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**Timely Cancer Genetic Counseling and Testing for Young Women with Breast Cancer: Impact on Surgical
Decision-Making for Contralateral Risk-Reducing Mastectomy**

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ABSTRACT

PURPOSE: Genetic testing (GT) can identify individuals with pathogenic variants (PV) in breast cancer (BC) predisposition genes, who may consider contralateral risk-reducing mastectomy (CRRM). We report on CRRM rates in young women newly diagnosed with BC who received GT through a multidisciplinary clinic.

METHODS: Clinical data was reviewed for patients seen between November 2014 and June 2019. Patients with non-metastatic, unilateral BC diagnosed at age ≤ 45 and completed GT prior to surgery were included. Associations between surgical intervention and age, BC stage, family history, and GT results were evaluated.

RESULTS: Of the 194 patients, 30 (15.5%) had a PV in a BC predisposition gene (*ATM*, *BRCA1*, *BRCA2*, *CHEK2*, *NBN*, *NFI*), with 66.7% in *BRCA1* or *BRCA2*. Of 164 (84.5%) uninformative results, 132 (68%) were negative and 32 (16.5%) were variants of uncertain significance (VUS). Overall, 67 (34.5%) had CRRM, including 25/30 (83.3%) PV carriers and 42/164 (25.6%) non-carriers. Only a positive test result was associated with CRRM ($p < 0.01$). For the 164 with uninformative results, CRRM was not associated with age ($p = 0.23$), a VUS, ($p = 0.08$), family history ($p = 0.19$), or BC stage ($p = 0.10$).

CONCLUSION: In this cohort of young women with BC, the identification of a PV in a BC predisposition gene was the only factor associated with the decision to pursue CRRM. Thus, incorporation of genetic services in the initial evaluation of young patients with a new BC could contribute to the surgical decision-making process.

Keywords: breast cancer, genetic counseling, genetic testing, risk-reducing mastectomy, variant of uncertain significance

INTRODUCTION

Breast cancer (BC) is the most common cancer diagnosis for women in the United States.[1] The average woman has an approximately 12.9% lifetime risk of developing BC, with a median diagnosis age of 62 years.[1] Approximately 5-10% of BC are attributable to pathogenic variants (PVs) in a BC predisposition gene.[2, 3] PVs in *BRCA1* and *BRCA2* (*BRCA1/2*) are the most common cause of hereditary BC, and are associated with a lifetime BC risk of up to 69-72%.[4] Lifetime BC risks associated with other BC predisposition genes vary from at least a 4-fold increase for the high-risk genes (*CDH1*, *PALB2*, *PTEN*, *STK11*, and *TP53*) to a 2- to 3-fold increase for the moderate-risk genes (*ATM*, *CHEK2*, *NBN*, and *NF1*).[4–12] Breast cancer associated with a hereditary predisposition may also be diagnosed at earlier ages; in particular, women with *BRCA1/2* or *TP53* PVs are often diagnosed with premenopausal BC.[4, 13]

Contralateral BC risks are influenced by multiple factors, including age at first BC diagnosis, family history of BC, previous treatments, and underlying genetic predisposition.[4, 14–18] The risk for a contralateral BC is approximately 10% within 20 years after the initial diagnosis for unselected women with no known hereditary BC predispositions, [18] but may be as high as 53-65% for *BRCA1/2* PV carriers.[4, 19] Contralateral BC risks have not been well-defined for most other BC predisposition genes, but may be increased for women with *ATM*, *PALB2*, *TP53*, and *CHEK2* truncating PVs.[13, 20–23]

Genetic testing (GT) is recommended for women with newly diagnosed BCs who meet specific criteria based on their personal and family cancer history, as the identification of a hereditary predisposition may impact care.[24–27] Women with PVs in high-risk genes with available data on contralateral BC risks could consider contralateral risk-reducing mastectomy (CRRM) at the time of surgical BC treatment, which provides a >90% reduction in future BC risk.[23, 27–29] However, CRRM is not routinely recommended for women without a BC predisposition, or for women with PVs in moderate-risk genes with insufficient data regarding second primary BC risks or long-term benefits of CRRM.[23, 28, 30–32]

Despite the limited data on survival benefits of CRRM, CRRM rates have been increasing in United States over the past two decades across cohorts of women with unilateral BC treated in various geographical locations between the mid-1990s to early 2010s. The increase in CRRM rates ranges from of 4.2% to 9.6% over 8 years, to an increase of 5.4% to 37.5% over 15 years.[23, 33–39]

Genetic testing availability has also increased over the past few decades, including increased utilization of multigene panel testing, which has increased the PV detection rates in genes other than *BRCA1/2*.^[40–42] However, limited information exists regarding the impact of PVs in other BC predisposition genes on surgical decision-making outcomes for BC patients.^[23, 43–46]

Regarding GT results, it is also important to consider the impact of variants of uncertain significance (VUSs) on surgical decision-making. As VUSs do not carry any clinical implications, patients with a VUS should follow management recommendations based on their personal and family history, rather than on the GT result.^[27, 47, 48] However, VUS identification can lead to patients being recommended the same management considerations as PV carriers, including CRRM.^[49–53]

Given broader GT availability and subsequent improvements in the ability to identify PVs in BC predisposition genes other than *BRCA1/2* in recent years, we sought to further explore the impact of GT on surgical decision-making. This study focused on a cohort of young female patients with a new diagnosis of unilateral BC, who were uniformly offered genetic counseling and GT as part of a multidisciplinary clinic designed to efficiently provide patients with comprehensive care at the time of diagnosis.

METHODS

Clinical data for patients seen in the multidisciplinary Breast Cancer Specialty Care Clinic at Magee-Womens Hospital of UPMC (Pittsburgh, PA) between November 2014 and June 2019 were abstracted. This chart review was performed under a Quality Improvement project to evaluate the utility of this clinic for young breast cancer patients. The project was reviewed and approved by the University of Pittsburgh Medical Center Quality Improvement Review Committee and was deemed exempt from approval by the Institutional Review Board.

Patients were included in the analysis if they were: 1) female, 2) newly diagnosed with non-metastatic, unilateral BC, 3) ≤ 45 years old, 4) had completed genetic counseling and GT, and 5) had completed surgical treatment of BC by the end of the study period. Patients were excluded if they had incomplete information regarding treatment, family history, or GT results.

The following data was collected via chart review: age; race and ethnicity; BC stage; type of breast surgery performed (lumpectomy, mastectomy, mastectomy with CRRM); and family history of BC and/or ovarian cancer (OC). Patients were considered to have a “significant” family history if they had at least one first- or second-degree

relative with: 1) OC at any age, 2) BC diagnosed ≤ 30 years old, 3) male BC at any age, or 4) ≥ 2 relatives with BC at any age.

The specific GT performed was not standardized across the study cohort; rather, testing for *BRCA1/2* or a multigene panel was tailored to each patient, based on their personal and family history of cancer, as well as patient preference. Results were: negative for a PV in a BC predisposition gene, positive for a PV in a BC predisposition gene, or uncertain (VUS). Given that the focus of this study was to evaluate the impact of GT results on BC risk management, PVs in genes that have not been shown to be associated with an increase in BC risks were considered to be negative. Of note, the *NBN* Slavic founder variant was included in analysis, as it was considered pathogenic during the study timeframe. Negative and VUS results were considered together as uninformative results.

Statistical analysis was performed using Chi-squared tests, Fisher's exact test, or t-tests, as appropriate, to examine the associations between surgical decisions (CRRM vs. no CRRM) and self-reported race/ethnicity, age, family history (significant vs. not significant), GT outcome (positive vs. uninformative), or BC stage (\leq II vs. III). Multivariate analysis was also performed to evaluate for any association between surgical decision and these factors. A *p*-value of < 0.05 was considered to be statistically significant. Additionally, the association between age, family history, stage, and surgical decision was examined among patients with uninformative results. All analyses were performed using the SAS statistical software package (SAS/STAT software, Version 9.4 SAS Institute Inc., Cary, NC).

RESULTS

Patient Population

A total of 194 eligible patients were seen between November 2014 and June 2019 and included in this analysis. A total of 82 patients (42.3%) had breast-conserving surgery (BCS), 45 (23.2%) had unilateral mastectomy (UM), and 67 (34.5%) had CRRM.

Genetic Testing Results

Regarding GT performed, 25 patients (12.9%) had testing for *BRCA1/2*, while 169 (87.1%) had testing via a multigene panel. Pathogenic variants in 6 BC genes were identified in 30 (15.5%) patients: *BRCA1* ($n = 11$, 36.7%), *BRCA2* ($n = 9$, 30%), *CHEK2* ($n = 6$, 20% overall; $n = 1$ truncating PV, $n = 5$ missense PV), *NBN* ($n = 2$ Slavic founder heterozygotes, 6.7%), *NF1* ($n = 1$, 3.3%), and *ATM* ($n = 1$, 3.3%, Figure 1). Additionally, PVs in

genes that have not been definitively associated with increased BC risks were identified in 2 patients and considered as a “negative” result for the purposes of this study (*BRIP1*, *MUTYH* heterozygote, $n = 1$ each).

A total of 164 (84.5%) women had uninformative GT results: 132 (68%) negative, and 32 (16.5%) with at least one VUS (Figure 1). Of the patients with a VUS, 18 (56.3%) had a VUS in at least one BC gene (*ATM*, $n = 6$; *BRCA1*, *BRCA2*, *PALB2*, *PTEN*, $n = 2$ each; *CHEK2*, *NF1*, *NBN*, $n = 1$ each; *BARD1* and *APC* VUSs in same patient, $n = 1$). Additionally, 14 (43.8%) had a VUS in a gene that has not been shown to be associated with BC predisposition (*APC*, *POLD1*, $n = 3$ each; *POLE* *MSH6*, $n = 2$ each; *BRIP1*, *MLH1*, *RAD51C*, and *SDHB*, $n = 1$ each).

Factors Associated with Surgical Decisions for the Whole Cohort

The median age of the entire cohort was 39 (range 23-45, Table 1). Most patients ($n = 169$, 87.1%) were white; 19 (9.8%) were Black, 5 (2.6%) were Asian, and 1 (0.5%) was of an unspecified race/ethnicity. Of the 67 patients who elected to have CRRM, 25 (37.3%) had a PV in a moderate-risk BC predisposition gene (*CHEK2*, $n = 4$; *ATM*, *NBN* heterozygote, $n = 1$ each) or high-risk BC gene (*BRCA1*, $n = 11$; *BRCA2*, $n = 8$; Figure 2). Five (16.7%) of the patients with a BC predisposition gene PV opted for a BCS/UM (*CHEK2*, $n = 2$; *BRCA2*, *NBN* heterozygote, *NF1*, $n = 1$ each) (Figure 2).

Compared with patients who chose a BCS/UM, patients who had a CRRM were younger (median age 37 vs. 39 years; $p = 0.03$), more likely to have a significant family history of BC/OC, (35.8% vs. 15%; $p < 0.01$), and similar stage distributions (38.8% early stage vs. 31% late stage; $p = 0.27$). However, only a positive GT result was statistically significantly associated with CRRM in the multivariate analysis, with an OR of 11.4 (95% CI = 3.95 – 32.97, $p = <0.001$) (Table 1).

Factors Associated with Surgical Decisions in Patients with Uninformative Results

Of the subset of 164 patients with uninformative results, 122 (74.4%) opted for BCS/UM, and 42 (25.6%) had a CRRM (Table 2; Figure 2). The median age at diagnosis for this group was 39 years (range 23-45 years). Most of the patients were white ($n = 142$, 86.6%); 17 (10.4%) were Black, 4 (2.4%) were Asian, and 1 (0.6%) was of an unspecified race/ethnicity. The genetic testing result (negative vs. VUS) was not observed to be associated with the decision to undergo CRRM. Of the 42 patients who elected to have CRRM, 12 had a VUS in any gene, while 20 of the 122 elected BCS/UM had a VUS in any gene (28.6% vs. 16.4%, $p = 0.09$). There was also

no statistically significant difference in age at diagnosis (median age 38 vs. 39 years; $p = 0.5$), significant family history (26.2% vs. 14.7%; $p = 0.09$), or early disease stage (45.2% vs. 30.6%; $p = 0.08$) between patients who opted for CRRM compared with those opted for BCS/UM among the subset of patients with an uninformative result (Table 2).

DISCUSSION

In this study, the identification of a PV in a BC predisposition gene was significantly associated with surgical decision for young women newly diagnosed with a BC. Patients with a PV in any BC predisposition gene were more likely to opt for CRRM at the time of surgery. Overall, 15.5% of patients were found to have a PV in a moderate- or high-risk BC predisposition gene, which is similar to the 12-18% rate previously reported in other premenopausal BC cohorts.[54–56]

Pathogenic variants in *BRCA1/2* accounted for approximately two-thirds of PVs identified in this study, and most patients with a *BRCA1/2* PV opted to have CRRM. Although there are limited data on long-term survival benefits, consideration of a CRRM is an established recommendation for women with a *BRCA1/2* PV.[4, 23, 28, 29, 57] The rates of CRRM in our study was also similar to those reported previously for individuals with a *BRCA1/2* PV who had been diagnosed with BC.[49, 51, 58]

In addition to *BRCA1/2*, PVs in moderate-risk genes, such as *ATM* and *CHEK2*, may confer increased risks for a second primary BC. However, data on estimated risks are limited, and the long-term benefit of CRRM in this setting is uncertain.[8, 9, 21–23, 28, 30, 43, 57] Despite this lack of data, more than half of the patients with a PV in a moderate-risk BC predisposition gene also opted to have CRRM, a rate similar to that previously reported among BC patients with a PV in a moderate-risk BC predisposition gene.[44–46] The number of patients identified to have a PV in a BC predisposition gene other than *BRCA1/2* in this study was small, which precluded our ability to adequately assess the association between the identification of a PV in a moderate-risk BC predisposition gene and the decision to pursue CRRM at the time of surgical BC treatment. However, patients with a *BRCA1/2* PV have been shown to be more likely than patients with PVs in other BC genes to choose CRRM.[44–46] Our study adds to the limited data available on surgical decisions on newly-diagnosed patients with a PV in a moderate-risk BC predisposition gene.

Decisions regarding risk reducing surgical intervention are complex, and likely influenced by factors other than knowledge of a genetic predisposition.[59] The risks of developing another primary BC after the first diagnosis have been shown to be higher in patients with younger age at first diagnosis, or a family history of BC/OC.[14–18] Consequently, earlier age at diagnosis and family history of BC/OC have been shown to be positively correlated with the decision to have CRRM in women with BC, regardless of genetic testing outcome.[19, 37, 38, 46, 60–62] In this study, we did not observe any association between age at diagnosis and surgical decision when adjusted for GT result. However, all patients included in this study were 45 years old or younger, which hindered the ability to evaluate the impact of age at diagnosis on surgical decision making. Similarly, family history of BC and/or OC were not shown to be associated with a decision to have CRRM after adjustment for GT result in our study population.

Previous studies showing an association between family history of BC/OC and CRRM in women with BC either did not include information on GT, or only considered test results for *BRCA1/2*. [19, 36, 37, 60, 63–65] In our study, comprehensive GT could have identified patients with a BC predisposition who otherwise would have chosen CRRM based on family history. Furthermore, patients diagnosed with BC might choose to have CRRM based on their perception of a high risk for contralateral BC, especially when there is a significant family history.[66] Thus, the provision of pre-surgical genetic counseling and GT in this study may have helped to clarify estimated contralateral BC risks, and promoted risk-appropriate surgical decision-making among those without a genetic predisposition. Although higher CRRM rates with early-stage disease have previously been reported, disease stage was not shown to be associated with CRRM in our study.[19, 37, 61]

Although cancer GT can provide valuable information in risk assessment and promote risk-appropriate management, some test results have the potential to lead to unnecessary interventions. Variants of uncertain significance (VUSs) in cancer predisposition genes do not have any clinical implications, and should not be used in risk assessment or risk management considerations. With appropriate pre- and post-test counseling, patients with VUSs in BC predisposition genes did not elect to undergo CRRM more often than average-risk women.[45, 46, 50, 51, 67] However, interpretation of a VUS result can often be challenging, and high-risk management recommendations based on VUS findings, have been reported, including CRRM.[42, 49, 52, 53] As part of the multidisciplinary clinic, all patients in our study received pre- and post-test genetic counseling from a genetics specialist to discuss test implications and possible results. In our study, among those with an uninformative result, the CRRM rate was not significantly different between patients with a VUS in any gene, compared with patients

with a negative result. Thus, incorporation of pre- and post-test genetic counseling as part of the multidisciplinary evaluation for young women newly diagnosed with BC could help ensure appropriate testing and accurate risk assessment.

Strengths of this study included systematic provision of genetic counseling to all patients. Additionally, all patients were seen by a genetic specialist. Limitations of this study included a small sample size of patients at one institution, which limits the ability to generalize the findings. While the type of GT offered was not standardized, the majority (86.4%) were tested via a multigene panel. Finally, this exploratory study focused on the utility of genetic counseling and GT at the time of diagnosis for surgical decision-making among young patients with BC. Other factors that could potentially influence decision making regarding CRRM, such as socioeconomic status, reproductive planning, psychosocial factors, or concerns regarding potential cosmetic outcomes, were not explored.

Conclusions

For young women newly diagnosed with BC seen in a multidisciplinary clinic, the identification of a BC genetic predisposition was associated with the decision to pursue CRRM at the time of surgical BC treatment. Young patients with uninformative results had lower rates of CRRM, even among those with a significant family history. Thus, early incorporation of genetic services in the treatment planning process for young patients newly diagnosed with BC has the potential to lead to more appropriate risk assessment, which in turn could promote more risk-appropriate management.

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Author contributions: SAD collected, analyzed, and interpreted the data, and prepared the manuscript; DLT interpreted the data and participated in manuscript preparation; PFM, JGS, and RRJ contributed to clinical data collection, and reviewed the manuscript; EJD conceived and designed the study, provided clinical data, critically reviewed the data, and reviewed the manuscript, PLM conceived and designed the study, analyzed and interpreted the data, and prepared the manuscript. All authors approved the final manuscript.

Data availability: The datasets generated during and/or analyzed during the current study are not publicly available in order to protect patient privacy; however, a de-identified dataset is available from author PLM upon reasonable request.

Ethics approval: This study was performed in line with the principles of the Declaration of Helsinki. The project was reviewed and approved by the University of Pittsburgh Medical Center Quality Improvement Review Committee and was deemed exempt from approval by the Institutional Review Board.

Consent to participate: This was a quality control study. The University of Pittsburgh Medical Center Quality Improvement Review Committee and Institutional Review Board has confirmed that informed consent was not required.

Consent to publish: Not applicable; no identifying information is included in this report or associated data, figures, or tables.

FIGURE LEGENDS

Fig 2

Breast cancer (BC) gene VUS:

CRRM: $n = 1$ each *ATM*, *BRCA2*, *CHEK2*, *NF1*, *PTEN*

BCS/UM: *ATM*, $n = 5$; $n = 2$ each, *BRCA1*, *PALB2*; $n = 1$ each, *APC/BARD1*, *BRCA2*, *NBN*, *PTEN*

Other gene VUS:

CRRM: *POLE*, $n = 2$; $n = 1$ each *APC*, *BRIP1*, *MLH1*, *RAD51C*, *POLD1*

BCS/UM: $n = 2$ each *APC*, *MSH6*, *POLD1*; *SDHB*, $n = 1$

FIGURE DESCRIPTIVE CAPTIONS

Fig 1

A pie chart indicating that 123 (68%) of patients had a negative genetic testing result, 32 (16.5%) had a variant of uncertain significance, and 30 (15.5%) had a positive result. A second pie chart indicates that of the 30 patients with a positive result, 11 (36.7%) had a *BRCA1* PV; 9 (30%) had a *BRCA2* PV; 6 (20%) had a *CHEK2* PV; 2 (6.7%) had an *NBN* variant; 1 (3.2%) had an *ATM* PV; and 1 (3.3%) had an *NF1* PV.

Fig 2

A bar graph indicating that of the 30 patients with a PV, 83.3% had a CRRM. A pie chart leading from this part of the bar graph indicates that of patients with a PV who had a CRRM, 11 (44%) had a *BRCA1* PV; 8 (32%) had a *BRCA2* PV; 4 (16%) had a *CHEK2* PV; 1 (4%) had an *ATM* PV; and 1 (4%) had an *NBN* variant.

The remaining 16.7% of patients with a PV had a BCS or UM. A pie chart leading from this part of the bar graph indicates that 2 (40%) had a *CHEK2* PV; 1 (20%) had a *BRCA2* PV; 1 (20%) had an *NF1* PV; and 1 (20%) had an *NBN* variant.

The remainder of the bar graph indicates that of patients with a VUS in a BC gene, 27.8% had a CRRM, while 76.5% had a BCS/UM. Of patients with a VUS in any other gene, 50% had a CRRM, and 50% had a BCS/UM. Finally, of patients with negative test results, 23.1% had a CRRM, and 77.3% had a BCS/UM.

Figures

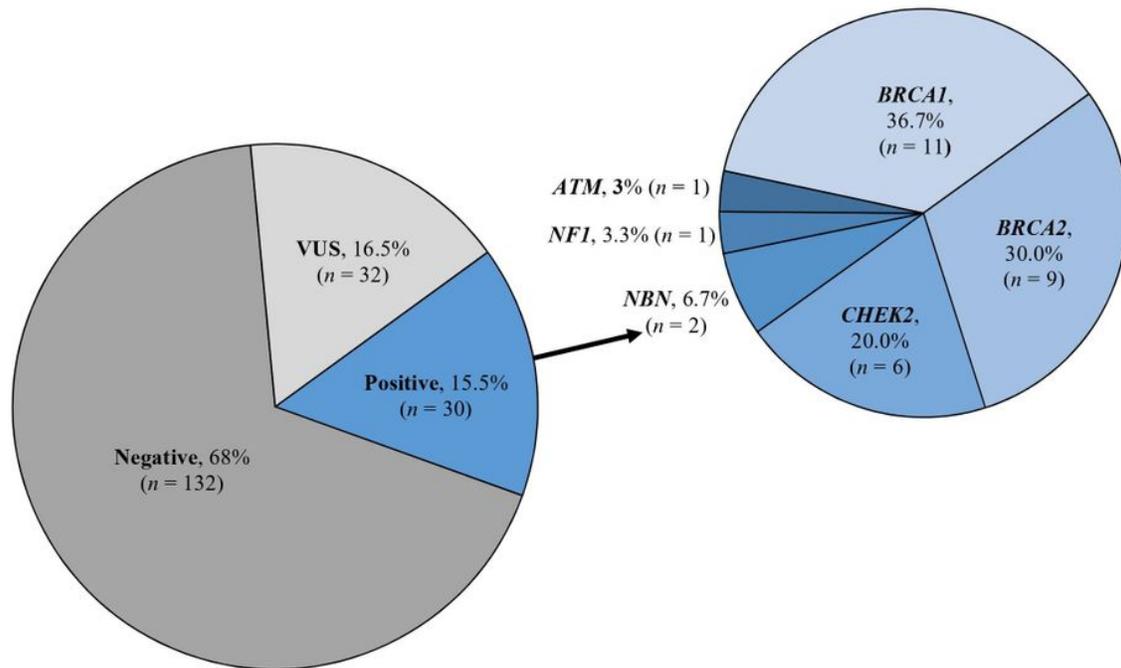


Figure 1

Genetic Testing Outcomes in All Patients (n = 194)

A pie chart indicating that 123 (68%) of patients had a negative genetic testing result, 32 (16.5%) had a variant of uncertain significance, and 30 (15.5%) had a positive result. A second pie chart indicates that of the 30 patients with a positive result, 11 (36.7%) had a BRCA1 PV; 9 (30%) had a BRCA2 PV; 6 (20%) had a CHEK2 PV; 2 (6.7%) had an NBN variant; 1 (3.2%) had an ATM PV; and 1 (3.3%) had an NF1 PV.

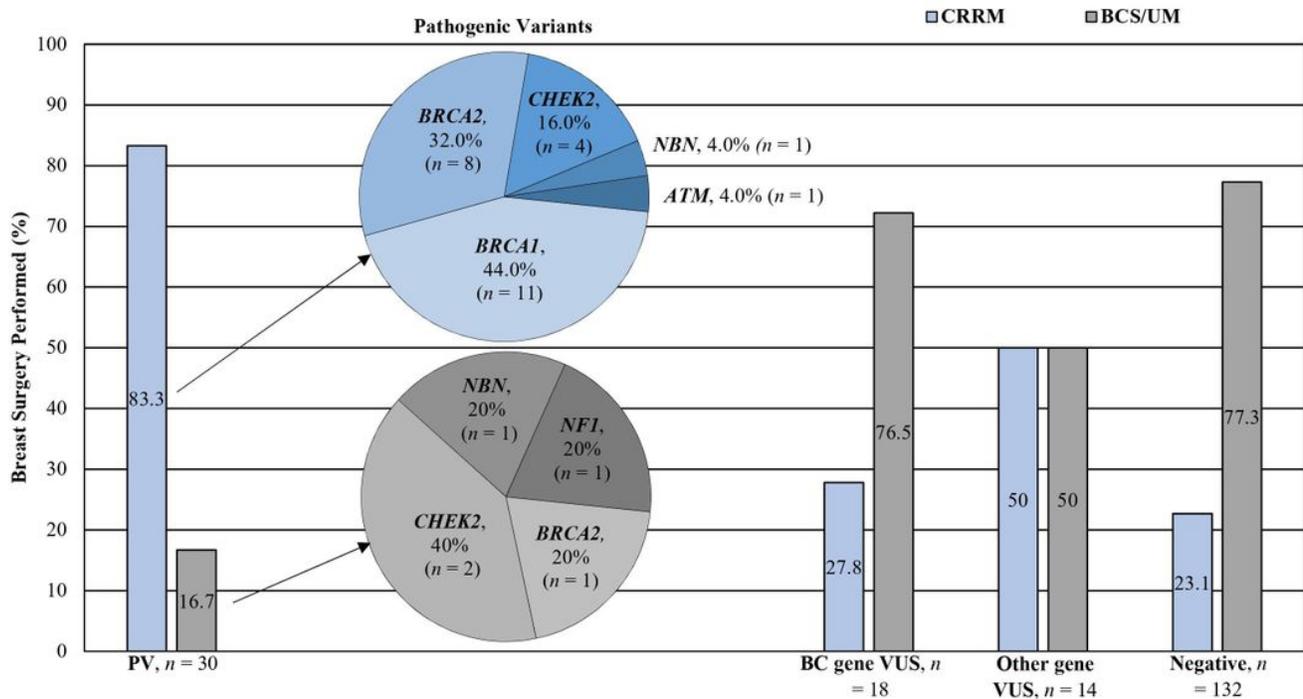


Figure 2

Overall Genetic Testing Results and Surgical Decision-Making Outcomes (n = 194)

Breast cancer (BC) gene VUS: CRRM: n = 1 each ATM, BRCA2, CHEK2, NF1, PTEN BCS/UM: ATM, n = 5; n = 2 each, BRCA1, PALB2; n = 1 each, APC/BARD1, BRCA2, NBN, PTEN

Other gene VUS: CRRM: POLE, n = 2; n = 1 each APC, BRIP1, MLH1, RAD51C, POLD1 BCS/UM: n = 2 each APC, MSH6, POLD1; SDHB, n = 1

A bar graph indicating that of the 30 patients with a PV, 83.3% had a CRRM. A pie chart leading from this part of the bar graph indicates that of patients with a PV who had a CRRM, 11 (44%) had a BRCA1 PV; 8 (32%) had a BRCA2 PV; 4 (16%) had a CHEK2 PV; 1 (4%) had an ATM PV; and 1 (45) had an NBN variant.

The remaining 16.7% of patients with a PV had a BCS or UM. A pie chart leading from this part of the bar graph indicates that 2 (40%) had a CHEK2 PV; 1 (20%) had a BRCA2 PV; 1 (20%) had an NF1 PV; and 1 (20%) had an NBN variant.

The remainder of the bar graph indicates that of patients with a VUS in a BC gene, 27.8% had a CRRM, while 76.5% had a BCS/UM. Of patients with a VUS in any other gene, 50% had a CRRM, and 50% had a BCS/UM. Finally, of patients with negative test results, 23.1% had a CRRM, and 77.3% had a BCS/UM.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [BCRTTable1.pdf](#)
- [BCRTTable2.pdf](#)