Clinical Management of High-Risk Breast Cancer Patients with Variants of Uncertain Significance in the Era of Multigene Panel Testing

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INTRODUCTION

• Since the discovery of the BRCA1 genes and their association with breast cancer nearly 25 years ago, 10% of newly diagnosed breast cancers are estimated to be caused by BRCA1 and BRCA2. There are now over 10 different genes associated with breast cancer susceptibility, including highly penetrant tumor suppressor genes BRCA1, BRCA2, PTEN, and TP53, and more numerous moderate penetrance genes.
• With wide availability of next generation sequencing, decreasing costs of genetic testing, and direct-to-consumer genetic testing, multigene panel testing has now become a frequently common and critical component of care for patients with and at risk for breast cancer. There is a lack of evidence regarding proper procedures and risk management strategies that should follow multigene panel testing.
• Rapid expansion of gene panels has led to an increase in frequency of variants of uncertain significance (VUS), which are DNA sequences identified within a gene that have an unknown effect on protein function and uncertain association with cancer risk. This source of difficulty and uncertainty can possibly lead to ambiguity in patient understanding and may result in suboptimal guidelines that clinicians should not make medical management decisions based on VUS findings.
• The objective of this study was to analyze the risk VUS results play in the surgical management, risk reduction and surveillance options for patients at increased risk for breast cancer.

METHODS

• All genetic testing reports from Loma Linda University Medical Center from January 1, 2015 to August 16, 2018 were reviewed. Cases were selected for inbreeding of personal and/or family history of breast cancer. Genes were variants as grouped: 1) biallelic or likely benign, 2) VUS, or 3) pathogenic or likely pathologic.
• Breast cancer associated genes included ATM, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, MRE11A, MUTYH, NBN, NF1, PALB2, PTEN, RAD50, RAD51C, RAD51D, TP53.
• Patient, variant, and post-test management characteristics were compared by pathogenicity of variant group classification (biallelic/likely benign [BLB] vs. VUS vs. pathogenic/likely pathologic [PLP]).
• Receipt of breast imaging, breast biopsies, oophorectomy and/or counseling after genetic testing was completed was recorded.
• Breast surgery analysis excluded any cosmetic or non-cancer risk related surgeries.

RESULTS

• Overall, 563 genetic tests were undertaken for breast indications and had results available for review. The mean patient age was 53.9±13.5 years (range 21-92 years). The number of genes tested in each panel ranged from 1 to 81. Testing companies included Myriad (50.6%), Ambry (12.5%), and Invitae (18.5%).
• Among those tested, 46.4% had VUS; 29.1% had only one VUS; 10.5%, two; 3.6%, three; 0.2%, four; 0.1%, five; and 0.5%, six or more.
• Overall, 353 (64.4%) of 563 patients had at least one VUS (range 1-6 VUS).
• Overall (n=563) breast cancer patients, 363 (91.2%) were female (range 21-89 years) and 63 (11.6%) were male.
• Overall, 35 (8.8%) breast cancer patients had at least one breast cancer-related VUS (range 1-2 VUS) (p=0.036).
• The most common VUS was CHEK2 with 76 (13.5%) cases.

DISCUSSION

• Our study demystifies VUS rates consistent with previous studies. Although most VUS are eventually reclassified as benign, research suggests that the ambiguity of VUS results may play a large role in the patient’s understanding and decision making regarding risk reduction and surveillance options, including prophylactic mastectomies. VUS is also associated with variations in patient care by physicians despite firm evidence supporting the role of these results to guide the management of patients.
• Previous reports have shown that BRCA1/2 VUS may influence clinical decision making, raising concern that the increasing frequency of VUS findings may change patient management decisions.

REFERENCES