MAVE Progress Report, How Ambry Genetics Validates and Deploys High-Throughput Functional Assays

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Abstract: As the research community becomes increasingly proficient at high-throughput experiments, clinical laboratories need to adapt their methodologies to accommodate large-scale variant classification. Analyzing variants on a case-by-case basis will inevitably fall behind the rapid pace of research, creating an ever-widening gap between the release of new MAVEs and implementation into clinical settings. At Ambry Genetics, we are developing automated workflows that identify newly released studies, validate the quality of data, and calibrate results to ACMG/AMP evidence strengths.

Ambry collaborates directly with the research community to facilitate variant reclassification by providing clinical data and expertise. New MAVEs are identified via ongoing partnerships with academic institutions, or through AutoLit, an automated search software, and prioritized according to their clinical impact. Data from ClinVar, Ambry, and gnomAD is pulled and filtered to generate a high-quality reference set of pathogenic and benign variants. Logistic regression and local likelihood ratio estimation models are then run to assign variant-specific strengths of evidence. To visualize MAVE data, we developed GeneGlance, an online webserver intended to enable large-scale reclassification, and MAVEtracker to coordinate reclassification efforts. As of November 2025, we have processed 7 MAVEs for genes on our CancerNext panel, enabling personalized care for 18,300 patients via reclassification of 2,161 VUS.