

Title: Clinical Impact of Integrating *BRCA2* MAVE Data for Variant Reclassification: A Real-World Evaluation

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Abstract: MAVE studies provide high-throughput functional data that can refine the interpretation of genetic variants, especially for genes like *BRCA2*, which plays a key role in hereditary breast and ovarian cancer (HBOC) risk. However, the clinical application of MAVE data in VUS reclassification has not been thoroughly evaluated in a real-world setting. This study investigates the clinical utility of integrating MAVE data into variant reclassification workflows and quantify the downstream patient impact.

Following ACMG/AMP guidelines, we incorporated functional data from two MAVEs to reclassify *BRCA2* VUS previously classified in a clinical laboratory. Known pathogenic/likely pathogenic (P/LP) and benign/likely benign (B/LB) variants were used to calibrate these assays. MAVE data were highly concordant with prior clinical interpretations, with only one laboratory-classified variant showing discordance across both assays. Of 981 VUS evaluated, 54% (530) were reclassified, with 97.5% (518) reclassified as LB/B and 2.5% (13) as P/LP. These reclassifications impacted 4,362 patients, with 4,290 reports reclassified as VUS to LB/B, and 72 reports reclassified as VUS to P/LP, providing improved diagnostic clarity. Variants reclassified as P/LP included canonical splice (1/13) and missense (12/13), whereas reclassified LB/B variants included missense (517/518) and synonymous (1/518). Cascade testing of 24 individuals across 13 families resulted in 14 additional positive reports, highlighting the broader impact of MAVE data on family-based risk evaluation and management.

This study provides one of the first large-scale, real-world applications of MAVE data integration into a clinical workflow, offering a valuable model for resolving VUS and improving precision in hereditary cancer risk assessment.