Large-scale integration of functional assay data for the resolution of germline *BRCA1* and *BRCA2* variants of uncertain significance

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Carriers of *BRCA1* and *BRCA2* pathogenic variants are at a significantly elevated risk for breast, ovarian, prostate, and pancreatic cancer. Mainstream germline genetic testing has led to a significant increase in the detection of variants of uncertain clinical significance (VUS) in these genes, the vast majority of which are missense variants. VUS are a significant barrier for the identification of individuals at risk. Here, we collate data for *BRCA1* and *BRCA2* missense variants from 187 and 149 individual instances of functional assays, respectively, including large multiplex assays of variant effects (MAVEs) and integrate data from validated assays to assess their pathogenicity. We have curated and harmonized functional data for 3,246 *BRCA1* missense variants and 6,208 *BRCA2* missense variants representing 26 % and 30.1% of possible missense variants caused by single nucleotide changes in *BRCA1 and BRCA2*, respectively. Results were harmonized across studies by converting data into ordinal categorical variables (0, benign; 1, intermediate; 2, pathogenic). We used a panel of 529 known reference missense variants to determine the sensitivity, specificity, and ACMG/AMP odds of pathogenicity of every assay. Variants were assigned ACMG/AMP criteria based on the level of evidence. We then applied ACMG/AMP variant interpretation guidelines to assign evidence criteria for classification. For *BRCA1*, integration of data from validated assays led to ACMG/AMP concordant evidence criteria in favor of pathogenicity for 344 variants or against pathogenicity for 2,122 representing 76% of current VUS functionally assessed. For *BRCA2* evidence criteria in favor of pathogenicity was assigned to 425 variants or against pathogenicity for 4488 representing 79% of current VUS functionally assessed. In addition to making available harmonized high quality functional data for *BRCA1 and BRCA2* missense variants to aid in classification, this resource can also support a data-driven refinement of classification rules.