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Bouwman and colleagues developed high-throughput functional complementation assays to predict the pathogenicity of BRCA1 variants of unknown significance (VUS). BRCA1 VUSs were evaluated for their ability to rescue proliferation defects, cisplatin sensitivity, and olaparib sensitivity in murine embryonic stem cells lacking endogenous Brca1. The ability of BRCA1 VUSs to rescue growth defects and drug sensitivity correlated with their homologous recombination activity, indicating that these assays can predict BRCA1 functionality. Interestingly, all unambiguously predicted pathogenic BRCA1 variants were located in the RING and BRCT domains. This approach has the potential to rapidly characterize BRCA1 sequence variants identified during screening for germline mutations associated with increased risk of breast and ovarian cancer. For details, please see the article by Bouwman and colleagues on page 1142.