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


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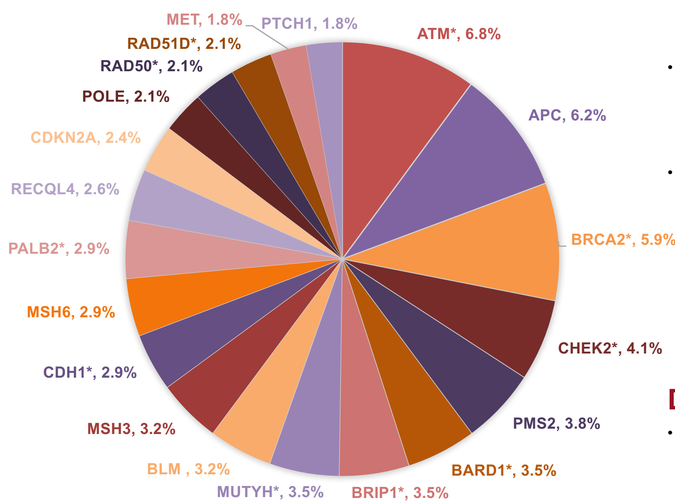
## INTRODUCTION

- Since the discovery of the BRCA genes and their association with breast cancer nearly 25 years ago, 10% of newly diagnosed breast cancers every year are estimated to be from hereditary causes. There are now over 10 different genes associated with breast cancer susceptibility, including highly penetrant tumor suppressor genes BRCA1, BRCA2, PTEN, and p53, 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 a 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 counseling despite consensus guidelines stating that clinicians should not make medical management decisions based on VUS findings.
- The objective of this study was to analyze the role 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 indications of personal and/or family history of breast cancer. Genetic variants were grouped as 1) benign or likely benign, 2) VUS, or 3) pathogenic or likely pathogenic.
- Breast cancer associated genes included ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, MRE11A, MUTYH, NBN, NF1, PALB2, PTEN, RAD50, RAD51C, RAD51D, and TP53.
- Patient, variant gene, and post-test management characteristics were compared by pathogenicity of variant group classification (benign/likely benign (B/LB) vs. VUS vs. pathogenic/likely pathogenic (P/LP)).
- Receipt of breast imaging, breast biopsies, oophorectomy and/or colonoscopy after genetic testing was completed was recorded.
- Breast surgery analysis excluded any cosmetic or non-cancer risk related surgeries.

## 20 MOST COMMON VUS CATEGORY VARIANTS




*Breast-specific variant

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

- Overall, 563 genetic tests were undertaken for breast indications and had records available for review. The mean patient age was 53.9+13.3 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 (30.7%), and Invitae (18.5%).
- Among those tested, 40.4% had VUS: 29.7% had one VUS; 10.5%, two; 3.6%, three; and 1.1%, four. Of 339 VUS identified, 44.0% were breast-specific variants. Sixty-one patients (10.8%) had LP/P results. During the interval time frame of this study, of all VUS results, 24 were reclassified as LB/B. One VUS was reclassified as LP/P.
- Breast surgery was performed after genetic testing in 208 (36.9%) patients, among whom there were no differences in rates of bilateral (0%, 2.3%, 7.1%) or contralateral prophylactic mastectomy (37.4%, 36.4%, 42.9%) based on B/LB, VUS, or P/LP classification, respectively (p=0.3). Of 355 (63.1%) patients without post-test breast surgery, those with P/LP were more likely to have oophorectomy after testing than those with B/LB or VUS (15.0% vs. 1.9% and 1.8%, respectively, p<0.0001). For both groups, there were no differences in use of post-test imaging, breast biopsy, or colonoscopy based on variant pathogenicity.

| ` | | Overall (n=563) | Surgery After Genetic Testing (n=208) | | | | No Surgery After Genetic Testing (n=355) | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Benign/Likely Benign (n=91) | Variables of Uncertain Significance (n=88) | Pathogenic/Likely Pathogenic (n=28) | p-value | Benign/Likely Benign (n=182) | Variables of Uncertain Significance (n=140) | Pathogenic/Likely Pathogenic (n=33) | p-value |
| Post-Testing Imaging | Yes | 335 (59.6%) | 59 (64.8%) | 53 (59.5%) | 15 (53.6%) | 0.6 | 112 (66.9%) | 82 (58.6%) | 14 (42.4%) | 0.1 |
| | No | 227 (40.4%) | 32 (35.2%) | 36 (40.5%) | 13 (46.4%) | | 69 (38.1%) | 58 (41.4%) | 19 (57.6%) | |
| Post-Testing Biopsy | Yes | 230 (41.2%) | 47 (52.2%) | 52 (58.4%) | 18 (64.3%) | 0.4 | 61 (34.1%) | 46 (32.9%) | 6 (18.8%) | 0.2 |
| | No | 328 (58.8%) | 43 (47.8%) | 37 (41.6%) | 10 (35.7%) | | 118 (65.9%) | 94 (67.1%) | 26 (81.3%) | |
| Post-Testing Oophorectomy | Yes | 12 (3.1%) | 2 (3.1%) | 2 (3.0%) | 1 (4.8%) | 0.8 | 2 (1.8%) | 2 (1.8%) | 3 (15.0%) | 0.0 |
| | No | 380 (96.9%) | 63 (96.9%) | 64 (97.0%) | 20 (95.2%) | | 106 (98.2%) | 110 (98.2%) | 17 (85.0%) | |
| Post-Testing Colonoscopy | Yes | 35 (8.8%) | 8 (12.1%) | 62 (92.5%) | 1 (4.8%) | 0.5 | 9 (8.3%) | 11 (9.7%) | 1 (4.3%) | 0.7 |
| | No | 363 (91.2%) | 58 (87.9%) | 5 (7.5%) | 20 (95.2%) | | 99 (91.7%) | 102 (90.3%) | 22 (95.7%) | |

| | | Overall (n=563) | Surgery After Genetic Testing (n=208) | | | | No Surgery After Genetic Testing (n=355) | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Benign/Likely Benign (n=91) | Variables of Uncertain Significance (n=88) | Pathogenic/Likely Pathogenic (n=28) | p-value | Benign/Likely Benign (n=182) | Variables of Uncertain Significance (n=140) | Pathogenic/Likely Pathogenic (n=33) | p-value |
| Age | | 53.9±13.3 | 55.0±13.1 y | 54.4±12.6 y | 50.9±14.3 y | 0.4 | 54.2+13.5 y | 53.1+13.0 y | 53.8+15.8 y | 0.5 |
| Personal history of breast cancer (current or past) | Yes | 358 (63.8%) | 89 (97.8%) | 83 (93.3%) | 27 (96.4%) | 0.1 | 85 (47.2%) | 58 (41.4%) | 16 (48.5%) | 0.5 |
| | No | 203 (36.2%) | 2 (2.2%) | 6 (6.7%) | 1 (3.6%) | | 95 (52.8%) | 82 (58.6%) | 17 (51.5%) | |
| First degree relatives with breast cancer | >1 | 25 (4.6%) | 2 (2,3%) | 7 (8.0%) | 4 (14.3%) | 0.1 | 7 (4.0%) | 4 (3.0%) | 1 (3.2%) | 0.7 |
| | 1 | 240 (44.2%) | 26 (30.2%) | 26 (29.5%) | 11 (39.3%) | | 86 (48.9%) | 72 (53.7%) | 19 (61.3%) | |
| | 0 | 278 (51.2%) | 58 (67.4%) | 55 (62.5%) | 13 (46.4%) | | 83 (47.1%) | 58 (43.3%) | 11 (35.5%) | |
| Breast-Specific Variant** | Yes | 177 (31.4%) | 0 (0.0%) | 54 (60.7%) | 25 (89.3%) | <0.001 | 0 (0.0%) | 71 (50.7%) | 27 (81.8%) | 0.0 |
| | No | 386 (68.6%) | 91 (100.0%) | 35 (39.3%) | 3 (10.7%) | | 182 (100.0%) | 69 (49.3%) | 6 (18.2%) | |
| Type of Surgery | Mastectomy | 162 (35.5%) | 49 (53.9%) | 48 (53.9%) | 16 (42.9%) | 0.8 | N/A | N/A | N/A | N/A |
| | Breast Conservation | 152 (33.3%) | 42 (46.1%) | 41 (46.1%) | 12 (57.1%) | | | | | |
| | None | 143 (31.3%) | N/A | N/A | N/A | N/A | | | | |
| Prophylactic Mastectomy | Contralateral | 103 (22.2%) | 34 (37.4%) | 32 (36.4%) | 12 (42.9%) | 0.3 | N/A | N/A | N/A | N/A |
| | Bilateral | 4 (0.01%) | 0 (0.0%) | 2 (2.2%) | 2 (7.1%) | | | | | |
| | None | 357 (76.9%) | 57 (62.6%) | 54 (61.4%) | 14 50.0%) | | | | | |

**ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, MRE11A, MUTYH, NBN, NF1, PALB2, PTEN, RAD50, RAD51C, RAD51D, TP53

## DISCUSSION

- Our study demonstrates 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 recommendations from the ACMG that clinicians should not make medical management decisions based on VUS findings
- This study was limited due to small sample size and selection biases inherent in retrospective reviews.
- Previous reports have shown that BRCA1/2 VUS may influence clinical decision making, raising concern that the increasing frequency of other VUS findings may change patient management decisions.
- The current study argues against the influence of VUS results from multigene panel testing on clinical management for patients at risk for hereditary breast cancer. Genetic information expands the physician's ability to individualize options and help to inform, but not dictate, complex decision-making in surveillance and management, not only for patients, but also for their families.

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