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ORIGINAL ARTICLE – BREAST ONCOLOGY

Clinical Management of Patients at Risk for Hereditary Breast Cancer with Variants of Uncertain Significance in the Era of Multigene Panel Testing

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ABSTRACT

Background. Rising use of multigene panel testing has led to increased identification of variants of uncertain significance (VUS). Consensus guidelines state that clinicians should not make medical management decisions based on VUS findings. We sought to analyze how VUS affect management of patients at risk for hereditary breast cancer.

Methods. All genetic testing reports for indications of hereditary breast cancer risk from a single tertiary-care institution from 2015 to 2018 were reviewed. Variants were grouped by pathogenicity (benign/likely benign, VUS, or pathogenic/likely pathogenic [P/LP]) and by breast cancer susceptibility (high, moderate, or none). Patient and management characteristics were compared by variant pathogenicity and breast cancer risk.

Results. Overall, 563 patients underwent genetic testing for breast cancer risk; 336 VUS were identified in 228 (40.5%) of patients of which 26.4% were in high or moderate penetrance genes. P/LP results were found in 61 (10.8%) patients, of which 61.2% were identified in breast-specific moderate and high penetrance genes, and 38.7% were found in non-breast specific genes. Of variants found in high-risk genes, 54.5% were P/LP and 45.5% were VUS. On multivariable analysis, prophylactic mastectomy was associated with younger age and personal history of cancer, but not variant pathogenicity or penetrance. There were no differences in the use of post-test imaging, oophorectomy, or colonoscopy based on variant findings or age.

Conclusions. In this era of multigene panel testing, genetic factors help to inform, but not dictate, complex decision-making in surveillance and management of patients at risk for hereditary breast cancer.

Since the discovery of the BRCA genes more than 25 years ago, there are now more than ten different genes associated with breast cancer susceptibility, including highly penetrant tumor-suppressor genes BRCA1, BRCA2, PTEN, and TP53, and more numerous moderate penetrance genes.[1–3] With wide availability of next generation sequencing (NGS), decreasing costs, and direct-to-consumer genetic testing, multigene panel testing has become a common and critical component of care for patients with and at risk for breast cancer.

Yet, there is a lack of evidence regarding proper procedures and risk management strategies that should follow multigene panel testing. Recent studies have identified clinical actionability associated with expanded multigene panels.[4–6] However, rapid expansion of genetic panels also 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.[7] Studies of multigene analyses from breast cancer patients have shown that one or more VUS is found in 33–54% of individuals.[4,6,8]

VUS are a source of difficulty and uncertainty for both patients and physicians, leading to discrepancies in patient understanding and counseling.[9–11] The American College of Medical Genetics and Genomics (ACMG) states that clinicians should not make medical management decisions based on VUS findings.[7] We sought to analyze the role

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VUS results play in the management of risk reduction and surveillance options for patients undergoing genetic testing to assess hereditary breast cancer risk.

METHODS

After institutional review board approval, all genetic testing reports from Loma Linda University Health between January 1, 2015 and August 16, 2018 were reviewed. In the Loma Linda Breast Health Center, before testing, patients meeting National Comprehensive Cancer Network (NCCN), Medicare or other insurance criteria for hereditary breast cancer risk assessment are counseled by board certified physicians who provide cancer risk assessment regularly. Patients also review educational materials with an advanced practice oncology nurse who has specialized education in cancer genetics and hereditary cancer predisposition syndromes. Pretesting education with the nurse consists of a review of printed and online materials and an educational video about hereditary breast cancer syndromes. Definitions of sporadic, familial and hereditary cancer are discussed. Management recommendations for a positive BRCA 1/2 are given, and patients are educated that if they test positive for another gene, recommendations will be based on cancer risks of that particular gene. The possibility of positive, negative, and VUS results are reviewed. The Genetic Information Nondiscrimination Act is reviewed. Tailored information regarding insurance coverage also is provided to the patient. Patients are notified if their out-of-pocket amount is expected to be more than $100 and are informed of cash pricing. Finally, the patient is provided an informed consent form. Post-test counseling is performed by both treating physicians and nurse practitioner. When outcomes from genetic testing results will impact surgical decisions, surgery is performed after test results are obtained. Certified genetics counselors are utilized on an individualized basis pre- and post-testing for complex or rare findings and when required by insurance.

Cases were selected for study with indications of hereditary breast cancer based on personal and/or family history. Genetic variants were recorded and grouped as (1) benign or likely benign (B/LB), (2) VUS, or (3) pathogenic or likely pathogenic (P/LP). Genes were classified according to association with breast cancer susceptibility according to NCCN guidelines. Highly penetrant genes for which "risk-reducing mastectomy should be discussed" include BRCA1/2, TP53, and PTEN. Moderately penetrant genes associated with increased breast cancer risk for which NCCN guidelines state, "There are no data on the benefit of risk-reducing mastectomy… but this procedure may be considered based on family history" or "There are no data on the benefit of risk-reducing mastectomy…therefore, risk-reducing mastectomy is not recommended in these patients, but this procedure may be considered based on family history" include ATM, CDH1, CHEK2, PALB2, NBN, NF1, and STK11.[12] Low penetrance genes with insufficient evidence for breast cancer association and/or management, including BARD1, FANCC, MRE11A, MUTYH heterozygotes, RECQL4, RAD50, RINT1, SLX4, SMARCA4, and XRCC2, were assigned to the non-breast-specific category.[12] Variants reclassified during the study period remained assigned to the original pathogenicity grouping at the time of initial testing.

Demographic and clinical data were collected from medical records. Variables included patient age at the time of genetic testing, self-reported race/ethnicity, history of breast cancer (past, current, none), family history of breast cancer, dates of breast surgery and genetic testing, type of breast surgery (partial mastectomy, total mastectomy), receipt of prophylactic mastectomy (bilateral or contralateral), receipt of breast imaging, breast biopsy, oophorectomy, or colonoscopy after genetic testing was completed, and date of last contact. The type of breast surgery variable included all breast operations performed in patients before and/or after genetic testing and excluded any cosmetic or non-breast cancer/risk-related procedures.

Patient characteristics and clinical management were compared by variant pathogenicity group classification (B/LB, VUS, and P/LP) and breast cancer susceptibility (high [BRCA1/2, TP53, and PTEN], moderate [ATM, CDH1, CHEK2, PALB2, NBN, NF1, and STK11], and no breast cancer-associated risk). Patients with more than one genetic variant finding were assigned to the variant gene with the highest pathogenicity group for comparisons. For example, a patient with a BRCA2 VUS and MSH6 P/LP would be classified as P/LP non-breast variant.

Comparisons of categorical variables with Pearson Chi square and continuous variables with Kruskal–Wallis tests were performed. Multivariable analyses were performed to address clinical management after genetic testing (prophylactic mastectomy, oophorectomy, breast imaging, breast biopsy, and colonoscopy) by variant penetrance and pathogenicity, age group, personal history of breast cancer (current or prior), and whether surgery was performed before or after genetic testing (NCSS 11 Statistical Software [2016]. NCSS, LLC. Kaysville, UT, ncss.com/software/ncss). A p value < 0.05 was considered significant.

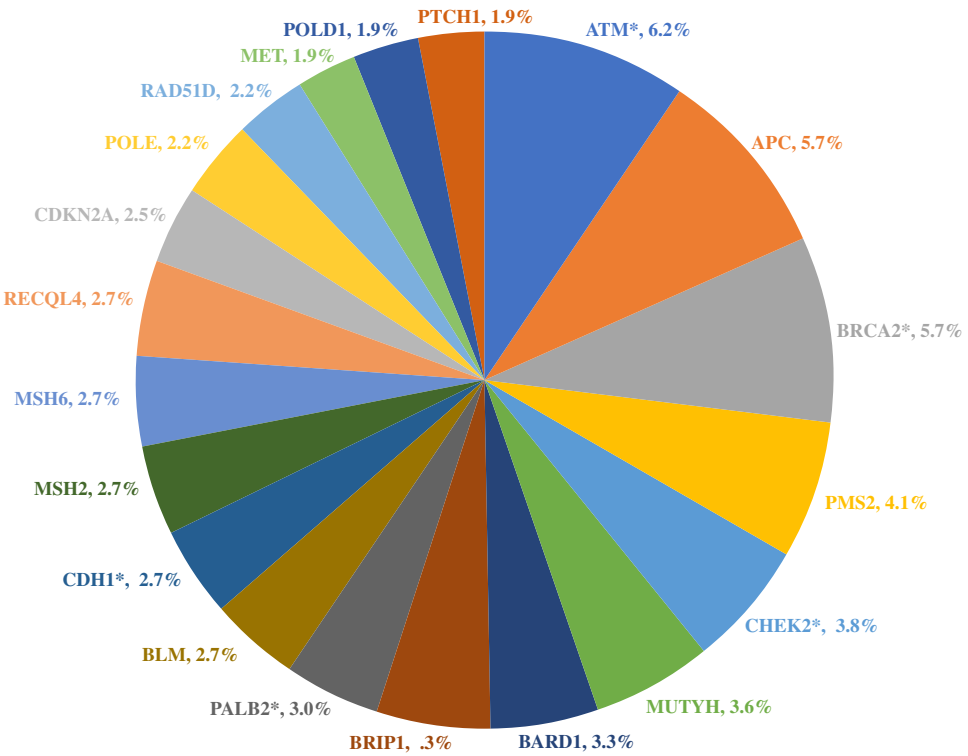

FIG. 1 The 20 most common VUS category variants. *Breast-specific variant of high and moderate penetrance. Not shown: BMPR1A, NF2, POLD1, RAD51C, TSC2, ALK, BRCA1, GALNT12, NBN, RET, STK11, BAP1, CDKN1B, DICER1, HOXB13, MLH1, NF1, TP53, AXIN2, DIS3L2, KIT, MRE11A, SDHA, SMARCA4, SUFU, TERT, TMEM127, TSC1, VHL, WRN, CEBPA, FANCC, FH, GATA2, MAX, MEN1, NMLH1, NTHL1, POT1, PRKAR1A, SMAD4, SMARCB1, TCS2, WT1, AIP, PTEN

RESULTS

Of 692 genetic tests performed during the study period, 563 were undertaken for assessment of hereditary breast cancer indications and had records available for review. The mean patient age was 53.9 ± 13.3 years (range 21–92 years). The majority of patients were non-Hispanic white (60.0%), followed by Hispanic (21.7%), Asian/Pacific Islander (7.8%), and non-Hispanic black (6.9%). Patients had a current or prior personal history of breast cancer in 38.7% and 24.9% of cases, respectively; 36.4% of patients had no history of breast cancer. Family history of one or more first-degree relative with breast cancer was present in 44.2% and 4.6% of patients, respectively. Contralateral prophylactic mastectomies were performed in 22.2%, and bilateral prophylactic mastectomies were performed in 0.9% of patients. Post-test oophorectomy was performed in 3.1% of patients, colonoscopy in 8.8%, breast imaging in 59.6%, and breast biopsy in 41.2%. Breast surgery was performed after genetic testing in 36.9% of patients, of whom 19.4% had a prior history of breast cancer, 79.2% had a current history of breast cancer, and 4.4% had no history of breast cancer. Among patients who had prophylactic mastectomies, 23.4% were performed before genetic testing and 76.6% were performed after testing. Median follow-up was 27.1 (range 0.3–109.5) months. The number of genes tested in each panel ranged from 9 to 83 in 538 (95.7%) of patients with the remainder receiving single-site or BRCA1/2 testing. Testing companies included Myriad (50.6%), Ambry (30.7%), and Invitae (18.5%).

Overall, 40.5% of patients had at least one VUS identified: 29.7% had one VUS; 10.5% two; 3.6% three; and 1.1% four. Of 366 VUS identified, 26.4% were high and moderate penetrance genes. The most common high and moderate penetrance genes with VUS were ATM (6.3%), BRCA2 (5.7%), CHEK2 (3.8%), PALB2 (3.0%), CDH1 (2.7%), NBN (1.4%), BRCA1 (1.3%), TP53 (1.1%), NF1 (0.8%), and PTEN (0.3%). The most common non-breast VUS were APC (6.2%) and PMS2 (3.8%). The 20 most common VUS variants are shown in Fig. 1. During the study period, 24 VUS were reclassified as B/LB. One VUS was reclassified as P/LP.

P/LP results were found in 61 (10.8%) patients, of which 61.2% were identified in moderate and high penetrance genes and 38.7% were in non-breast specific genes. The most common breast-specific P/LP variants were BRCA1 (17.7%) and BRCA 2 (17.7%), followed by ATM (8.1%),

TABLE 1 Overall distribution of variant pathogenicity by breast cancer susceptibility, $N = 563$

	Not breast specific	Moderate penetrance	High penetrance
Benign/likely benign	273 (61.5%)	0 (0.0%)	0 (0.0%)
Variant of uncertain significance	149 (33.5%)	60 (80.0%)	20 (45.5%)
Pathogenic/likely pathogenic	22 (5.0%)	15 (20.0%)	24 (54.5%)

$p < 0.0001$

CHEK2 (6.5%), TP53 (3.2%), PALB2 (3.2%), PTN (1.6%), NF1 (1.6%), and CDH1 (1.6%). The most common non-breast specific P/LP variants were MUTYH (14.5%), PMS2 (6.5%), RECQL4 (3.2%), FANCC (3.2%), and CDKN2A (3.2%).

Of variants found in high risk alleles, 54.5% were P/LP and 45.5% were VUS. Of those found in moderate risk alleles, 20.0% were P/LP and 80.0% were VUS ($p < 0.0001$; Table 1). Comparison of patient demographics, breast cancer susceptibility and pathogenicity of identified variants, and clinical management of patients who underwent genetic testing is shown in Table 2. On univariate analyses, patients with high penetrance genes (10.7%) were more likely to undergo post-test oophorectomy than those with moderate (1.7%) or no (2.6%) breast cancer risk ($p = 0.05$). Those with P/LP variants (9.8%) also were more likely to undergo post-test oophorectomy than those with VUS (2.3%) or B/LB (2.3%) findings ($p = 0.03$).

On multivariate analysis adjusting for variant pathogenicity and breast cancer susceptibility, factors associated with receipt of prophylactic mastectomy included younger age group (vs. older, OR 2.40, 95% CI 1.44–3.99), personal history of breast cancer (vs. no cancer, OR 14.9, 95% CI 4.31–51.4), and performance of surgery after genetic testing (vs. before testing, OR 2.91, 95% CI 1.69–5.02). Prophylactic mastectomy was not associated with VUS or P/LP versus B/LB findings or moderate or high breast susceptibility versus non-breast specific genes. Post-test biopsies were more commonly performed in patients with a history of breast cancer (vs. no cancer, OR 5.34, 95% CI 3.50–8.16). Patient age group, variant pathogenicity, and breast cancer susceptibility were not significantly associated with use of post-test oophorectomy, breast imaging or biopsy, or colonoscopy (Table 3).

DISCUSSION

In this study of patients at risk for hereditary breast cancer using predominantly multigene panel testing, VUS were identified in 40% of patients and P/LP variants, in 10%. As expected, the majority of P/LP findings were in breast cancer susceptibility genes; however, nearly 40% of P/LP variants were found in other cancer genes. Of VUS identified, one-fourth were found in genes associated with breast cancer risk. High VUS rates in our study match other reports.[4,6,8,13] Critics of multigene panel testing cite concern regarding these VUS rates.[14] NCCN recommendations for multigene panel testing caution that panel testing should only be completed in the context of professional genetic expertise, due to the lack of evidence regarding post-test strategies, especially when P/LP variants are found for moderate-penetrance genes.[12] The ACMG firmly recommends that clinicians not make medical management decisions based on VUS findings.[7] In the current series, VUS results from multigene panel testing did not affect post-test clinical decisions regarding prophylactic mastectomy, oophorectomy, or other surveillance measures when controlled for associated breast cancer risk of the identified variant.

However, the potential of VUS identification to influence management decisions made by patients and physicians has been documented and is highly contested. Kurian et al.[15] in 2017 demonstrated that amongst 666 breast cancer survivors who self-reported a VUS in BRCA1/2, 51% underwent bilateral mastectomy. Higher rates of contralateral prophylactic mastectomy in patients with BRCA1/2 VUS compared with BRCA-negative and untested patients (33% vs. 25%) also were reported by Welsh et al.[16] In patients without cancer, 39% of BRCA VUS carriers underwent bilateral prophylactic mastectomy; the decision to do so was significantly associated with elevated cancer risk and first degree family history of breast cancer.[16] In contrast, Pederson's study of triple-negative breast cancer patients showed similarly low rates of contralateral prophylactic mastectomy in patients who tested negative (20%) and those who had VUS (21%) compared with those with pathogenic mutations (88%).[17] Kurian's follow-up study linking Surveillance, Epidemiology and End Results data with actual genetic testing reports showed prophylactic mastectomy rates of 30% in breast cancer patients with VUS, 35% with negative tests, 38% with non-BRCA pathogenic variants, and 79% with BRCA pathogenic variants.[8]

Remarkably, P/LP findings in the current series did not significantly change management, even when identified in high penetrance genes. Of patients with P/LP variants, more than two-thirds had not undergone prophylactic mastectomy. Previous studies have shown 45–60% of unaffected P/LP carriers choose surveillance strategies

TABLE 2 Patient characteristics and clinical management by variant pathogenicity and breast cancer susceptibility, $N = 563$

	Breast variant penetrance				Variant classification group			
	Not breast-specific	Moderate penetrance[a]	High penetrance[b]	*p* Value	Benign/likely benign	Variant of uncertain significance	Pathogenic/likely pathogenic	*p* Value
Age group (yr)								
< 50	280 (60.1%)	48 (64.0%)	25 (56.8%)	0.7	178 (65.2%)	139 (60.7%)	36 (59.0%)	0.5
≥ 50	164 (36.9%)	27 (36.0%)	19 (43.2%)		95 (34.8%)	90 (39.3%)	25 (41.0%)	
Race/ethnicity								
Asian/Pacific Islander	34 (7.7%)	9 (12.0%)	1 (2.3%)	0.2	14 (5.1%)	26 (11.3%)	4 (7.8%)	0.1
Hispanic	93 (21.0%)	15 (20.0%)	14 (41.8%)		60 (22.0%)	45 (19.7%)	17 (21.7%)	
Non-Hispanic black	30 (6.8%)	5 (6.7%)	4 (9.1%)		14 (5.1%)	21 (9.2%)	4 (6.9%)	
Non-Hispanic white	267 (60.1%)	46 (61.3%)	25 (56.8%)		175 (64.1%)	130 (56.8%)	33 (60.0%)	
Other	20 (4.5%)	0 (0.0%)	0 (0.0%)		10 (3.7%)	7 (3.0%)	3 (3.6%)	
First-degree relatives with breast cancer								
0	223 (52.1%)	37 (50.7%)	18 (42.9%)	0.8	141 (53.8%)	113 (50.9%)	24 (40.7%)	0.3
1	186 (43.5%)	32 (43.8%)	22 (52.4%)		112 (42.8%)	98 (44.1%)	30 (50.9%)	
≥ 1	19 (4.4%)	4 (5.5%)	2 (4.8%)		9 (3.4%)	11 (5.0%)	5 (8.5%)	
Personal history of breast cancer								
No diagnosis	159 (38.0%)	27 (42.7%)	17 (38.6%)	1.0	97 (35.9%)	88 (38.8%)	18 (29.5%)	0.7
Current diagnosis	167 (36.2%)	32 (36.0%)	17 (38.6%)		104 (38.5%)	87 (38.3%)	25 (41.0%)	
Prior diagnosis	113 (25.7%)	16 (21.3%)	10 (22.7%)		69 (24.6%)	52 (22.9%)	18 (29.5%)	
Type of surgery								
None	112 (31.3%)	18 (29.0%)	13 (35.1%)	0.9	65 (30.1%)	62 (33.7%)	16 (28.1%)	0.8
Breast conservation	120 (33.5%)	20 (32.3%)	12 (32.4%)		76 (35.2%)	57 (31.0%)	19 (33.3%)	
Mastectomy	126 (35.2%)	34 (38.7%)	12 (32.4%)		75 (34.7%)	65 (35.3%)	22 (38.6%)	
Prophylactic mastectomy								
None	282 (77.7%)	46 (70.8%)	29 (80.6%)	0.4	173 (78.3%)	146 (78.1%)	38 (67.9%)	0.2
Bilateral/contralateral	81 (22.3%)	19 (29.2%)	7 (19.4%)		48 (21.7%)	41 (21.9%)	18 (32.1%)	
Post-test imaging								
No	173 (39.1%)	35 (46.7%)	19 (43.2%)	0.4	101(37.1%)	94 (41.1%)	32 (52.5%)	0.1
Yes	270 (60.9%)	40 (53.3%)	25 (56.8%)		171 (62.9%)	135 (58.9%)	29 (47.5%)	
Post-test biopsy								
No	260 (59.1%)	43 (58.1%)	25 (56.8%)	1.0	161 (59.9%)	131 (57.2%)	36 (60.0%)	0.8
Yes	180 (40.9%)	31 (41.9%)	19 (43.2%)		108 (40.1%)	98 (42.8%)	24 (40.0%)	

TABLE 2 continued

	Breast variant penetrance				Variant classification group			
	Not breast-specific	Moderate penetrance[a]	High penetrance[b]	*p* Value	Benign/likely benign	Variant of uncertain significance	Pathogenic/likely pathogenic	*p* Value
Post-test oophorectomy								
No	298 (97.4%)	57 (98.3%)	25 (89.3%)	0.05	169 (97.7%)	174 (97.8%)	37 (90.2%)	0.03
Yes	8 (2.6%)	1 (1.7%)	3 (10.7%)		4 (2.3%)	4 (2.2%)	4 (9.8%)	
Post-test colonoscopy								
No	282 (91.3%)	51 (86.4%)	31 (100.0%)	0.1	157 (90.2%)	164 (91.1%)	42 (95.5%)	0.5
Yes	27 (8.7%)	8 (13.6%)	0 (0.0%)		17 (9.8%)	16 (8.9%)	2 (4.5%)	

[a]Moderate penetrance: ATM, CDH1, CHEK2, PALB2, NBN, NF1, and STK11

[b]High penetrance: BRCA1/2, TP53, PTEN

TABLE 3 Odds ratios (95% confidence intervals) for post-test clinical management

	Prophylactic mastectomy	Post-test breast imaging	Post-test breast biopsy	Post-test oophorectomy	Post-test colonoscopy
Breast cancer susceptibility					
None	Ref	Ref	Ref	Ref	Ref
Moderate	1.31 (0.61–2.82)	0.86 (0.49–1.49)	1.02 (0.57–1.85)	0.42 (0.04–4.15)	2.01 (0.74–5.46)
High	0.49 (0.16–1.44)	1.18 (0.57–2.44)	1.25 (0.58–2.70)	2.06 (0.35–12.18)	0.00 (0–10,000+)
Variant pathogenicity					
Benign/likely benign	Ref	Ref	Ref	Ref	Ref
Variant of uncertain significance	1.00 (0.57–1.79)	0.88 (0.59–1.31)	1.14 (0.74–1.74)	1.01 (0.23–4.45)	0.78 (0.34–1.79)
Pathogenic/likely pathogenic	1.99 (0.83–4.75)	0.53 (0.27–1.03)	0.81 (0.40–1.64)	3.81 (0.60–24.20)	0.51 (0.10–2.66)
Age group (yr)					
< 50	2.40 (1.44–3.99)	0.91 (0.63–1.30)	1.15 (0.78–1.70)	2.52 (0.75–8.43)	0.57 (0.25–1.27)
≥ 50	Ref	Ref	Ref	Ref	Ref
Personal history of breast cancer					
None	Ref	Ref	Ref	Ref	Ref
Prior	14.9 (4.31–51.4)	0.87 (0.60–1.25)	5.34 (3.50–8.16)	1.40 (0.39–5.00)	0.85 (0.40–1.79)
Timing of breast surgery					
Before genetic testing	Ref	–	–	–	–
After genetic testing	2.91 (1.69–5.02)	–	–	–	–

over mastectomy.[18,19] The current report shows age and cancer history influence surgical choice more than gene pathogenicity or associated risk. Consensus statements from the American Society of Breast Surgeons and Society of Surgical Oncology attest to the complexity of shared decision making regarding prophylactic mastectomy.[20–22]

Our study evaluated whether variant test results contributed to other cancer screening and risk reduction. Not surprisingly, patients with a personal history of breast cancer received more post-test breast biopsies, likely due to increased surveillance compared with noncancer patients. Nearly 40% of P/LP variants were found in non-breast-related genes with actionable risk strategies, of which MUTYH and PMS2 were most common. Although no significant difference in post-test colonoscopy rates was found among variant classes, the study period likely did not accurately capture colonoscopy rates due to the decennial frequency at which they are recommended for most patients. Studies have shown that oophorectomy, more so than mastectomy, confers a survival advantage in BRCA carriers.[23,24] In the current study, increased uptake of post-

test oophorectomy in P/LP and highly penetrant carriers could not be confirmed on multivariable analysis, likely due to small sample size.

According to the ACMG and 2015 Association for Molecular Pathology guidelines, initial classifications should be based on all available information regarding variant pathogenicity, including population frequency, functional data, segregation analysis, and phenotype analysis.[7] Despite concern that increasing use of multigene panels increases VUS findings, the clinical utility of multigene panel testing improves as more data on the significance of gene variant pathogenicity are collected from large, cancer genetic testing studies. Concern has been raised regarding racial/ethnic disparities in VUS.[8] Our diverse patient population adds to the literature. As multigene panel use increases, the frequency of VUS is expected to decrease. From 2006 to 2016, nearly one quarter of VUS findings were reclassified, of which 91.2% were downgraded to B/LB.[25] In our short study period, 25 of the identified VUS were reclassified.

This report is limited by selection biases inherent in retrospective reviews. The meticulous process of shared decision making and the innumerable combinations of personal and socioeconomic variables contributing to this decision cannot be captured in such a retrospective review. Additionally, our study is limited by short follow up and small sample size and inability to distinguish prior from current breast cancer diagnoses in our multivariable model. While a newly diagnosed breast cancer patient with a P/LP mutation is more likely to have a prophylactic mastectomy than a patient with a past diagnosis of breast cancer, in the era of update panel testing, just as in the prior era of update BRACAnalysis Large Rearrangement Test for patients who tested negative for BRCA1/2, a new variant finding could influence subsequent clinical management of the patient. In the HEBON study, among breast cancer patients who had genetic testing performed more than 5 years after their diagnosis, 37.5% elected prophylactic mastectomy. Therefore, for this analysis, the cancer diagnosis variable combined those who had a past or current diagnosis of breast cancer.[26] Finally, all post-test interventions may not have been captured for patients undergoing screening or risk reduction beyond the study period or at another facility.

Notwithstanding the debate regarding multigene panel testing, use of multigene panels has increased.[8,17] Recent studies favor expanded panel testing due to the clinical actionability of other cancer susceptibility genes found on multigene panel testing for patients with breast cancer and missed opportunities for patients outside standard testing criteria. In a study of 959 patients, there were no statistically significant difference in the rates of P/LP results in patients who did (9.39%) and did not (8.65%) meet NCCN criteria for genetic testing.[6] A study of 4196 Medicare patients showed rates of P/LP variants were not statistically different between those who did (10.5%) and did not (9%) meet national coverage criteria.[5] NGS technology is currently accessible through online services and is heavily marketed to customers, with minimal regulation.[27] Direct-to-consumer genetic tests eliminate the involvement of a healthcare provider or insurance company and can provide information ranging from a customer's ancestry to cancer risk.[28,29] It is imperative that health care providers are able to interpret these tests, including VUS results, so patients are empowered to make evidence-based shared medical decisions. A 2017 survey of 377 surgeons in the United States found that 50% of surgeons with lower breast cancer volumes (< 20 cases/year) and even 25% with higher volume (> 51 cases/year) managed patients with BRCA1/2 VUS the same as patients with BRCA1/2 pathogenic mutations.[15] A 2015 survey of 398 genetic counselors showed that while 50% of counselors were extremely confident in explaining a BRCA VUS result to a patient, only 26.4% were extremely confident in discussing clinical management options or achieving a high level of patient understanding.[10] The ENIGMA consortium has published a framework for improving genetic literacy regarding VUS for patients, families, and providers.[11]

Regardless of whether a patient has a VUS or other variant in high or moderate risk breast cancer genes, management of patients at risk for hereditary breast cancer is complicated. The current study argues against VUS in any gene on a multigene panel altering management decisions. Genetic information expands the physician's ability to individualize options not only for patients, but also for their families. In this patient population at risk for hereditary cancer, genetic factors help to inform, but not dictate, complex decision-making in surveillance and management.

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