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Contralateral Risk Reducing Mastectomy in Breast Cancer Patients Who Undergo Multi-gene Panel Testing

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Abstract

Background—An increasing number of breast cancer patients are undergoing expanded genetic testing and are being identified as germline mutation carriers. We sought to determine rates of contralateral risk reducing mastectomy (CRRM) in patients with various germline mutations.

Methods—All women 18 years-of-age with unilateral breast cancer who underwent multigene panel testing between 1/1/2014–8/1/2019 at our academic institution were identified. Demographic, tumor, and treatment variables were identified from the medical record. Multivariable analyses were performed to compare factors associated with performance of CRRM.

Results—We identified 1613 patients, of whom 28.1% had a pathogenic variant and 40.1% had variants of uncertain significance (VUS). Overall, 420 patients (26.0%) underwent a CRRM. On multivariable analysis, factors associated with CRRM included age <50 years (OR 3.8, 95% CI 3.0, 5.0), race (OR 0.5 [95% CI 0.3, 0.7] and 0.4 [95% CI 0.2, 0.7]) for Black and Asian women respectively vs White women) and the presence of any germline mutation or VUS with OR of 13.2 (95% CI 8.7, 20.2) for BRCA 1/2, 3.9 (95% CI 2.7, 5.8) for non-BRCA germline mutation and 1.8 (95% CI 1.3, 2.6) for VUS.

Conclusion—In breast cancer patients who undergo multi-gene panel testing, a sizeable number of women with pathogenic non-BRCA germline findings are opting for CRRM. Given that the risk of contralateral breast cancer in women with most pathogenic mutations other than BRCA 1/2 remains poorly characterized, these data have implications for risk counseling and for ascertaining the true risks of contralateral breast cancer in this population.

Keywords

breast cancer; contralateral risk reducing mastectomy; germline mutation; BRCA

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Introduction

Breast cancer continues to be the most commonly diagnosed cancer in women, with approximately 20% of diagnoses being attributed to a germline mutation.¹⁻³ While the National Comprehensive Cancer Network (NCCN) has specific criteria for genetic testing including breast cancer diagnosed in a woman before age 50, triple negative breast cancer, and male breast cancer, the American Society of Breast Surgeons recently released a consensus statement suggesting genetic testing should be considered in all patients with a personal history of breast cancer, to include BRCA 1/2 and PALB2 testing.⁴⁻⁵ Such recommendations, in addition to declining costs of genetic testing, has resulted in increasing performance of panel testing.⁶⁻⁷ As more tests are being performed, a greater number of mutations and variants of uncertain significance (VUS) are being identified in the population.⁸ In a study by Theobald et al, 700 pathogenic variants were reported amongst 678, with just over half of these variants in germline mutations other than BRCA 1/2.⁹

While BRCA 1/2 mutations have been well studied, less is known about the non-BRCA germline pathogenic mutations regarding risk of contralateral breast cancer. Given the lack of data for second breast cancer risk amongst women with non-BRCA germline mutations, how such a finding influences the decision for surgical care is not well characterized. A previous study from our group evaluated 314 patients who underwent genetic panel testing and determined that patients with a BRCA 1/2 mutation and those with a non-BRCA mutation undergo CRRM at similar rates.¹⁰ We sought to expand on our group's early experience to determine if current rates of CRRM in patients with a non-BRCA germline mutation continue to parallel prior trends.

Methods

Cohort Selection

After institutional review board approval, we identified all women ≥ 18 years of age with a history of unilateral breast cancer who underwent multi-gene panel testing between January 1, 2014 and August 1, 2019 at University of Texas MD Anderson Cancer Center using an institutional database. All patients who had undergone testing and had at least one intact breast at time of multi-gene testing were included. Referral to the genetics service and decision for germline testing by the genetics counselors was based on contemporaneous NCCN guidelines in addition to shared decision making between the patient and provider. Patients without surgical information, synchronous bilateral cancer, and patients who had a CRRM prior to genetic testing results were excluded. Multi-gene panel testing was performed either at the time of the initial cancer diagnosis, or at a later date (Figure 1). Nine hundred seventy-eight patients who met eligibility criteria for this study underwent testing at the time of an initial cancer diagnosis, while 635 patients had panel testing after initial breast preserving surgery for their index cancer (Figure 1).

Cohort Characterization

A review of the electronic medical record was performed to collect patient, clinical tumor status, and treatment factors. Factors associated with the patient's first breast cancer

diagnosis were used for analyses. Clinical tumor and nodal category were evaluated and when missing, pathological data was used as a surrogate, unless the patient received neoadjuvant systemic therapy. Follow-up time was determined by calculating the difference between the date of surgery for the first cancer diagnosis and the last clinic visit date, or date of death if applicable. Performance of CRRM was considered to be at the time of therapeutic mastectomy if it occurred within 12 months of therapeutic mastectomy or considered delayed if occurred at the time of definitive reconstruction for the primary cancer.

Statistical Analysis

Patient, tumor, and treatment characteristics were evaluated and compared among genetic testing result: BRCA 1/2, non-BRCA mutation, VUS, and no germline mutation (Table 1) and between performance of CRRM (Table 3). A X^2 test or Fisher exact test was used for univariate comparison of categorical variables. Kruskal-Wallis equality-of-populations rank test was used to compare the means of continuous variables among genetic testing result groups. The Wilcoxon rank-sum test/student t test was used to compare the means of continuous variables between CRRM groups. A multivariable logistic regression model was used to predict performance of CRRM. All variables in Table 3 were entered into a full model, and the final model was selected by using a backwards elimination procedure with Akaike's information criterion to determine whether a factor should be deleted from the model. All analyses were performed with Stata statistical software (SE 16, StataCorp LP, College Station, TX). All p values were two tailed, $p = 0.05$ was considered significant.¹¹ Median follow-up time was 2.9 years.

Results

Cohort Demographics

We identified 1613 patients who met inclusion criteria; demographics of this cohort are detailed in Table 1. Average age ($\pm$ standard deviation) at time of genetic testing was 52.3 ± 12.6 years and most patients were White (68.5%), followed by Black (12.5%) and Asian (7.5%). Thirty-one percent of patients reported 1 or more first-degree relatives affected with breast cancer. The overall rate of pathogenic variants in our cohort was 28.1%: 192 (11.9%) with a BRCA 1/2 mutation, 262 (16.2%) with a non-BRCA 1/2 mutation, 646 (40.1%) with a VUS, and 513 (31.8%) with no germline mutation. Among women identified with a non-BRCA deleterious mutation, most common germline findings were CHEK2 ($n=70$, 26.7%), PALB2 ($n=48$, 18.3%), and ATM ($n=36$, 13.8%), and approximately 1/3 to 1/2 of women with these mutations underwent CRRM, Table 2.

BRCA 1/2 mutation carriers were noted to be significantly younger as compared to the rest of the cohort (47 years for BRCA 1/2 carriers vs 51 years for non-BRCA mutation carriers, 52 years for VUS carriers and 55 years for patients with no pathogenic germline mutation, $p=0.0001$). Significant differences in race distribution were also noted, with White women having substantially higher rates of representation amongst non-BRCA mutation carriers as compared to BRCA 1/2 carriers and women with VUS. Patients with a BRCA 1/2 mutation had a larger proportion of triple negative cancers (40.3%) than those with a non-BRCA mutation (18.0%), VUS (19.4%) or no pathogenic germline mutation (19.2%), $p<0.001$;

however, most cases were hormone receptor positive/HER 2 negative in all cohorts. There were no significant differences in reporting of first-degree relatives affected with breast cancer between groups. At last follow up, approximately 90% of all patients were alive without disease, Table 1.

Performance of CRRM

Overall rate of CRRM in this cohort was 26.0% (420 patients). Of patients who had a CRRM, surgery was performed at the time of therapeutic mastectomy for the index cancer in most cases, 364 (86.6%) (Figure 1). Patients with VUS and those without germline mutation had a steady decline in CRRM rates over the course of the study period with rates of CRRM in the most recent year of study 8% and 4% respectively (Figure 2). In contrast, women with BRCA 1/2 mutations saw a sharp increase in rates of CRRM between 2014 and 2016, with majority of these women thereafter opting for CRRM. For women with non-BRCA germline mutations, the annual rate of CRRM was relatively stable at 30–40%, although a sharp decline to 10% was noted in the final year of the study.

Factors Associated with CRRM

On univariate analysis (Table 3), a greater proportion of patients with a BRCA 1/2 mutation underwent CRRM than those with a non-BRCA mutation, VUS, or no mutation (126 [65.6%] BRCA 1/2, 98 [37.4%] non-BRCA mutation, 133 [20.6%] VUS, and 63 [12.3%] no germline mutation, $p<0.001$), Table 3. A greater proportion of White patients underwent CRRM as compared to Black and Asian women (27.0% White, 17.9% Black, 17.2% Asian) although rates were also high in women who did not report a specific race designation (other race, 35.1%), $p<0.001$. There was no significant association between the performance of CRRM with clinical tumor size, or clinical stage. Of patients who underwent CRRM, a greater proportion (32.6% vs 25.2%) had node positive disease, $p=0.005$. A strong trend was noted for proportion of patients with triple negative disease who underwent CRRM compared to hormone receptor positive disease or HER2 positive disease (33.5% vs 26.1% vs 27.5%, respectively, $p=0.05$). There was no significant difference in performance of CRRM based on the number of first-degree relatives with breast cancer.

On multivariable analysis, compared to patients without a germline mutation, patients with a BRCA 1/2 mutation were 13.2 (95% CI 8.7–20.2) times more likely to undergo CRRM, non-BRCA mutation carriers were 3.9 (95% CI 2.7–5.8) times as likely, and VUS carriers were 1.8 (95% CI 1.3–2.6) times as likely. Patients less than age 50 were 3.8 (95% CI 3.0–5.0) times as likely as those older than age 50 to undergo CRRM. Compared to White women, Black and Asian women were substantially less likely to undergo CRRM with odds ratio of 0.5 (95% CI 0.3–0.7) and 0.4 (95% CI 0.2–0.7) respectively, Table 4.

Discussion

Through evaluation of patients with unilateral breast cancer who underwent multigene panel testing at a large academic institution, we found that approximately 1 in 4 women undergoing such testing opt for CRRM. While the proportion of women undergoing CRRM was highest in patients with BRCA 1/2 mutations, a substantial number of patients with a

non-BRCA germline mutation underwent the procedure as well. Additionally, patients with a VUS were almost twice as likely to undergo a CRRM compared to those with no germline mutation. These findings suggest that while the risk of contralateral breast cancer (CBC) is not well understood in non-BRCA mutation carriers and is considered uninformative in VUS carriers, a significant proportion of such patients nonetheless are opting for CRRM.

Similar to our previous study, we found in this updated analysis that younger patients were more likely to undergo CRRM.¹⁰ In contrast to our previous report, we now find significant associations between race and CRRM, which is also in line with other studies.¹² Previous studies have attributed insurance status, health care literacy, and cultural perceptions to the variances seen in CRRM based on race.¹³ We also now find significant differences in CRRM rates between patients with a BRCA 1/2 germline mutation versus those with a non-BRCA germline mutation, likely due to the larger sample size in this current study, coupled with a substantial increase in the utilization of CRRM in BRCA1/2 mutation carriers over this time period.

Overall, 28% of patients who underwent multi-gene testing at our institution were found to have a pathogenic variant. This is higher than other reported studies and likely reflects differences in institutional practice in the criteria used for germline testing as well as the scope of panel testing. Our institutional standard for genetic testing has largely followed NCCN criteria and the scope of panel testing is tailored to the individual family pedigree. Theobald et al reported pathogenic variants in 678/7127 (9.5%) patients referred for expedited panel testing between 2013 and 2017.⁹ Other than pending surgery, no additional selection criteria for testing was provided. Beitsch et al reported a pathogenic variant rate of 8.65% in a series of 959 newly diagnosed breast cancer patients all of whom underwent 80 gene testing regardless of whether they met NCCN criteria, and Buys et al reported 9.3% in a series of over 35,000 patients, most of whom met NCCN criteria and underwent a standardized 25 gene panel test.^{14–15} These variances in referral criteria for multi-gene panel testing and scope of panel testing underscore the ongoing debate about how to best leverage the availability of extended germline testing to advance the care of breast cancer patients.

Management of the contralateral breast for patients with a BRCA 1/2 mutation includes consideration of CRRM, as these patients have a 2–6 times greater chance of developing a future breast cancer in the contralateral breast than those without a germline mutation.^{16–20} While the utility of CRRM has been extensively studied in patients with a BRCA 1/2 mutation, the benefits in patients with mutations other than BRCA 1/2 remain unknown, as the CBC risk in this patient cohort is not well described.^{21–22} Risk reducing mastectomy in BRCA 1/2 mutation carriers reduces the risk of future breast cancer by 85–100%.² A number of recent studies suggest that there may be a survival advantage associated with CRRM in patients with a BRCA 1/2 mutation.^{23–25} This advantage, however, should be interpreted with caution as the majority of the patients included in these studies were diagnosed with breast cancer prior to the identification of the BRCA 1/2 genes. Therefore, there is significant bias in the decision for CRRM in these series and for the subset of women in these reports who chose to undergo breast preservation, screening would not have included modern-day digital mammography and MRI. The use of MRI in particular has proven to be a highly effective tool for early detection of disease in high risk populations,

with series consistently demonstrating stage shift and, more recently excellent survival when cancers are detected by MRI.^{26–27}

With the possible exception of patients with the CHEK21100delC mutation and those with a rare ATM mutation receiving radiation for the index cancer,^{28–31} the risk of CBC is not well understood in the overwhelming majority of patients with non-BRCA mutations. Thus the magnitude of risk reducing benefit from the CRRM procedure in women with most non-BRCA germline mutations is unknown, creating unique challenges for appropriate counseling. Furthermore, the high rate of CRRM performance in this patient population will skew the observed number of contralateral breast cancer events and may limit the accurate assessment of CBC risk in these populations. While there are established methodologies to estimate breast cancer risks in unaffected carriers, whether such methods can reliably estimate risks of CBC remains to be seen.^{32–33}

The NCCN recommends consideration of CRRM for patients with TP53 and PTEN mutations, in addition to patients with other non-BRCA mutations based on family history.¹⁸ Based on the family history, shared decision making may be used to determine the best management of the contralateral breast for each individual patient. Interestingly, we did not find an association between family history and performance of CRRM and in general, the proportion of women with non-BRCA germline mutation with an affected first-degree relative was lower than the rates of CRRM. Therefore, as has been shown in other studies of women undergoing CRRM, factors such as cancer fear and anxiety may be driving the relatively high rates of CRRM in women with non-BRCA mutations in our study.³⁴ Alternatively, family history of affected second and third-degree relatives, which we did not assess, may have influenced patients toward CRRM.

It has been estimated that a VUS is identified in approximately 40% of patients who undergo germline testing.⁸ Prior studies have found high rates of CRRM (21–43%) in patients with a VUS, in comparison to patients without a genetic mutation.^{7, 35–36} Although rates of CRRM in VUS carriers in our series were on the lower end of previously reported ranges, we nonetheless note that this rate remained almost double the frequency seen in patients with no pathogenic germline mutation. Pending subsequent reclassification, a VUS is considered uninformative to decision making and thus the recommendations by the American College of Medical Genetics and Genomics recommend that medical management decisions are not based on a finding of a VUS in a gene, but are rather based on family history.^{8, 37} The high rates of CRRM in patients with a VUS highlights the importance of genetic counseling and surgeon education regarding the interpretation of a VUS. Reasons that our institution had higher rates of CRRM performance in patients with a VUS are unclear, as it is standard for our patients to be evaluated by a genetic counselor. Similar to the reasons behind the high rates of CRRM in our non-BRCA mutation population, the presence of extended relatives with breast cancer may have influenced the decision for CRRM in patients with VUS. Additionally, the uncertainty surrounding the finding of a VUS may be associated with increased anxiety, which may lead to the choice to undergo CRRM.³⁴

Limitations to this study include its retrospective design, and the evolving guidelines for genetic testing over the 6-year time frame included in this analysis, which may have

underrepresented the true prevalence of germline mutations and the associations with CRRM. In addition, given the availability of a robust genetics counseling program, our rates of CRRM may not be representative of areas where such services are more limited. Important strengths of our study include the large sample size and the availability of a readily accessible genetics program that ensured a consistent approach to testing and counseling, thus removing potential provider bias and influence.

Conclusion

In patients with a history of unilateral breast cancer who undergo broad based genetic testing, rates of CRRM are greatest in patients with a BRCA 1/2 mutation, although a sizeable number of women with a pathogenic non-BRCA germline finding are also opting for CRRM. Given that the risk of contralateral breast cancer in women with most pathogenic mutations other than BRCA 1/2 remains poorly characterized, these data have implications for both risk counseling in patients and for ascertaining the true risks of contralateral breast cancer.

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Synopsis:

Among patients with unilateral breast cancer who underwent multi-gene panel testing, patients with a BRCA 1/2 mutation were thirteen times more likely than those without a germline mutation to undergo CRRM, patients with a non-BRCA mutation were four times as likely, and a VUS were twice as likely.

Figure 1:
Timing of Genetic Testing and Risk Reducing Mastectomy

Figure 2:
Trends of Contralateral Risk Reducing Mastectomy over Time

Table 1:

Patient Demographics

Variable	Total (N=1613)	No Mutation (N=513)	BRCA (N=192)	Non-BRCA (N=262)	VUS (N=646)	P value
CRRM						<0.001
No	1193 (74.0)	450 (87.7)	66 (34.4)	164 (62.6)	513 (79.4)	
Yes	420 (26.0)	63 (12.3)	126 (65.6)	98 (37.4)	133 (20.6)	
Age at Genetic Testing						0.0001 *
Mean (SD)	52.3 (12.6)	55 (12.6)	47 (12.9)	51 (12.5)	52 (12.0)	
Range	20–87	25–87	20–78	25–84	24–86	
Race						<0.001
White	1105 (68.5)	382 (74.5)	119 (62.0)	206 (78.6)	398 (61.6)	
Black	201 (12.5)	55 (10.7)	26 (13.5)	19 (7.3)	101 (15.7)	
Asian	122 (7.5)	25 (4.9)	13 (6.8)	9 (3.4)	75 (11.6)	
Others	185 (11.5)	51 (9.9)	34 (17.7)	28 (10.7)	72 (11.1)	
Clinical Tumor Category						<0.001 ^
0	225 (14.0)	73 (17.0)	18 (10.2)	38 (16.0)	96 (15.8)	
T1	532 (33.0)	151 (35.2)	46 (26.2)	84 (35.1)	251 (41.4)	
T2	521 (32.3)	160 (37.3)	92 (52.3)	87 (36.4)	182 (30.0)	
T3	129 (8.0)	31 (7.2)	12 (6.8)	22 (9.2)	64 (10.5)	
T4	44 (2.7)	14 (3.3)	8 (4.5)	8 (3.3)	14 (2.3)	
Missing	162 (10.0)	84	16	23	39	
Clinical Nodal Category						<0.001 ^
Negative	1069 (66.3)	331(77.3)	101 (56.7)	171 (71.0)	466 (76.6)	
Positive	386 (23.9)	97(22.7)	77 (43.3)	70 (29.0)	142 (23.4)	
Missing	158 (9.8)	85	14	21	38	
Stage of disease						<0.001
0	158 (9.8)	45 (10.8)	13 (7.5)	17 (7.6)	83 (13.7)	
I	431 (26.7)	134 (32.1)	31 (17.8)	69 (31.0)	197 (32.5)	
II	600 (37.2)	173 (41.3)	93 (53.4)	96 (43.0)	238 (39.2)	
III	210 (13.0)	60 (14.4)	33 (19.0)	33 (14.8)	84 (13.8)	
IV	23 (1.4)	6 (1.4)	4 (2.3)	8 (3.6)	5 (0.8)	
Missing	191 (11.8)	95	18	39	39	
Tumor Biology						<0.001 ^
HR+/HER2-	854 (52.9)	251 (63.6)	82 (48.0)	148 (66.7)	373 (65.1)	
HER2+	211 (13.1)	68 (17.2)	20 (11.7)	34 (15.3)	89 (15.5)	
TNBC	296 (18.4)	76 (19.2)	69 (40.3)	40 (18.0)	111 (19.4)	
Missing	252 (15.6)	118	21	40	73	
Number of First-degree Relatives with Breast Cancer						0.9
0	1113 (69.0)	345 (67.3)	134 (69.8)	185 (70.6)	449 (69.5)	

Variable	Total (N=1613)	No Mutation (N=513)	BRCA (N=192)	Non-BRCA (N=262)	VUS (N=646)	P value
1	415 (25.7)	140 (27.3)	49 (25.5)	66 (25.2)	160 (24.8)	
2	85 (5.3)	28 (5.4)	9 (4.7)	11 (4.2)	37 (5.7)	
Status Last Clinic Visit						0.06
Alive no Disease	1438 (89.1)	445 (86.7)	173 (90.1)	234 (89.3)	585 (90.6)	
Alive Disease	88 (5.5)	27 (5.3)	10 (5.2)	15 (5.7)	36 (5.6)	
Dead no Disease	48 (3.0)	26 (5.1)	6 (3.1)	8 (3.1)	8 (1.2)	
Dead Disease	39 (2.4)	15 (2.9)	3 (1.6)	5 (1.9)	16 (2.6)	

* Kruskal-Wallis equality-of-populations rank test;

^ p value calculated after exclude unknown

Table 2:

Non-BRCA Germline Mutation Distribution

Germline Mutation	Number of Patients	Proportion of all Non-BRCA Mutation Patients	Number who underwent CRRM (n=98)	Proportion CRRM among patients with Individual Mutation	Proportion CRRM among all Non-BRCA Mutation Patients who underwent CRRM
CHEK2	70	26.7%	30	42.8%	30.5%
PALB2	48	18.3%	23	47.8%	23.5%
ATM	36	13.8%	11	30.5%	11.2%
MUTYH	19	7.3%	5	26.3%	5.1%
TP53	18	6.9%	7	38.9%	7.1%
RAD50/RAD51	13	5%	6	46.1%	6.1%
BRIP1	11	4.2%	1	9.1%	1.0%
CDH1	9	3.4%	6	66.7%	6.1%
BARD1	5	1.9%	2	40.0%	2.0%
MSH	5	1.9%	0	0%	0%
APC	4	1.5%	1	25.0%	1.0%
PMS2	4	1.5%	0	0%	0%
PTEN	4	1.5%	1	25.0%	1.0%
CDKN2A	3	1.1%	1	33.3%	1.0%
MEN1	3	1.1%	0	0%	0%
NBN	2	0.8%	1	50.0%	1.0%
MLH	1	0.4%	1	100.0%	1.0%
NF1	1	0.4%	0	0%	0%
SDHA	1	0.4%	1	100.0%	1.0%
SDHD	1	0.4%	0	0%	0%
Multiple	4	1.5%	1	25.0%	1.0%

Table 3:

Univariate analysis evaluating the association between variables and performance of contralateral risk reducing mastectomy

Characteristic	Total N= 1613	No CRRM N= 1193	CRRM N = 420	p-Value
Age at Genetic Testing (years)				<0.001 [*]
Mean (SD)	52.3 (12.6)	54.8 (12.2)	45.3 (11.0)	
Range	20–87	25–87	20–87	
Race				<0.001
White	1105 (68.5)	807 (73.0)	298 (27.0)	
Black	201 (12.5)	165 (82.1)	36 (17.9)	
Asian	122 (7.5)	101 (82.8)	21 (17.2)	
Others	185 (11.5)	120 (64.9)	65 (35.1)	
Type of Mutation				<0.001
No Mutation	513 (31.8)	450 (87.7)	63 (12.3)	
BRCA Mutation	192 (11.9)	66 (34.4)	126 (65.6)	
Non-BRCA Pathogenic Mutation	262 (16.2)	164 (62.6)	98 (37.4)	
VUS	646 (40.1)	513 (79.4)	133 (20.6)	
Clinical Tumor Category				0.2 [^]
T0	225 (14.0)	168 (74.7)	57 (25.3)	
T1	532 (33.0)	401 (75.4)	131 (24.6)	
T2	521 (32.3)	366 (70.2)	155 (29.8)	
T3	129 (8.0)	88 (68.2)	41 (31.8)	
T4	44 (2.7)	34 (77.3)	10 (22.7)	
Missing	162 (10.0)	136	26	
Clinical Nodal Category				0.005 [^]
Negative	1069 (66.3)	800 (74.8)	269 (25.2)	
Positive	386 (23.9)	260 (67.4)	126 (32.6)	
Missing	158 (9.8)			
Stage of Disease				0.3 [^]
0	158 (9.8)	119 (75.3)	39 (24.7)	
I	431 (26.7)	327 (75.9)	104 (24.1)	
II	600 (37.2)	420 (70.0)	180 (30.0)	
III	210 (13.0)	152 (72.4)	58 (27.6)	
IV	23 (1.4)	17 (73.9)	6 (26.1)	
Missing	191 (11.8)	158	33	
Tumor Biology				0.052 [^]
HR+/HER2-	854 (52.9)	631 (73.9)	223 (26.1)	
HER2+	211 (13.1)	153 (72.5)	58 (27.5)	
TNBC	296 (18.4)	197 (66.5)	99 (33.5)	
Missing	252 (15.6)	212	40	
Number of First-degree Relatives with Breast Cancer				0.6

Characteristic	Total N= 1613	No CRRM N= 1193	CRRM N = 420	p-Value
0	1113 (69.0)	818 (73.5)	295 (26.5)	
1	415 (25.7)	308 (74.2)	107 (25.8)	
2	85 (5.3)	67 (78.8)	18 (21.2)	

* Wilcoxon rank-sum test;

^ p value calculated after exclusion of unknown patients; Abbreviations: SD: standard deviation; VUS: variant of uncertain significance; HR: hormone receptor; TNBC: triple negative breast cancer

Table 4.

Multivariable logistic regression of factors associated with undergoing CRRM

	Odds Ratio	SE	P	95% Confident interval	
Age <50 years	3.8	0.5	<0.001	3.0	5.0
Panel Testing Result					
No Mutation	Reference				
BRCA Mutation	13.2	2.8	<0.001	8.7	20.2
Non-BRCA Pathogenic Mutation	3.9	0.8	<0.001	2.7	5.8
VUS	1.8	0.3	<0.001	1.3	2.6
Race					
White	Reference				
Black	0.5	0.1	0.001	0.3	0.7
Asian	0.4	0.1	0.001	0.2	0.7
Others	0.9	0.2	0.8	0.6	1.4

Abbreviations: VUS: variant of uncertain significance