

## ORIGINAL RESEARCH

# Contralateral prophylactic mastectomy rate and predictive factors among patients with breast cancer who underwent multigene panel testing for hereditary cancer

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## Keywords

*BRCA* carriers, CPM, multigene panel, non-*BRCA* carriers, VUS

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## Abstract

Although multigene panel testing is increasingly common in patients with cancer, the relationship between its use among breast cancer patients with non-*BRCA* mutations or variants of uncertain significance (VUS) and disease management decisions has not been well described. This study evaluated the rate and predictive factors of CPM patients who underwent multigene panel testing. Three hundred and fourteen patients with breast cancer who underwent multigene panel testing between 2014 and 2017 were included in the analysis. Of the 314 patients, 70 elected CPM. Election of CPM by gene status was as follows: *BRCA* carriers (42.3%), non-*BRCA* carriers (30.1%), and VUS (10.6%). CPM election rates did not differ between non-*BRCA* carriers and *BRCA* carriers ( $P = 0.6205$ ). Among non-*BRCA* carriers, negative hormone receptor status was associated with CPM ( $P = 0.0115$ ). For those with a VUS, hormone receptor status was not associated with CPM ( $P = 0.1879$ ). Although the rate of CPM between *BRCA* carriers and non-*BRCA* carriers was not significantly different, the predictors of CPM were different in each group. Our analyses shed the light on the increasing use of CPM among patients who are non-*BRCA* carriers as well those with a VUS. Our study elucidates the differing predictive factors of CPM election among *BRCA* carriers, non-*BRCA* carriers, and those with a VUS. Our findings reveal the need for providers to be cognizant that non-*BRCA* genes and VUS drive women to elect CPM despite the lack of data for contralateral breast cancer risk associated with these genes.

## Introduction

Although most breast cancers are sporadic, approximately 5–10% of breast cancers are hereditary, caused by a germline mutation in a myriad of genes implicated in carcinogenesis [1–3]. Mutations in the *BRCA1* and *BRCA2* genes account for 60–80% of inherited breast cancers [4]. Defining mutation carrier status is crucial because carriers have a 43–84% risk of developing breast cancer and up to a 65% risk of developing contralateral breast cancer (CBC) [4, 5]. Rarer, highly penetrant genes, such as *CDH1*, *PTEN*, *STK11*, and *TP53*, have similarly been shown to be associated with significantly increased risks of

developing breast cancer and some potential association with an increased risk of developing CBC [6–9].

In the past decade, moderately penetrant genes associated with breast cancer, such as *ATM*, *CHEK2*, and *PALB2*, have also been shown to increase the risk of developing breast cancer (between 18.3% and 44%) [10, 11]. Studies on these more recently described genes have yet to definitively determine the likelihood of second primary breast cancers owing to the paucity of data. Multiple sources report a significant increase in CBC risk among *CHEK2* mutation carriers, yet other studies did not show a significant association between *CHEK2* and CBC [12–15]. The WECARE study showed that *ATM* mutations are associated with an elevated risk

of CBC, but that association is largely dependent on the use of radiotherapy during treatment of initial breast cancer [16–18]. Tischkowitz et al. also published data from the WECARE study showing a higher rate of *PALB2* mutations in women with CBC compared with those with unilateral breast cancer [19]. Many of these studies had small sample sizes or presented conflicting data, suggesting that the risk of developing CBC in patients with moderately penetrant gene mutations is still up for debate.

Clinical guidelines developed over the past two decades, such as those presented by the National Comprehensive Cancer Network (NCCN), recommend additional breast cancer screening and consideration of contralateral prophylactic mastectomy (CPM) for breast cancer patients with *BRCA1* and *BRCA2* mutations to address the risk of developing a second primary cancer. The most recent iteration of these guidelines now addresses the appropriate screening considerations for individuals with deleterious mutations in moderately penetrant genes, like the guidelines for rarer, highly penetrant genes with a less established association with risk of developing a second primary breast cancer. The National Comprehensive Cancer Network (NCCN) guidelines encourage consideration of family history for CPM decisions. In the absence of sufficient data and clear consensus guidelines, patients and their physicians are tasked with determining the appropriate course of treatment as the rate of CPM increases among all patients with breast cancer [20, 21].

While there has been an uptake in multigene panel testing in patients with cancer, the management trends of breast cancer patients with non-*BRCA* mutations or variants of uncertain significance (VUS) have not been well described. This study aimed to evaluate the rate and predictive factors of CPM in a cohort of individuals who underwent multigene panel testing. We also aimed to determine whether predictors of CPM differed by gene implicated or result type.

## Methods

Three hundred and fifty patients diagnosed with ductal carcinoma in situ or invasive breast cancer who underwent genetic counseling and multigene panel testing between 2014 and 2017 were identified from a prospectively maintained research registry in the Department of Clinical Cancer Genetics at The University of Texas MD Anderson Cancer. The study was approved by the MD Anderson institutional review board. Each patient underwent genetic testing and received pretest genetic counseling per standard of care. The following genes were included in the multigene panel: *APC* (2), *ATM* (17), *BARD1* (2), *BRCA1* & *BRCA2* (71), *BRIP1* (4), *CDH1* (5), *CDKN2A* (2), *CHEK2* (19), *MEN1* (1), *MLH1* (1), *MUTYH* (2), *NBN* (1), *PALB2*

(17), *PMS2* (2), *PTEN* (5), *RAD51C* (1), and *TP53* (11). After the testing, all results were disclosed by a genetic counselor.

Patients with bilateral breast cancer and patients who had CPM before they underwent multigene panel testing were excluded from our analysis, as were patients with a negative genetic test result. After excluding the 36 patients who elected CPM before genetic testing, we were left with 314 patients who had a pathogenic or likely pathogenic mutation or VUS. For analysis simplicity and the very small number of non-*BRCA* genes included in the panel, we combined all the non-*BRCA* carriers together, all patients with VUS in either *BRCA* or non-*BRCA* genes together. Therefore, the analysis compared three groups: non-*BRCA* carriers (all other genes listed above), *BRCA* (*BRCA1* or *BRCA2*) carriers, and those with a VUS.

We examined predictors of CPM that occurred between the date on which test results were disclosed and the time of CPM election. For patients who had not elected CPM by the time of data analysis, times were censored at the last contact at which the patient was known not to have elected CPM, alive, or dead. The median follow-up time was 8.6 months. The distribution of time to CPM election for each group was estimated using the Kaplan–Meier method [22]. The log-rank test was used to determine the differences in the distributions of time to CPM between groups [23].

Regression analyses of time to CPM were conducted using the Cox proportional hazards model [24]. Martingale residuals were used to check the function form of continuous variables, including age at diagnosis and at genetic testing, in the Cox proportional hazards models. A multivariable Cox proportional hazards model was obtained by first including a set of candidate predictor variables with a *P* value <0.10 in a univariate analysis. Because age at diagnosis and age at genetic testing were correlated, we chose age at genetic testing for the multivariable analysis because its association with time to CPM was more pertinent to answering our research question. Backward elimination was then performed using *P* < 0.05 for the significance level of the Wald chi-square for an effect to stay in the model. Once the list of variables in our final model was selected, we further assessed the interaction effect on time to CPM between gene status and other variables to determine whether the predictors of electing CPM after genetic testing differed by final gene status. SAS version 9.4 and S-Plus version 8.2 were used to carry out the computations for all analyses.

## Results

Table 1 shows patient demographic and clinical characteristics. Of the 314 patients, 70 elected CPM and 244 did not. Election of CPM by gene status was as follows: 30 of

**Table 1.** Demographic and clinical characteristics of patients with breast cancer who underwent multigene panel testing ( $n = 314$ ).

Characteristic	No. (%)
Contralateral prophylactic mastectomy	
Yes	70 (22.3)
No	244 (77.7)
Personal history of ovarian cancer	
Yes	55 (17.5)
No	259 (82.5)
Marital status	
Divorced	29 (9.2)
Married	212 (67.5)
Separated	5 (1.6)
Single	39 (12.4)
Widowed	11 (3.5)
Unknown	18 (5.7)
Race/ethnicity	
Hispanic	46 (14.6)
White	203 (64.6)
Black	34 (10.8)
Other	29 (9.2)
Unknown	2 (0.6)
Education	
Advanced degree	45 (14.33)
Bachelor's degree	71 (22.61)
High school	11 (3.50)
Some college or technical school	14 (4.46)
Unknown	173 (55.10)
First-degree family history of breast cancer	
0	215 (68.5)
$\geq 1$	97 (30.9)
Unknown	2 (0.6)
Total no. of relatives with a breast cancer diagnosis	
0	101 (32.2)
$\geq 1$	211 (67.2)
Unknown	2 (0.6)
First-degree family history of ovarian cancer	
0	297 (94.6)
$\geq 1$	15 (4.8)
Unknown	2 (0.6)
Total no. of relatives with an ovarian cancer diagnosis	
0	262 (83.4)
$\geq 1$	50 (15.9)
Unknown	2 (0.6)
Estrogen receptor status	
Negative	69 (22.0)
Positive	223 (71.0)
Unknown	22 (7.0)
Progesterone receptor status	
Negative	103 (32.8)
Positive	187 (59.6)
Unknown	24 (7.6)

(Continued)

the 71 *BRCA1/BRCA2* carriers (42.3%), 22 of the 73 non-*BRCA* carriers (30.1%), and 18 of the 170 with a VUS (10.6%). The mean age at genetic testing was 49.3 years.

Univariate analysis (Table 2) showed that patients aged 50 years or younger at the time of genetic testing were

**Table 1.** (Continued)

Characteristic	No. (%)
Nuclear grade	
I	29 (9.2)
II	112 (35.7)
III	136 (43.3)
Unknown	37 (11.8)
TNM stage	
0	31 (9.9)
1	89 (28.3)
2	106 (33.8)
3	53 (16.9)
4	18 (5.7)
Unknown	17 (5.4)
Gene status	
<i>BRCA</i> carrier	71 (22.6)
<i>BRCA</i> variant of uncertain significance	38 (12.1)
Non- <i>BRCA</i> carrier	73 (23.2)
Non- <i>BRCA</i> variant of uncertain significance	132 (42.0)
Hormone receptor status	
Positive	223 (71.0)
Negative	69 (22.0)
Unknown	22 (7.0)
Her2 status	
Positive	42 (13.4)
Negative	216 (68.8)
Unknown	56 (17.8)

more likely to elect CPM ( $P = 0.0006$ ). Educational status was also significantly associated with CPM such that those with advanced degree were likely to elect CPM than those lower educational level ( $P = 0.03$ ).

After adjustment for age, the multivariable Cox proportional hazards regression model revealed that *BRCA* carriers and non-*BRCA* carriers were both more likely to elect CPM than those who had a VUS ( $P < 0.0001$ ; Table 3). CPM election rates did not significantly differ between patients who were non-*BRCA* carriers and those who were *BRCA* carriers ( $P = 0.6205$ ; Table 3), even after adjustment for age.

A cumulative incidence plot for election of CPM after genetic testing showed that the rate of CPM election among *BRCA* carriers over 6 months and non-*BRCA* carriers over 12 months was greater than the rate of CPM election among those who had a VUS for these periods (Table 4, Figure 1). More specifically, the rates of CPM election were as follows: among *BRCA* carriers, 29.9% over 6 months and 55.4% over 12 months; among non-*BRCA* carriers, 36.4% over 6 months and 43% over 12 months; and among those who had a VUS, 9.2% over 6 months and 13.4% over 12 months (Table 4, Figure 1).

Analysis of predictors of CPM election revealed an interaction between gene mutation status and hormone receptor status in predicting CPM election, after adjustment for age at genetic testing ( $P = 0.0053$ ). As shown in Table 5, for

**Table 2.** Univariate analysis of time to election of contralateral prophylactic mastectomy in patients with breast cancer who underwent multigene panel testing ( $n = 314$ ).

Parameter	<i>P</i>	Hazard ratio	95% confidence interval	<i>P</i> for overall effect
Age at diagnosis				
≤50 years vs. >50	0.0399	1.919	1.031–3.574	0.0399
Age at genetic testing				
≤50 years vs. >50	0.0006	2.674	1.528–4.680	0.0006
Race/ethnicity				
Black vs. White	0.7602	0.890	0.420–1.883	0.6736
Hispanic vs. White	0.5465	0.811	0.410–1.604	
Others vs. White	0.2546	0.553	0.199–1.533	
Education				
Bachelor's degree/some college or technical school vs. advanced degree	0.0171	2.728	1.196–6.224	0.03
High school vs. advanced degree	0.7432	0.704	0.086–5.738	
Marital status				
Single, divorced, separated, or widowed vs. married	0.8376	1.057	0.621–1.801	0.8376
First-degree family history of breast cancer yes vs. no	0.9782	0.993	0.599–1.645	0.9782
First-degree family history of ovarian cancer yes vs. no	0.6614	0.772	0.243–2.456	0.6614
Personal history of ovarian cancer yes vs. no	0.0873	0.542	0.269–1.094	0.0873
Total no. of relatives with a breast cancer diagnosis ≥1 vs. 0	0.3914	1.255	0.747–2.108	0.3914
Total no. of relatives with an ovarian cancer diagnosis ≥1 vs. 0	0.7702	0.908	0.477–1.731	0.7702
Gene status				
BRCA carrier vs. VUS	<0.0001	4.695	2.611–8.441	<0.0001
Non-BRCA carrier vs. VUS	<0.0001	3.689	1.973–6.896	
BRCA carrier vs. non-BRCA carrier	0.3908	1.2727	0.7337–2.2076	
Nuclear grade				
III vs. I	0.3120	1.556	0.660–3.665	0.0560
II vs. I	0.6465	0.805	0.320–2.030	
Hormone receptor status				
Negative vs. positive	0.6237	1.144	0.668–1.960	0.6237
Her2 status				
Positive vs. negative	0.3755	1.345	0.698–2.593	0.3755
Lymphovascular invasion present vs. absent	0.8540	0.941	0.493–1.795	0.8540
Stage				
4 vs. 0	0.9518	0.958	0.239–3.838	0.2290
3 vs. 0	0.4653	0.666	0.224–1.983	
2 vs. 0	0.2638	1.643	0.688–3.928	
1 vs. 0	0.5213	1.348	0.541–3.361	

BRCA carriers, hormone receptor status was not associated with CPM election ( $P = 0.5657$ ), but for non-BRCA carriers, negative hormone receptor status was associated with CPM election ( $P = 0.0115$ ). For those with a VUS, hormone receptor status was not associated with CPM election ( $P = 0.1879$ ). However, age ≤50 years was associated with CPM election in this group ( $P = 0.0286$ ).

## Discussion

Our results showed that, overall, 23% of patients with breast cancer who underwent multigene panel testing with

a non-negative result, including BRCA carriers, non-BRCA carriers, and those with a VUS, opted for CPM, up from the average of 7% among breast cancer patients [20]. Patients who had a pathogenic variant identified were more likely to elect CPM than those with a VUS, no matter which gene was implicated.

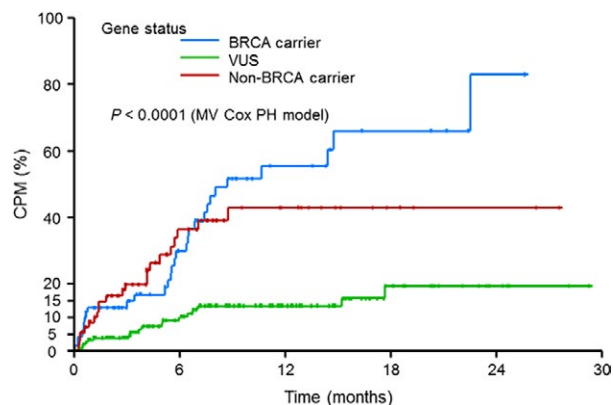
Moreover, patients aged 50 years or younger were more likely to elect CPM than older patients for all genes included in this cohort, and patients with an advanced educational level were also more likely to elect CPM than those with a lower educational level. Predictors and rates of CPM have already been established among patients

**Table 3.** Multivariate Cox PH model of time to election of contralateral prophylactic mastectomy in patients with breast cancer who underwent multigene panel testing (n = 314).

Parameter		Hazard ratio	95% Hazard ratio confidence limits	P	P for overall effect
Gene Status	BRCA carriers vs. VUS	4.162	2.307–7.509	<.0001	<.0001
	Non-BRCA carriers vs. VUS	3.618	1.932–6.775	<.0001	<.0001
	BRCA carriers vs. non-BRCA carriers	1.1504	0.6606–2.004	0.6205	<.0001
Age at genetic testing	<50 vs. ≥50	2.321	1.321–4.080	0.0034	<.0001

**Table 4.** Rates of contralateral prophylactic mastectomy (CPM) election by age at genetic testing and test results among patients with breast cancer who underwent multigene panel testing (n = 314).

Variable	CPM/total	CPM rate (range), %	
		6 months after genetic testing	12 months after genetic testing
Age at genetic testing			
<50 years	54/182	26.0 (19.3–34.4)	40.3 (31.8–50.0)
≥50 years	16/132	11.7 (6.9–19.6)	15.0 (9.1–24.3)
Genetic test results			
BRCA carrier	30/71	29.9 (19.5–44.2)	55.4 (41.1–70.8)
Variant of uncertain significance	18/170	9.2 (5.3–15.7)	13.4 (8.3–21.2)
Non-BRCA carrier	22/73	36.4 (24.7–51.4)	43 (29.7–59.1)



**Figure 1.** Cumulative incidence plot of contralateral prophylactic mastectomy among all patients.

**Table 5.** Predictors of contralateral prophylactic mastectomy election among patients with breast cancer who underwent multigene panel testing (n = 314).

Variable	P	Hazard ratio	95% Confidence interval
Age <50 vs. ≥50 years			
BRCA carrier	0.5703	1.283	0.543–3.029
Non-BRCA carrier	0.0941	2.382	0.862–6.578
Variant of uncertain significance	0.0286	3.801	1.150–12.56
Negative hormone receptor status			
BRCA carrier	0.5657	0.796	0.366–1.732
Non-BRCA carrier	0.0115	3.278	1.305–8.230
Variant of uncertain significance	0.1879	0.316	0.057–1.756

carrying *BRCA1* or *BRCA2* pathogenic variants, but data are lacking regarding predictors and rates of CPM among patients who are carriers of non-*BRCA* pathogenic variants or those with a VUS. Our study revealed that while the rate of CPM between *BRCA* carriers and non-*BRCA* carriers was not significantly different, the predictors of CPM were different in each group.

Few studies have examined the rate and predictors of CPM among non-*BRCA* carriers, although one noteworthy study by Kurian et al. [25] showed a similar trend of self-reported CPM election to that of our study. Their study revealed that patients with a pathogenic variant in

*BRCA1/BRCA2* or another gene associated with breast cancer were more likely to elect CPM than those with negative results or a VUS. Our study took this a step further to determine that there is no significant difference in CPM rate between *BRCA* carriers and non-*BRCA* carriers. While these groups are receiving CPM at similar rates, it is important to note that their surgical recommendations and risk profiles are significantly different due to the lack of data on CBC rates in non-*BRCA* carriers. Despite the lack of data on CBC risk and the absence of consensus guidelines recommending CPM, both studies confirm a trend of more invasive surgical intervention



for individuals with breast cancer and any hereditary predisposition to cancer.

The rate of CPM election among *BRCA* carriers has been well established given that bilateral prophylactic mastectomy (BPM) reduces the risk of developing breast cancer by more than 90% [26]. Among *BRCA* carriers, 65% of those with breast cancer and 15–60% of unaffected individuals elect prophylactic surgeries [27–30]. Factors associated with prophylactic surgery among *BRCA* carriers with breast cancer include age, type of initial breast cancer surgery, prophylactic oophorectomy, desire to have children, and family history of breast cancer [31–34]. Moreover, a study of CPM election rates among patients with ductal carcinoma in situ who were *BRCA*-positive, *BRCA*-negative, or untested showed that 27% opted for the surgery, and age, family history of ovarian cancer, and *BRCA* positivity predicted CPM election. The present study showed similar factors associated with CPM election in the cohort as a whole, including *BRCA* carriers, non-*BRCA* carriers, and those with a VUS. The predictors varied, though, when comparing each of these groups with one another.

Among non-*BRCA* carriers, negative hormone receptor status predicted CPM election. Moreover, previous studies without an emphasis on genetic testing results indicated that the risk of developing CBC in hormone receptor-negative breast cancers is 1.6-fold higher than in hormone receptor-positive breast cancers [35]. Given the increased risk, it stands to reason that patients with hormone receptor-negative breast cancer are more likely to elect CPM than those with hormone receptor-positive breast cancer [36]. Additionally, Brewster et al. [37] found that CPM was associated with improved disease-free survival in patients with hormone receptor-negative breast cancer. Although these factors could explain the CPM election rate in the general population, their application to our population is less clear because genetic results were not included in that analysis. Future studies are needed to determine whether the same factors are evident among patients who undergo multigene panel testing. It is important to note that the small sample size in the group of patients who were non-*BRCA* carriers makes it hard to reach a solid conclusion that hormone receptor-negative status is a significant factor for CPM among non-*BRCA* carriers. However, we think the magnitude of the hazard ratio associated with it is not negligible. This finding warrants further validation in future large studies. Additionally, the insignificant association between hormone receptor status and CPM for the *BRCA* carrier's group in this study could be due to the small sample size. This finding also needs to be further explored with a larger sample size.

Finally, age  $\leq 50$  years predicted CPM election for those who had a VUS in our analysis. Age is a well-established

significant predictor of CPM election among *BRCA* carriers [27–30]. Our study provided evidence that age also seems to affect the decision to elect CPM among those with a VUS. However, future studies with a larger sample are needed to confirm these findings further clarify how the VUS population differs from the general population of patients with breast cancer.

The decision-making process for the election of CPM is complex and entails several driving forces, including the possible anxiety of receiving a positive genetic testing result. Studies suggest that CPM election may also be influenced by biopsies, screening costs and fatigue, cosmetic considerations, psychological factors, and perceived emotional advantages of CPM, among others [38, 39]. Also, these patients had to make their decision about CPM on the basis of the treatment planned for their unilateral breast cancer, so their desire to avoid repeated treatment (CBC) could have influenced the decision.

Future prospective studies are needed to determine whether the same psychosocial factors influence the surgical decision making of individuals with hereditary cancer predispositions beyond *BRCA1* and *BRCA2*.

Despite the rapid growth of next-generation sequencing allowing for simultaneous testing of multiple genes linked to cancer risk, the clinical impact of pathogenic variants in genes beyond *BRCA1* and *BRCA2*, especially in terms of CBC risk, is still largely unknown. Therefore, physicians are faced with the dilemma of making surgical recommendations without CBC risk data for genes often included on multigene panel tests marketed for patients with breast cancer. Our study indicates that patients are still opting for CPM as a measure of prevention even though substantive data on the potential need for this surgery is unavailable. It is also important to note that there are potential harms associated with CPM, such as postsurgical complications and concerns with body image, femininity, and sexuality [39]. It is not clear that increased CPM in non-*BRCA* carriers will improve disease-specific or overall survival. While long-term prospective studies are needed to determine whether CPM is the ideal clinical intervention for non-*BRCA* carriers, our data suggest the need for additional provider and patient education on the known and unknown CBC risks to aid in treatment planning.

To the best of our knowledge, our study is the first to uniquely evaluate CPM election rates and predictors of CPM election among patients who are non-*BRCA* carriers and those with a VUS. Our findings suggest that predictors of CPM election may differ among non-*BRCA* carriers and those with a VUS from those who are *BRCA* carriers. Our findings also highlight the similarity in CPM election rates among *BRCA* carriers and non-*BRCA* carriers despite the lack of evidence concerning CBC risk

among those with a non-*BRCA* mutation. This finding suggests that patients with a non-*BRCA* mutation may have similar perception of CBC risk as those with a *BRCA* mutation. The follow-up in this study time was less than a year from the time of genetic testing to date of CPM; it is important to highlight that the rate of CPM may increase with longer follow-up. Future studies are needed to track CPM rate in this cohort for longer follow-up period.

A few limitations of this study are worthy of consideration when interpreting the results. The authors recognize that this is a retrospective review in a cohort of patients who were referred for genetic counseling and testing at a large academic research hospital with genetic services integrated into the patient care team. Therefore, this population likely has a different level of post-test education on their genetic testing results than the average breast cancer patient.

The predictors of CPM and issues of patient education may differ in hospital settings without easy access to genetic counseling. Our findings may need to be replicated in a study with a larger sample size to allow for generalizability; subgroup analyses should be interpreted with caution given the small sample sizes. Moreover, previous research has found an association between preoperative MRI and CPM [40]. However, we did not collect information on the use of preoperative MRI in this cohort which posed another limitation to our findings. Future prospective studies need to address this association among individuals undergoing multigene panel testing. Finally, future prospective studies are needed to evaluate the complex decision-making processes and the potential implication of genetic test results leading to CPM for individuals who undergo multigene panel testing. The present study identified demographic and clinical predictors of CPM in individuals undergoing multigene panel testing, but further research into patient's motivation to undergo CPM is needed.

## Conclusion

The present study reports CPM election rates specifically among patients with breast cancer who underwent multigene panel testing. Our analyses shed the light on the increasing use of CPM among patients who are non-*BRCA* carriers as well those with a VUS. Our study elucidates the differing predictive factors of CPM election among *BRCA* carriers, non-*BRCA* carriers, and those with a VUS. These differing predictors may need to be considered in clinical recommendations for potential preventive surgeries. Our findings reveal the need for providers to be cognizant that non-*BRCA* genes and VUS drive women to elect CPM despite the lack of data for CBC risk associated

with these genes. Factors driving their decision need to be carefully addressed.

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## Conflict of Interest

The manuscript has never been published and is not under consideration for publication elsewhere. The authors have no financial disclosures to declare.

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