**Triple negative breast cancer predisposition genes**

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**Background:** Germline cancer testing panels provide an effective method for identifying individuals at increased risk for breast cancer. However, estimates of risk for triple negative breast cancer (TNBC) (estrogen receptor-negative, progesterone receptor-negative, HER2-negative) associated with pathogenic mutations in panel genes have not been established. We sought to define the genes that contribute to TNBC.

**Methods:** Germline hereditary cancer multigene panel testing results were obtained for 8,753TNBCs evaluated by a clinical testing laboratory. Associations between pathogenic mutations in individual genes and TNBC were assessed by comparing mutation frequencies in TNBCs and in the Exome Aggregation Consortium, non-Finn European, non-Cancer Genome Atlas reference controls.

**Results:** Inactivating mutations in 21 known cancer predisposition genes were identified in 14.6% of TNBCs. BRCA1, BRCA2, PALB2, BARD1, and RAD51D alterations were associated with high risks (odds ratio(OR)>5.0) of TNBC and variants in BRIP1, RAD51C, MSH6, and TP53 were associated with moderate risks (OR>2). In contrast, ATM, CHEK2, NBN, and RAD50 yielded no clinically relevant risks of TNBC. Pathogenic mutations in these established non-BRCA1/2 TNBC susceptibility genes were detected in 6.3% of TNBCs. Similar trends were observed among African American TNBCs. Overall, 5.5% of TNBCs with pathogenic mutations did not meet NCCN clinical testing criteria for BRCA1/2.

**Conclusion:** The identification of genes associated with elevated risk of TNBC will improve understanding of the etiology of this aggressive form of breast cancer and inform risk management of individuals receiving panel testing. The high frequency of pathogenic variants suggests that all patients with TNBC, regardless of age of diagnosis or family history of cancer, should be considered for multigene panel testing.