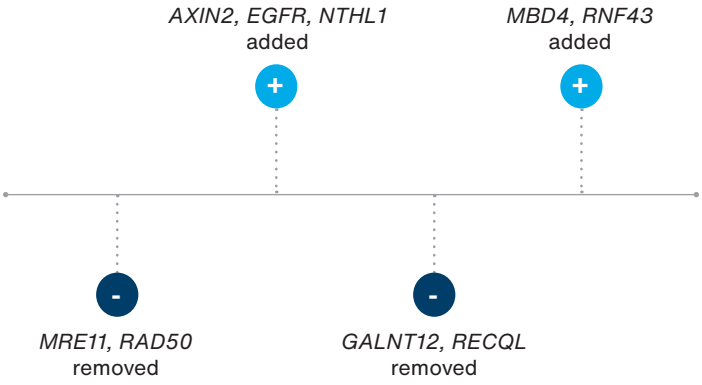

Figure 3. Evolution of Gene Content

Conversely, if evidence accumulates over time indicating that a gene does not contribute significantly to disease risk as previously thought, laboratories must consider removing it to minimize the risk of misleading results.

Balancing Flexibility and Utility

When designing a test portfolio, labs should include "base" or core test that includes a minimum number of genes known to be associated with the disease indication.[6] This usually consists of genes with the strongest evidence of gene-disease association and penetrance (Figure 4). The next tier of test options typically includes characterized genes with corresponding management guidelines (100% of genes on CancerNext® have management guidelines) but may have moderate evidence strength or decreased penetrance. Labs can also choose to include genes with limited evidence to allow for the broadest coverage, with the caveat that results from these genes will not be clinically actionable (65.8% of genes on CancerNext-*Expanded*® have management guidelines).

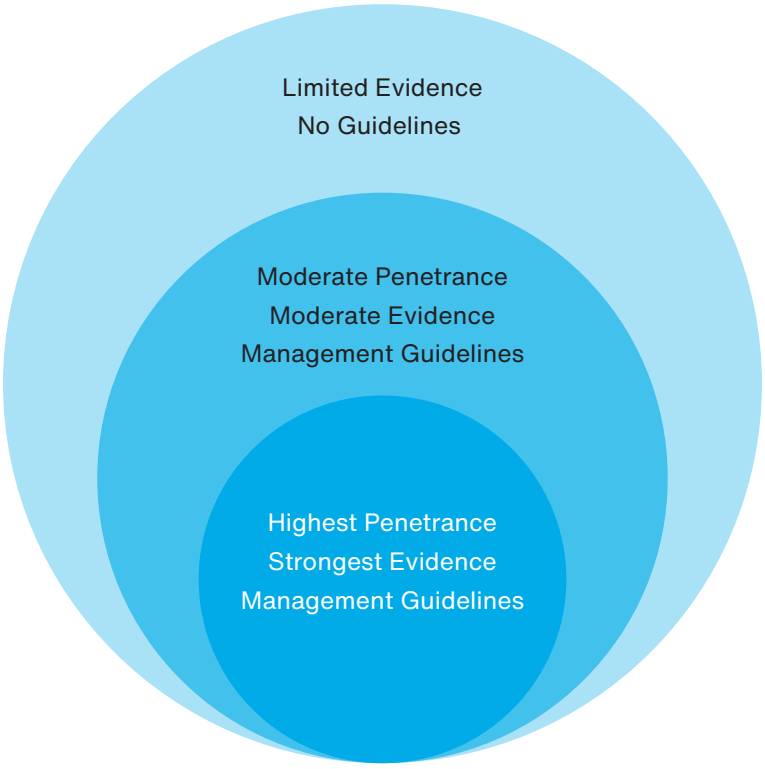

Figure 4. Gene Content and Evidence Strength

For example, requiring clients to opt-in to ordering limited evidence genes by adding them to existing panels can help maximize provider choice while mitigating risk of misinterpretation.

Conclusions

Robust panel design requires ongoing evaluation of emerging scientific evidence and clinical needs. Using gene-disease validity as a foundation for design creates the highest level of accuracy and utility for patients undergoing genetic testing.

References

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