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Concurrent DNA and RNA genetic testing identifies more patients with hereditary breast cancer than DNA testing alone

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Abstract:
BACKGROUND: Germline genetic testing is routinely incorporated into clinical care for breast cancer patients to inform management decisions and reduce risk for developing subsequent cancers. While the diagnostic yield of cancer genetic testing has increased over the years due to adoption of multigene panels, a substantial portion of breast cancer patients remain without a molecular diagnosis yet are suspected to have a genetic mutation that could not be detected and/or classified with standard DNA testing techniques. We assessed the ability of a novel genetic testing approach involving simultaneous DNA and RNA analysis to increase the diagnostic yield and decrease the number of variants of unknown significance (VUS). **METHODS:** Women with a personal history of breast cancer were ascertained from a larger cohort of patients referred for concurrent RNA sequencing alongside DNA hereditary cancer panel testing by ordering clinicians from 18 collaborating medical centers across the United States. Test result classifications were evaluated for women whose testing included sixteen clinically-actionable hereditary breast and/or ovarian cancer (HBOC) genes (*ATM*, *BRCA1*, *BRCA2*, *BRIP1*, *CDH1*, *CHEK2*, *MLH1*, *MSH2*, *MSH6*, *NF1*, *PALB2*, *PMS2*, *PTEN*, *RAD51C*, *RAD51D*, and *TP53*). **RESULTS:** In this cohort of 746 breast cancer patients, the addition of RNA sequencing increased the pathogenic variant detection rate from 8% to 9% across sixteen HBOC genes. These RNA-related positive results included two pathogenic variants in *BRCA1* occurring outside the standard analytical range of DNA testing and three VUS (one each in *ATM*, *BRCA2*, and *PMS2*) that were reclassified as likely pathogenic as a result of additional information provided by RNA sequencing. In addition, two VUS were reclassified to benign/likely

benign (one each in *MSH2* and *BRCA2*). Together, these five variant reclassifications contributed to a 3% relative decrease in the number of unique VUS classifications (reduced from 182 to 177 unique VUS). In addition, 31 previously-tested patients received reclassification reports. **CONCLUSIONS:** Concurrent DNA and RNA genetic testing has shown immediate promise in this pilot study, leading to the identification of five breast cancer patients with mutations in clinically actionable genes that would otherwise have received inconclusive or negative results with DNA testing alone. By increasing the detection of germline pathogenic variants and reducing VUS classifications, concurrent DNA and RNA genetic testing increases the diagnostic yield and clinical impact of hereditary cancer testing for breast cancer patients.

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Author Disclosure Information:

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