RNA genetic testing improves detection of patients with hereditary breast cancer

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Abstract:
Background: DNA genetic testing is commonly used to inform treatment decisions for breast cancer patients. In recent years, RNA genetic testing has shown promise for increasing the detection of disease-causing variants and decreasing inconclusive results. Here we describe the impact of concurrent DNA and RNA genetic testing on identifying breast cancer patients with germline cancer predisposition who may have been missed by DNA-only testing. Methods: We performed a retrospective review of breast cancer patients who received concurrent DNA and RNA hereditary cancer panel testing between March 2019 and February 2020 at Ambry Genetics. Patients underwent DNA and RNA genetic testing of up to 18 hereditary cancer genes at the discretion of the ordering healthcare provider (*APC, ATM, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, MLH1, MSH2, MSH6, MUTYH, NF1,A PLB2, PMS2 exons 1-10, PTEN, RAD51C, RAD51D, and TP53*). Breast cancer patients with positive results, defined as the presence of a pathogenic or likely pathogenic variant in any of these 18 genes, were selected for inclusion in this study (n=946). Results: Concurrent DNA and RNA genetic testing led to the identification of 23 breast cancer patients with positive results who would have otherwise received inconclusive or negative results with DNA-only testing. These cases represented 2.4% of all positive results reported in the 18 genes studied (n=23/946). The majority of RNA-related positive results occurred in either *ATM* (n=14) or *BRCA1/2* (n=7). The remaining two cases involved alterations in NF1 and PMS2. Guidelines for risk-reducing breast surgery (BRCA1/2) and breast imaging surveillance *(ATM, BRCA1/2, NF1*) were relevant for 30.4% and 95.7% of patients with RNA-dependent positive results, respectively. In addition, treatment options such as PARP inhibitors or clinical trial eligibility were potentially implicated for 91.3% of RNA-dependent positives (*BRCA1/2, ATM*). In 16 of the 23 cases, variants would have been detected by DNA-only testing but would have remained inconclusive without supporting RNA data. In the remaining 7 cases, abnormal RNA results led to the identification of pathogenic/likely pathogenic intronic variants beyond the analytical range of DNA testing. Thus, these seven patients would have received negative results from DNA-only testing. Four of these cases involved pathogenic/likely pathogenic intronic variants in *ATM* and three involved pathogenic intronic variants in *BRCA1*. Conclusions: One in 41 breast cancer patients who test positive on concurrent DNA and RNA genetic testing would have received negative or inconclusive results from DNA-only testing. These findings demonstrate the impact of a comprehensive diagnostic testing approach that includes concurrent DNA and RNA analysis and highlights the important implications for the personalized management of these breast cancer patients including potential missed opportunities for early detection and prevention of additional cancer and familial testing in the absence of RGT.