

MAVEs Inform Variant Interpretation in Clinical Oncology Practice

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The accurate interpretation of genetic variants is critical for guiding therapeutic decisions in oncology, yet a substantial proportion of identified variants remain classified as Variants of Uncertain Significance (VUS). This ambiguity complicates patient management and limits the utility of precision oncology. Multiplex Assays of Variant Effects (MAVEs) provide a high-throughput method to functionally characterize numerous genetic variants simultaneously, offering a potential solution to reduce the VUS burden and enhance clinical actionability.

KEY TAKEAWAYS

- **The Pivot:** MAVEs systematically quantify the functional impact of thousands of genetic variants, moving beyond traditional single-variant analyses.
- **The Data:** MAVE data can reclassify a significant proportion of VUS into pathogenic or benign categories, improving diagnostic yield.
- **The Action:** Clinicians should anticipate MAVE-derived data integrating into variant interpretation guidelines, potentially refining treatment selection for patients with cancer.

The landscape of precision oncology relies heavily on the precise classification of genetic variants to inform targeted therapies. However, a persistent challenge is the high number of Variants of Uncertain Significance (VUS) identified through next-generation sequencing. These VUS cannot be definitively linked to disease causation or therapeutic response, leading to diagnostic uncertainty and limiting the application of genotype-driven treatments. Current variant interpretation guidelines, such as those from the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP), integrate various lines of evidence, including population frequency, computational predictions, and functional studies. However, traditional functional studies are often low-throughput and cannot keep pace with the volume of variants discovered.¹

Multiplex Assays of Variant Effects (MAVEs), also known as deep mutational scanning, represent a high-throughput experimental approach designed to quantify the functional impact of thousands of genetic variants within a gene or protein. These assays involve generating large libraries of variants, expressing them in a relevant biological system, and then measuring their functional consequences through various readouts, such as protein stability, enzyme activity, or cellular fitness. By systematically assessing the effect of each variant, MAVEs generate comprehensive functional maps that can directly inform variant classification. For example, a MAVE might assess the impact of every possible single amino acid substitution within a tumor suppressor gene on its ability to suppress cell growth. Variants that significantly impair this function would be flagged as likely pathogenic, while those with no discernible effect would be considered

benign.²

The methodology of MAVEs typically begins with the creation of a comprehensive variant library, often encompassing all possible single nucleotide variants (SNVs) or small insertions/deletions within a defined region of interest. Researchers achieve this through various molecular biology techniques, including oligonucleotide synthesis and site-directed mutagenesis. Following library generation, these variants are introduced into a suitable expression system, which can range from bacterial cells to human cell lines, depending on the protein and function being studied. A selective pressure or readout system then quantifies the functional consequence of each variant. This might involve growth selection, reporter gene assays, or direct biochemical measurements. Deep sequencing of the variant library before and after selection or functional readout allows for the quantification of the relative abundance of each variant, providing a quantitative measure of its functional effect. This systematic approach generates a functional score for each variant, reflecting its impact on the measured biological activity.

Integrating MAVE Data into Clinical Practice

The integration of MAVE data into clinical oncology practice holds promise for reducing the VUS rate and improving the precision of therapeutic decisions. MAVE-derived functional scores can be incorporated into existing variant interpretation frameworks, providing strong evidence for pathogenicity or benignity. For instance, a variant previously classified as VUS might receive a functional score indicating severe loss of function, thereby reclassifying it as pathogenic according to ACMG/AMP criteria. This reclassification can directly impact treatment selection, allowing clinicians to consider targeted therapies for which the patient's tumor was previously not deemed eligible due to variant uncertainty. Conversely, a VUS reclassified as benign could prevent unnecessary or ineffective treatments.³

The utility of MAVEs extends beyond single-gene analyses. They can be applied to characterize variants in genes associated with drug resistance or sensitivity, providing insights into patient response to specific chemotherapies or targeted agents. For example, MAVEs could be used to map the functional effects of variants in genes like EGFR or BRAF, identifying specific mutations that confer resistance to tyrosine kinase inhibitors. This information could guide the selection of alternative therapies or inform the design of combination regimens. Furthermore, MAVE data can contribute to the development of more accurate computational prediction algorithms by providing a large, experimentally validated dataset for training and validation.⁴

Despite their potential, the clinical implementation of MAVEs faces several challenges. Standardization of assay design, execution, and data analysis is critical to ensure reproducibility and comparability across different laboratories. The biological relevance of the functional assays must be carefully considered; an in vitro assay may not perfectly recapitulate the complex cellular environment in vivo. Furthermore, the sheer volume of data generated by MAVEs necessitates robust bioinformatics pipelines and clear guidelines for interpreting and reporting results in a clinical context. Regulatory bodies will need to establish frameworks for validating MAVE-derived evidence for clinical use. The cost-effectiveness of integrating MAVE technology into routine clinical sequencing workflows also requires evaluation.⁵

Another significant limitation involves the generalizability of MAVE results across diverse patient populations. Genetic backgrounds and environmental factors can influence variant penetrance and expressivity, which a single MAVE assay might not fully capture. The interpretation of MAVE data also requires careful consideration of the specific functional assay used, as different assays may measure distinct aspects of protein function. For instance, an assay measuring protein stability might yield different results than one measuring enzyme kinetics. Therefore, a comprehensive understanding

of the biological context and the specific mechanism of action of the gene product is essential for accurate clinical interpretation. The integration of MAVE data with other clinical and genomic information will be crucial to maximize its utility in personalized oncology.

CLINICAL IMPLICATIONS

The prospect of MAVEs systematically resolving the VUS dilemma in oncology is compelling. For clinicians, this means moving beyond the frustrating 'unknown significance' label that often stalls therapeutic decisions. Imagine a future where a patient's tumor sequencing report provides definitive classifications for nearly all identified variants, directly informing the selection of targeted therapies or enrollment in specific clinical trials. This shift would reduce diagnostic uncertainty and potentially improve patient outcomes by ensuring that treatment aligns more precisely with the tumor's molecular profile. It also implies a reduced reliance on empirical treatment choices or extensive, often inconclusive, family studies to resolve variant significance. From an industry perspective, the widespread adoption of MAVE data will necessitate significant investment in standardized assay development and validation. Companies offering diagnostic sequencing panels will need to integrate MAVE-derived functional scores into their reporting systems, potentially requiring partnerships with academic centers or specialized MAVE providers. This could also spur the development of novel bioinformatics tools and databases specifically designed to manage and interpret MAVE data. Furthermore, pharmaceutical companies developing targeted therapies will benefit from a clearer understanding of variant pathogenicity, enabling more precise patient stratification for clinical trials and potentially expanding the eligible patient population for their drugs, provided the evidence base is robust. For patients, the impact could be profound. A reduction in VUS means fewer instances of 'wait and see' or empirical treatment, and a greater likelihood of receiving a therapy specifically tailored to their cancer's genetic makeup. This precision could translate to improved response rates, reduced side effects from ineffective treatments, and a more streamlined diagnostic journey. However, it also places a greater onus on clinicians to understand the nuances of MAVE data interpretation and to communicate these complex findings clearly to patients. The ethical implications of using highly granular functional data to guide life-altering treatment decisions will also require careful consideration as this technology matures.

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