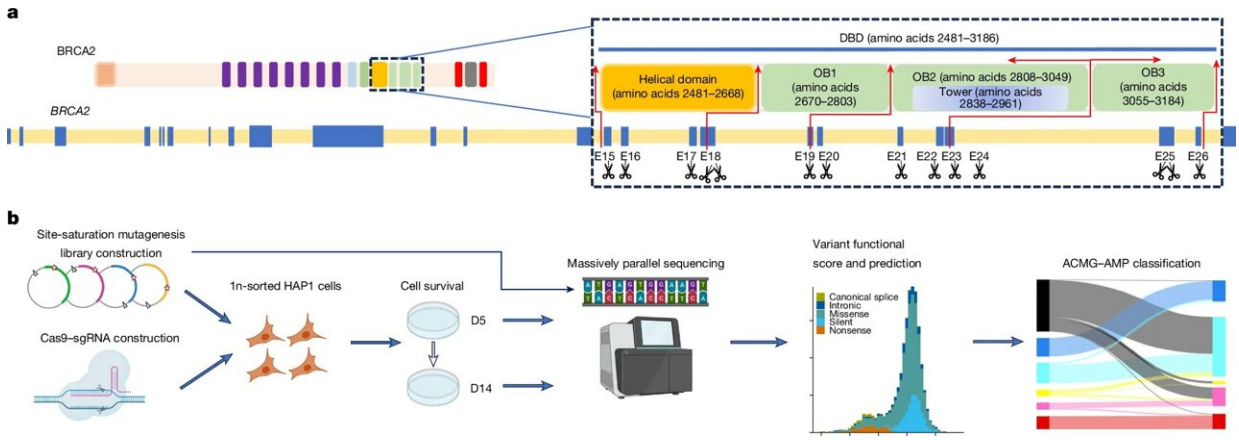
Improving cancer risk assessment and patient care: Researchers resolve uncertainty in BRCA2 testing

January 8 2025, by Kelley Luckstein



Schematic overview of the SGE MAVE of all SNVs in the BRCA2 DBD. Credit: *Nature* (2025). DOI: 10.1038/s41586-024-08388-8

Findings from a multi-institutional, international study led by researchers from the Mayo Clinic Comprehensive Cancer Center have significantly advanced the understanding of genetic alterations in the BRCA2 gene, a key player in hereditary cancer risk.

The researchers completed a comprehensive functional assessment of all possible variants within the crucial DNA-binding domain of BRCA2, resulting in the clinical classification of 91% of variants of uncertain

significance (VUS) in this part of the gene. This finding dramatically improves the accuracy of genetic testing and will allow health care professionals to offer more precise risk assessments and personalized treatment plans for people carrying these variants.

The study, published in *Nature*, utilized CRISPR-Cas9 gene-editing technology to analyze the functional impact of almost 7,000 BRCA2 variants, definitively identifying those that increase cancer risk and those that do not. This new information will eliminate much of the uncertainty surrounding VUS, allowing for more informed decisions regarding cancer screening, preventive measures and treatment strategies.

"This research is a major advancement in understanding the role of many BRCA2 variants in cancer predisposition," says Fergus Couch, Ph.D., Zbigniew and Anna M. Scheller Professor of Medical Research at Mayo Clinic.

"Until now, patients who carried VUS often worried if they would develop cancer, but now, with the classification of these variants, we can provide a clearer picture of cancer risk and tailor both prevention strategies as well as breast cancer treatment accordingly."

The findings have immediate implications for genetic testing laboratories and health care professionals, aiding them in offering more precise and personalized care to patients with VUS. Many people with VUS may be notified about the reclassification of their VUS as the ClinVar BRCA1/2 expert panel and testing laboratories use the new information in testing reports and updates. In addition, this new insight will aid in identifying patients with breast, ovarian, pancreatic or prostate cancer who might benefit from targeted therapies such as PARP inhibitors.

"We now have a catalog of every possible VUS in this part of BRCA2

that can be used to guide clinical care," says Dr. Couch.

The researchers say that this research lays the groundwork for future studies characterizing and classifying all BRCA2 variants across diverse populations and cancer types, improving risk assessment for everyone.

More information: Fergus Couch, Functional evaluation and clinical classification of BRCA2 variants, *Nature* (2025). DOI: 10.1038/s41586-024-08388-8.
www.nature.com/articles/s41586-024-08388-8

Provided by Mayo Clinic