CURRENT VARIANT OF UNKNOWN SIGNIFICANCE RATES IN MULTIGENE PANEL TESTING

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BACKGROUND/OBJECTIVE: As information regarding familial genetic syndromes increases, more patients are undergoing genetic testing. With the introduction of panel testing (ranging from 5-43 genes), the incidence of variants of unknown significance (VUS) identified at our institution is increasing however this has not been well documented in the literature. The lay press has described VUS as a “medical mystery” with “implications entirely uncertain.” We sought to define the VUS rates at our institution, hypothesizing that the non-BRCA VUS rate is higher than what is currently reported in the literature (13.4%).

METHODS: Of a total of 930 patients seen by two genetic counselors at our community hospital from July 2013 to October 2016, 351 patients underwent genetic panel testing. A retrospective review was performed using an institutional database to determine incidence of mutations and VUS in BRCA as well as non-BRCA genes.

RESULTS: Genetic panel testing identified BRCA mutations in 2.8% of patients (10/351). The total BRCA VUS incidence was 4.3% (15/351), consistent with published reports. Non-BRCA mutations were identified in 17 patients (4.8%), with the most common being CHEK2 (4 patients), ATM (2 patients), MLH1 (2 patients) and TP53 (2 patients). There was one patient each with a mutation in BARD1, MSH2, NBN, PALB2, PTEN, RAD51C, and SDHB.

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The total non-BRCA VUS rate was 34% (120/351). The genes most frequently demonstrating VUS included APC (n=14), ATM (n=14), CHEK2 (n=12), CDH1 (n=11), PALB2 (n=5), and PMS2 (n=5). VUS were also identified in BARD1 (n=1), BARD2 (n=1), BRCA2 (n=1), BRIP1 (n=1), MSH3 (n=1), NBN (n=1), BRIP1 (n=1), CDH1 (n=1), MLH1 (n=1), MSH3 (n=1), NBN (n=1), PALB2 (n=1), PTEN (n=1), RAD50 (n=1), STK11 (n=1), CHEK2 (n=1), PM1 (n=1), PM2 (n=1), RAD50 (n=1), SMAD4 (n=1), and TP53 (n=1).

CONCLUSIONS: The incidence of VUS at our institution (combining both BRCA and non-BRCA genes) was high (39%) with panel testing. Myriad has previously reported that for the BRCA gene, with time as more diverse populations are tested, the rate of VUS has dropped (12.8% in 2002 to 2.9% in 2012 for all comers, with highest initial incidence and drop in patients from African and Latin American ancestry). Our institution does have a large proportion of African American and Hispanic patients, which may contribute to our high VUS rate. A limitation of our study is that a small subset of the patients identified to have a VUS were already tested by the oncologists or primary physicians and then referred to the genetic counselors after the variant was identified, which would also partially account for the high incidence we report. Our hope is that demonstrating the high rate of VUS will dissuade both clinicians and patients from making clinical decisions based on a variant result. Furthermore, the importance of testing diverse populations is essential to further characterize these variants and cancer risk.

REFERENCES