Wong A, Leonard S, An K, et al. Utilization of Genetic Testing and Surgical Implications in an Ethnically Diverse Hawaiian Population. *Hawaii J Health Soc Welf*. 2025;84(11):251-260. doi:10.62547/ZFYG5300

Utilization of Genetic Testing and Surgical Implications in an Ethnically Diverse Hawaiian Population

Amelia Wong, DO[1], Saskia Leonard, MD[2], Katlyn An, MS[2], Brendan Seto, MD[2], Jared Su, MD[2], Jessica Kieu, MD[2], Hyeong Jun Ahn, PhD[3], Ashley Marumoto, MD[4]

[1] Surgery, University of Hawai'i John A. Burns School of Medicine, [2] University of Hawai'i, John A. Burns School of Medicine, [3] Quantitative Health Sciences, University of Hawai'i, John A. Burns School of Medicine, [4] Surgery, University of Hawai'i, John A. Burns School of Medicine

Keywords: Breast cancer, genetic testing, Native Hawaiian/Pacific Islander, variants of unknown significance, mastectomy

https://doi.org/10.62547/ZFYG5300

Abstract

Genetic testing is recommended for young women diagnosed with breast cancer. While studies have demonstrated an increased likelihood of variants of unknown significance (VUS) among racial/ethnic minorities compared to non-Hispanic Whites, results in the ethnically diverse population of Hawai'i are largely unknown. Additionally, current consensus guidelines dictate that VUS mutations are not clinically actionable and surgical decision-making is not standardized. This study aims to examine the utilization of genetic testing in Hawai'i and evaluate for any subsequent impacts on surgical practice patterns. A retrospective chart review of women age <45 diagnosed with breast cancer between 2016 and 2020 was performed at a single institution in Honolulu, Hawai'i. Ethnicity, cancer history, detected genes/variants, and surgical intervention were extracted. Of 236 patients identified, 134 (56.7%) were Asian, 57 (24.1%) Native Hawaiian/Pacific Islander (NHPI), and 45 (19.1%) Other. The majority (n=201, 85.2%) underwent genetic testing. A family history of breast cancer was predictive of testing (P<.001). The most common finding was VUS (n= 95, 47.2%) with no statistical difference by ethnicity. Pathogenic mutations were more common in Other (Non-Asian /Non-NHPI) populations (P=.047). All patients with pathogenic mutations underwent bilateral mastectomy (n=16). In contrast, patients with VUS were more likely to undergo partial (n=53, 50.9%) or unilateral mastectomy (n=28, 26.9%) rather than bilateral mastectomy (n=21, 20.2%) regardless of tumor staging (P<.001). This study demonstrated high utilization of genetic testing among young women diagnosed with breast cancer. Pathogenic and non-pathogenic mutations varied according to race. The high prevalence of VUS in this ethnically diverse cohort emphasizes the importance of genetic testing in this population and warrants further research.

Abbreviations

B/LB = benign/likely benign variant
BCT = breast-conserving therapy
MP/HP = moderate penetrance /high penetrance
NCCN = National Comprehensive Cancer Network
NHPI = Native Hawaiian/Pacific Islander
OP = other pathogenic
P/LP = pathogenic/likely pathogenic
QMC = The Queen's Medical Center
VUS = variants of unknown significance

Introduction

Breast cancer is the most prevalent cancer among women in the United States, with an estimated 297 290 new cases and 43 170 fatalities among women projected for 2023.[1] Risk factors for breast cancer include female sex, obesity, sedentary lifestyle, alcohol consumption, hormonal and menstrual history, and personal or family history of breast cancer.[1,2] Approximately 10-30% of breast cancer cases are hereditary, defined as those who inherit mutations in cancer-predisposing genes such as tumor suppressor, DNA mismatch repair, and oncogenes. *BRCA1* and *BRCA2* (BReast CAncer genes 1 and 2) are the most common mutations associated with hereditary breast cancer and confer a 50-80% increased lifetime risk of breast cancer, however, other genes are also emerging.[3] Moderate to low penetrance genes (PALB2, ATM, CHEK2, BRIP1, RAD51C, RAD50) are associated with a 1.5- to 5-fold increased risk of developing breast cancer while high penetrance genes (TP53, PTEN, STKII, CDHI, LKBI) confer up to 5- to 20-fold higher risk.[2,4-7] Generally, the higher the penetrance, the higher the risk for developing breast cancer, and mutations in these genes are known as pathogenic variants.[8]

Patients identified with hereditary breast cancer syndromes benefit from increased surveillance, and potentially risk-reducing medications and/or surgery. The current National Comprehensive Cancer Network (NCCN) guidelines recommend genetic testing for patients 50 years or younger diagnosed with breast cancer.[9] The American Society of Breast Surgeons (ASBRS) expands this recommendation to all patients with a personal history of breast cancer as identification of certain pathogenic variants can greatly impact selection of radiation, systemic therapies, and operative decision making.

In addition to pathogenic variants, results may be classified as variant of uncertain significance (VUS), likely benign, and benign variants.[10] As newer multi-gene sequencing panels are developed, the rates of identifying a VUS have risen with reported rates ranging between 6.7% and 41.7% compared to 1-5% in BRCA 1/2 only panels.[10-22] While it is widely known that germline testing is an essential component of cancer management, racial minorities are under-represented in large genomic sequencing databases.[23,24] Furthermore, multi-gene sequencing panels assessing hereditary cancer risk appear to identify VUS, pathogenic, or likely pathogenic (P/LP) variants more frequently among these Non-White minorities.[25] VUS lack enough data to know whether or not this increases a patient's risk

of developing cancer. As such, current consensus guidelines dictate that the presence of VUS is not clinically actionable.[26] Over time and as more information is gathered, VUS may be re-classified as benign or pathogenic with the majority (91%) of VUS becoming reclassified as benign variants.[27] This has the potential to guide surgical decision making and adjunct therapies. Therefore, increased referral for genetic testing for racial minorities has been advocated.[24]

The incidence of hereditary breast cancer syndromes in Hawai'i, and specifically among Native Hawaiians, is limited to a single retrospective case series performed at the Kapi'olani Medical Center in Honolulu by Carney et al.[28] This study was published over a decade ago. Additionally, no studies have been conducted at the Queen's Medical Center (QMC), which serves as the tertiary referral center for all of the Hawaiian Islands, the US Pacific territories, as well as the independent Pacific Island nations. Furthermore, recent studies have demonstrated higher rates of early breast cancer, diagnosed age <50 particularly in Asian populations.[29,30] This further highlights the need for adequate and comprehensive testing as Asians make up largest ethnic demographic in the state of Hawai'i.[31,32] This study aimed to examine the utilization of genetic testing and evaluate surgical practice patterns after testing in an ethnically diverse Hawai'i cohort.

Methods

Medical records from patients aged 45 and younger diagnosed with breast cancer between January 1, 2016, through December 31, 2020, at QMC in Honolulu, Hawai'i were retrospectively reviewed. Patients identified as male were excluded. A total of 236 patients met this criterion. Patient data was extracted from the QMC Oncology Database Registry and supplemented by clinical records in CareLink (Medtronic, Minnesota, MN) for data fields not provided by the registry. All data were deidentified prior to analysis and thus was exempt from patient consent requirements. This study was approved by the Institutional Review Board of The Queens Medical Center and complies with ethical regulations.

The following data was extracted: age at diagnosis, self-reported ethnicity, personal and family history of cancers, referral and completion of genetic testing, detected genes or variants, gene penetrance, date and type of surgical intervention, final histology, and biomarkers. Of note, detected genes and variant data were initially extracted as VUS, other pathogenic (OP), moderate penetrance (MP), or high penetrance (HP). Those with HP, MP, and OP genes were grouped as pathogenic genes for analysis. High penetrance genes included BRCA1 and BRCA 2. Moderate penetrance genes included ATM and CHEK2. Other penetrance genes included APC, MSH, MUTYH, BLM, and BMPR1A. Those who underwent genetic testing after surgical intervention were excluded from secondary analysis. The primary objective of this study was to determine if genetic testing is being appropriately utilized in Hawai'i. Secondary objectives were to examine the prevalence of genetic variants by ethnicity and type of operation performed. The statistical analysis was conducted by using SAS software, version 9.4 (SAS Institute Inc., Cary, NC). ANOVA, Fischer's Exact, Chi-Squared, or Welch T-tests were used to identify statistical significance set at level $P \leqslant .05$. Logistic regression models were used to predict the likelihood of genetic testing, presence of pathogenic mutation, and surgical intervention.

Results

Of 236 patients identified with breast cancer at age ⩽ 45, 134 (56.7%) were Asian, 57 (24.1%) Native Hawaiian/Pacific Islander (NHPI), and 45 (19.1%) Other (Non-Asian or Non-NHPI). The mean age at diagnosis was 40.4. Over half of the patients had a family history of breast cancer (n=133, 56.3%) or other cancers (n=164, 69.5%). Most patients demonstrated invasive carcinoma on final histology (n=191, 80.9%) with early stage 1A disease (n=74, 31.4%). Of the patients whose biomarker status was identified, the majority were hormone (ER/PR) positive (n=136, 69.0%), 46 (23.4%) were HER2 positive, and 15 (7.6%) had triple-negative disease (TNBC). Overall, partial mastectomy was the most common surgical procedure (n=109, 46.2%) followed by bilateral mastectomy (n=62, 26.3%), unilateral mastectomy (n=49, 20.8%), and no surgery (n=16, 6.7%) (**Table 1**).

The majority underwent genetic testing (n=201, 85.2%). Women with a family history of breast or other cancers were more likely to have genetic testing (both $P<.001$). There was no association between genetic testing and age at diagnosis ($P=.28$), ethnicity ($P=.23$), histology ($P=.080$), or biomarker status ($P=.121$) (**Table 2**).

The most common testing result was VUS (n=95, 47.2%), followed by negative (n=82, 40.8%), then pathogenic mutation (n=24, 11.9%). No statistically significant association was identified between VUS and ethnicity ($P=.667$). VUS were more common in those with a family history of cancer ($P=.031$) but not breast cancer specifically ($P=.150$). Pathogenic mutations were proportionally more common $P=.047$ in Other (n=5, 12.2%) compared to NHPI (n=3, 6.7%) and Asian populations (n=8, 7.0%). Family history of breast cancer was not significant for predicting pathogenic mutations ($P=.058$) and other family history of cancers was non-contributory ($P=.654$). There was no association between gene pathogenicity and final surgical histology (invasive, non-invasive, or other malignancy, $P=.072$) or biomarker status ($P=.213$) (**Table 3**).

All patients with pathogenic mutations underwent bilateral mastectomy (n=16). In contrast, patients with VUS were more likely to undergo partial (n=53, 50.9%) or unilateral mastectomy (n=28, 26.9%) rather than bilateral mastectomy (n=21, 20.2%) (**Figure 1**). The surgical management of patients with negative genetic results and VUS did not differ significantly ($P=.66$).

Discussion

Genetic testing has greatly augmented the detection and management of hereditary breast cancer syndromes; how-

Table 1. Demographics of Women Aged 45 and Younger Diagnosed with Breast Cancer at Queens Medical Center, January 1, 2016-December 31, 2020.

		Number (%)
Overall		236
Age (mean, SD)		40.4 ± 4.4
Ethnicity	*Asian*	134 (56.7%)
	NHPI	57 (24.1%)
	Other	45 (19.1%)
Family History of Breast Cancer		133 (56.3%)
Other Family History of Cancer		164 (69.5%)
Genes	*BRCA1*	5 (2.5%)
	BRCA2	8 (4.0%)
	ATM	2 (1.0%)
	CHEK2	1 (0.5%
	APC	1 (0.5%)
	MSH6	1 (0.5%)
	MUTYH	4 (2.0%)
	BMPR1A	1 (0.5%)
	BLM	1 (0.5%)
	VUS	95 (47.3%)
Histology	*Invasive carcinoma*	191 (80.9%)
	Non-invasive carcinoma	37 (15.7%)
	Other	8 (3.4%)
Biomarkers	*ER/PR+*	136 (69.0%)
	HER2+	46 (23.4%)
	TNBC	15 (7.6%)
Pathologic Stage (AJCC 8th Edition)	*0*	38 (16.1%)
	1A	74 (31.4%)
	1B	22 (9.3%)
	2A	41 (17.4%)
	2B	20 (8.5%)
	3A	12 (5.1%)
	3B	5 (2.1%)
	3C	3 (1.3%)
	4	11 (4.7%)
Surgery	*Bilateral Mastectomy*	62 (26.3%)
	Unilateral Mastectomy	49 (20.8%)
	Partial Mastectomy	109 (46.2%)
	No Surgery	16 (6.8%)

NHPI = Native Hawaiian/Pacific Islander
AJCC = American Joint Committee on Cancer Staging Manual

ever, its utilization in Hawai'i has not been well examined. The incidence of hereditary breast cancer syndromes in Hawai'i is limited to a single retrospective case series by Carney et al published in 2010. This study demonstrated higher utilization of genetic testing than previously reported Carney et al (85% vs 20%). Furthermore, higher utilization was also noted in comparison to nationwide (6-24%) studies of similar timeframe to this study, with most recent data extracted in 2019.[17,18,33] Prior studies have demonstrated that the strongest predictor for referral and completion of genetic testing was any personal or family history of breast cancer.[17-20] This study found that in addition to a personal or family history of breast cancer, family history of other malignancies was also predictive of testing. Further studies evaluating utilization of genetic testing in more resource-restricted community hospitals such as those from neighbor and Polynesian islands are needed.

In 2005, Armstrong et al identified significant racial disparities in breast and ovarian genetic testing between African Americans and Whites even after adjusting for socioeconomic status, perception, and attitudes.[3] Since then, larger and multicenter studies have been published demonstrating no significant difference in rates of testing between racial/ethnic groups.[17-19] This study echoes these recent findings of appropriate use of testing in ethnic minorities, suggesting current practice habits are becoming more equitable in this regard.

Socioeconomic factors also may be a barrier to testing in some populations.[17,19] In Japan, genetic testing for hereditary and ovarian cancer syndromes was not covered by insurance until 2020.[34] Following the revision of public insurance policy, rates of risk reducing surgery and presumably genetic testing increased. While socioeconomic barriers were not examined in this study, this may be an area of

Table 2. Predictors of Genetic Testing in Women Aged 45 and Younger Diagnosed with Breast Cancer at Queens Medical Center, January 1, 2016-December 31, 2020.

		All Patients	Genetic Testing Performed?		
			No No. (%)	Yes No. (%)	*P*-value
Overall		236	35 (14.8%)	201 (85.2%)	
Age		40.4 ± 4.4	41 ± 3.3	40.3 ± 4.5	.28[a]
Ethnicity	*NHPI*	57	12 (20.1%)	45 (78.9%)	.23[c]
	Asian	134	19 (14.2%)	115 (85.8%)	
	Other	45	4 (8.9%)	41 (91.1%)	
Family History of Breast Cancer		133	8 (6.7%)	125 (93.3%)	<.001[b]
Other Family History of Cancer		164	15 (9.1%)	149 (90.9%)	<.001[b]
Histology	*Invasive carcinoma*	191	28 (14.6%)	163 (85.3%)	.080[c]
	Non-invasive carcinoma	37	5 (13.5%)	32 (86.4%)	
	Other	8	2 (25.0%)	6 (75.0%)	
Biomarkers	*ER/PR+*	136	20 (14.7%)	116 (85.3%)	.121[c]
	HER2+	46	9 (19.6%)	37 (80.4%)	
	TNBC	15	0	15 (100%)	

NHPI= Native Hawaiian/Pacific Islander

a,b,c P-values calculated using Fischer's Exact[a], Welch T-test[b], or Chi-Squared[c]. Rates of genetic testing in those with a family history of breast or other cancers compared to those without any history (values not shown)

future research and focus in order to increase testing and risk reducing strategies for at risk populations.

Current databases are primarily derived from individuals of European descent. This deficiency is further augmented by lower awareness and limited access to healthcare in addition to more negative attitudes regarding safety and risk of genetic discrimination amongst racial and ethnic minorities.[20,35] This paucity of racial diversity in hereditary cancer databases translates to higher rates of VUS in non-White populations. Asian populations have nearly double rates of VUS (13-42%) compared to Europeans (6-27%), and similar patterns exist in Hispanic and African Americans as well.[36-38] While the correlation between the incidence of VUS and ethnicity was not statistically significant in this study, the distribution of results is concordant with prior studies which suggest a trend toward higher incidence of VUS in Other (Non-Asian and Non-NHPI) populations.[19,22,25,26,28,39,40]

While BRCA1/2 are the most cited hereditary susceptibility genes for breast cancer, prevalence varies by ethnicity.[41,42] Several genes including TP53, BARD1, PALB2, PTEN, ATM, and CHEK2 have been implicated more frequently in non-European patients and at varying rates depending on race.[41,43-46] A large retrospective study published in 2021 by Yadav et al is the most recent study to explore this discrepancy and identified variants such as BARD1 which conferred higher risks (OR>4) of malignancy in Blacks, Hispanics, and Asians, while ATM conferred an increased risk of cancer in all races except Asians.[41] This study's findings of significantly higher incidence of pathogenic genes in non-Whites (*P*=.047) reaffirms the findings identified by Yadav et al and further highlights the importance of selecting the appropriate genetic testing panels when referring and counseling patients.

Results of genetic testing have the potential to impact operative decision making. A 2021 systematic review by Makhnoon et al demonstrated that BRCA 1/2 patients with P/LP variants were 7.5 times more likely to undergo bilateral mastectomy than those with VUS, while rates of BCT, partial and unilateral mastectomy were not significantly different.[36] This is unsurprising as BRCA L/LP variants confer up to a 60% risk of developing contralateral disease and multiple prospective studies have demonstrated 0-2% incidence of breast cancer after risk-reducing mastectomy within a 3-6 year follow up. Bilateral mastectomy is an appropriate risk reducing strategy.[47-50] In this cohort, bilateral mastectomy was performed for all patients with pathogenic mutations regardless of tumor staging (n=16/16); however, this study's small sample size may bias this finding. No significant surgical trends were found in those with negative or VUS mutations. VUS are clinically unactionable, and the lack of a trend seen in this study is highly reflective of the shared decision making between the patient and provider for each individual case.

Six large randomized control trials have demonstrated similar survival and local recurrence rates with breast-conserving therapy (BCT) compared to mastectomy in early-stage cancers.[51-60] While no randomized controlled trials exist comparing BCT and mastectomy in patients with hereditary breast and ovarian cancer syndromes, several retrospective studies have demonstrated the safety of breast-conserving surgery followed by lifelong high-risk surveillance in patients with high penetrant mutations.[51-53,61-64] A few studies including a systematic review published in 2020 demonstrated similar survival rates with

Table 3. Genetic Testing Results in Women Aged 45 and Younger Diagnosed with Breast Cancer at Queens Medical Center, January 1, 2016-December 31, 2020.

		All Patients	Results of Genetic Testing				
			Pathogenic Mutation No. (%)	*P*-value	VUS No. (%)	*P*-value	Negative No. (%)
Overall		201	24 (11.9%)		95 (47.2%)		82 (40.8%)
Ethnicity	*NHPI*	45	3 (6.7%)	.047[b]	22 (48.9%)	.67[b]	20 (44.4%)
	Asian	115	8 (7.0%)		63 (54.8%)		44 (38.3%)
	Other	41	5 (12.2%)		19 (46.3%)		17 (41.5%)
Family History of Breast Cancer		125	13 (10.4 %)	.058[a]	59 (47.2%)	.150[a]	53 (42.4%)
Other Family History of Cancer		149	13 (8.7%)	.65[a]	83 (55.7%)	.031[a]	53 (35.6%)
Histology	*Invasive carcinoma*	163	11 (10.7%)	.072[b]	82 (50.3%)	.22	70 (42.9%)
	Non-invasive carcinoma	32	4 (12.5%)		20 (62.5%)		8 (25.0%)
	Other	6	1 (16.7%)		1 (16.7%)		4 (66.7%)
Biomarkers[c]	*ER/PR+*	116	14 (12.1%)	.21[b]	49 (42.2%)	.32	53 (45.7%)
	HER2+	37	4 (10.8%)		18 (48.7%)		15 (40.5%)
	TNBC	15	1 (6.7%)		8 (53.3%)		6 (40.0%)

[a,b] P-values calculated using Welch T-testa or Chi-Squared[b].
[c] Biomarker status unavailable for all tested patients

BCT compared to mastectomy, however, results are conflicting regarding ipsilateral recurrence.[63,65] While current practice here in Hawai'i appears to favor bilateral mastectomy, a breast conservation approach may also be considered for patients with pathogenic mutations who are well informed and can commit to lifelong high risk surveillance.

This study was limited by the retrospective nature and acquisition of data from a single center in Hawai'i. Furthermore, the study analysis did not account for the type of testing (Myriad, Invitae, other) nor number of genes tested for each individual. While current NCCN guidelines recommend genetic testing for individuals age less than 50, at the time of this study age 45 and under was recommended. Therefore, this age of testing was utilized for this study. The dataset was also limited in its small sample size of Other (Non-Asian/Non-NHPI) participants (n=45, 19%) which encompassed all White, Black, Hispanic/Latino, and American/ Indian and Alaska Native individuals and were subsequently grouped together as a result. Therefore, the effect of Non-Asian ethnicity on the incidence of pathogenic mutations may be biased and the granularity between White and Non-White individuals is not reflected in this study. Additionally, there was no differentiation between multi and single-race individuals, therefore the true ethnic distribution of this cohort may in fact be more similar to the state census than currently reflected. Nonetheless, this study captures a more diverse ethnic cohort compared to the nationwide average and provides valuable insight into the incidence of VUS on genetic testing.

Conclusions

Genetic testing was appropriately utilized in this ethnically diverse cohort of women with breast cancer. VUS was the most common genetic testing result and appears to be more prevalent in Asian populations. Continued implementation of genetic testing to build upon these findings is imperative to expand our knowledge of hereditary breast and ovarian cancer syndrome in these groups of patients.

Conflicts of Interest and Disclosures

All authors have no conflicts of interest or disclosures to declare.

Submitted: August 27, 2025 PDT. Accepted: September 20, 2025 PDT. Published: November 01, 2025 PDT.

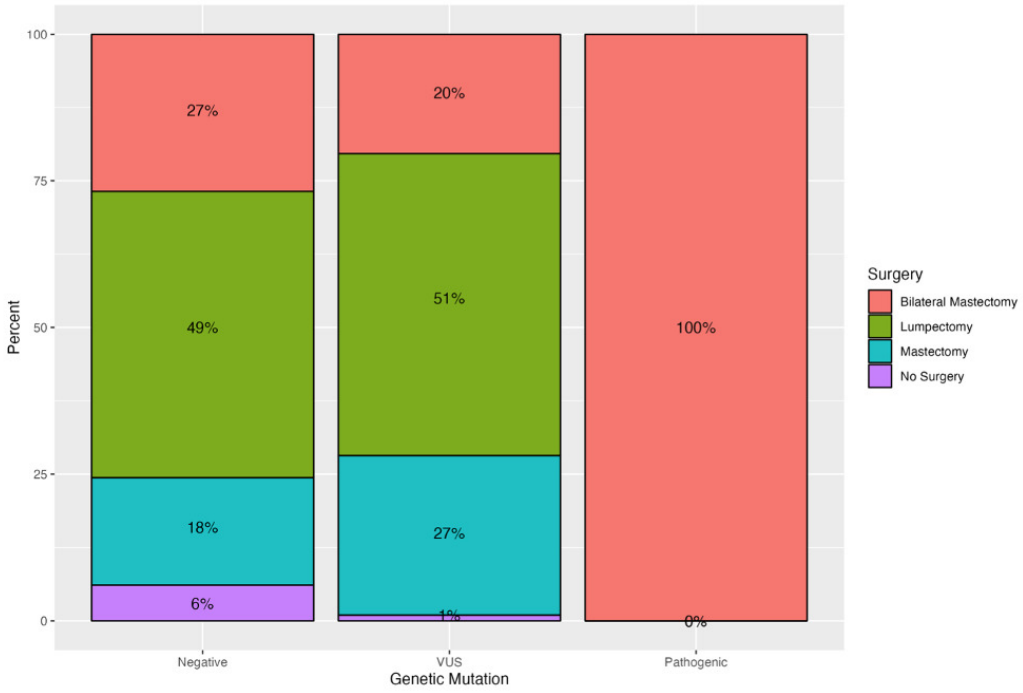

Figure 1. Genetic Testing Results and Subsequent Surgical Intervention in Women Aged 45 and Younger Diagnosed with Breast Cancer at Queens Medical Center, January 1, 2016-December 31, 2020.

VUS = variants of unknown significance

References

1. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. *CA Cancer J Clin*. 2023;73(1):17-48. doi:10.3322/caac.21763

2. Apostolou P, Fostira F. Hereditary breast cancer: the era of new susceptibility genes. *Biomed Res Int*. Published online 2013:747318. doi:10.1155/2013/747318

3. Armstrong K, Micco E, Carney A, Stopfer J, Putt M. Racial differences in the use of BRCA1/2 testing among women with a family history of breast or ovarian cancer. *JAMA*. 2005;293(14):1729-1736. doi:10.1001/jama.293.14.1729

4. Lee A, Moon BI, Kim TH. BRCA1/BRCA2 pathogenic variant breast cancer: Treatment and prevention strategies. *Ann Lab Med*. 2020;40(2):114-121. doi:10.3343/alm.2020.40.2.114

5. Lee ES, Kim J, Han W. Multigene panel testing for hereditary cancer and genetic counseling. *Adv Exp Med Biol*. 2021;1187:455-471. doi:10.1007/978-981-32-9620-6_24

6. Han SA, Kim SW. BRCA and breast cancer-related high-penetrance genes. *Adv Exp Med Biol*. 2021;1187:473-490. doi:10.1007/978-981-32-9620-6_25

7. Berger ER, Golshan M. Surgical management of hereditary breast cancer. *Genes (Basel)*. 2021;12(9). doi:10.3390/genes12091371

8. Napoli M, Lewis J, Hopper J, Widmeyer K. Factors that impact risk management decisions among women with pathogenic variants in moderate penetrance genes associated with hereditary breast cancer. *J Genet Couns*. 2020;29(6):960-970. doi:10.1002/jgc4.1220

9. National comprehensive cancer network guidelines version 1.2022. National Comprehensive Cancer Network.

10. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med*. 2015;17(5):405-424. doi:10.1038/gim.2015.30

11. Adam F, Fluri M, Scherz A, Rabaglio M. Occurrence of variants of unknown clinical significance in genetic testing for hereditary breast and ovarian cancer syndrome and Lynch syndrome: a literature review and analytical observational retrospective cohort study. *BMC Med Genomics*. 2023;16(1):7. doi:10.1186/s12920-023-01437-7

12. Gould D, Walker R, Makari-Judson G, Seven M. Experiences of individuals with a variant of uncertain significance on genetic testing for hereditary cancer risks: a mixed method systematic review. *J Community Genet*. 2022;13(4):371-379. doi:10.1007/s12687-022-00600-4

13. Chen CH, Lu YS, Cheng AL, et al. Disparity in tumor immune microenvironment of breast cancer and prognostic impact: asian versus western populations. *Oncologist*. 2020;25(1):e16-e23. doi:10.1634/theoncologist.2019-0123

14. Davis MB. Breast cancer disparities, how can we leverage genomics to improve outcomes? *Surgical Oncology Clinics of North America*. 2018;27(1):217-234. doi:10.1016/j.soc.2017.07.009

15. Cragun D, Weidner A, Lewis C, et al. Racial disparities in BRCA testing and cancer risk management across a population-based sample of young breast cancer survivors. *Cancer*. 2017;123(13):2497-2505. doi:10.1002/cncr.30621

16. Consensus guideline on genetic testing for hereditary breast cancer. The American Society of Breast Surgeons.

17. Kurian AW, Ward KC, Howlader N, et al. Genetic testing and results in a population-Based cohort of breast cancer patients and ovarian cancer patients. *J Clin Oncol*. 2019;37(15):1305-1315. doi:10.1200/jco.18.01854

18. Childers CP, Childers KK, Maggard-Gibbons M, Macinko J. National estimates of genetic testing in women With a history of breast or ovarian cancer. *J Clin Oncol*. 2017;35(34):3800-3806. doi:10.1200/jco.2017.73.6314

19. Jones T, Trivedi MS, Jiang X, et al. Racial and ethnic differences in BRCA1/2 and multigene panel testing among young breast cancer patients. *J Cancer Educ*. 2021;36(3):463-469. doi:10.1007/s13187-019-01646-8

20. Hann KEJ, Freeman M, Fraser L, et al. Awareness, knowledge, perceptions, and attitudes towards genetic testing for cancer risk among ethnic minority groups: a systematic review. *BMC Public Health*. 2017;17(1):503. doi:10.1186/s12889-017-4375-8

21. United States Census Bureau. United States Quick Facts v2024. United States Census.

22. Lee R, Beattie M, Crawford B, et al. Recruitment, genetic counseling, and BRCA testing for underserved women at a public hospital. *Genet Test*. 2005;9(4):306-312. doi:10.1089/gte.2005.9.306

23. Spratt DE, Chan T, Waldron L, et al. Racial/ethnic disparities in genomic sequencing. *JAMA Oncology*. 2016;2(8):1070-1074. doi:10.1001/jamaoncol.2016.1854

24. Palmer JR, Polley EC, Hu C, et al. Contribution of germline predisposition gene mutations to breast cancer risk in african american women. *J Natl Cancer Inst*. 2020;112(12):1213-1221. doi:10.1093/jnci/djaa040

25. Bishop MR, Omeler-Fenaud SM, Huskey ALW, Merner ND. Gene panel screening for insight towards breast cancer susceptibility in different ethnicities. *PLoS One*. 2020;15(8):e0238295. doi:10.1371/journal.pone.0238295

26. Ndugga-Kabuye MK, Issaka RB. Inequities in multi-gene hereditary cancer testing: lower diagnostic yield and higher VUS rate in individuals who identify as Hispanic, African or Asian and Pacific Islander as compared to European. *Fam Cancer*. 2019;18(4):465-469. doi:10.1007/s10689-019-00144-6

27. Mersch J, Brown N, Pirzadeh-Miller S, et al. Prevalence of variant reclassification Following hereditary cancer cenetic testing. *JAMA*. 2018;320(12):1266-1274. doi:10.1001/jama.2018.13152

28. Carney ME, Basiliere MS, Mates K, Sing CK. Detection of BRCA1 and BRCA2 mutations in a selected Hawaii population. *Hawaii Med J*. 2010;69(11):268-271.

29. Gomez SL, Quach T, Horn-Ross PL, et al. Hidden breast cancer disparities in asian women: disaggregating incidence rates by ethnicity and migrant status. *Am J Public Health*. 2010;100 Suppl 1(Suppl 1):S125-31. doi:10.2105/ajph.2009.163931

30. Gao Y, Heller SL. Health disparity and breast cancer outcomes in asian women. *RadioGraphics*. 2022;42(7):1912-1924. doi:10.1148/rg.220074

31. Hironaka-Mitsuhashi A, Matsuzaki J, Takahashi RU, et al. A tissue microRNA signature that predicts the prognosis of breast cancer in young women. *PLoS One*. 2017;12(11):e0187638. doi:10.1371/journal.pone.0187638

32. Siddig A, Tengku Din T, Mohd Nafi SN, et al. The Unique Biology behind the Early Onset of Breast Cancer. *Genes (Basel)*. 2021;12(3). doi:10.3390/genes12030372

33. Kurian AW, Abrahamse P, Furgal A, et al. Germline genetic testing after cancer diagnosis. *JAMA*. 2023;330(1):43-51. doi:10.1001/jama.2023.9526

34. Hayashi S, Kubo M, Kaneshiro K, et al. Genetic medicine is accelerating in Japan. *Breast Cancer*. 2022;29(4):659-665. doi:10.1007/s12282-022-01342-4

35. Canedo JR, Miller ST, Myers HF, et al. Racial and ethnic differences in knowledge and attitudes about genetic testing in the US: Systematic review. *J Genet Couns*. 2019;28(3):587-601. doi:10.1002/jgc4.1078

36. Makhnoon S, Bednar EM, Krause KJ, et al. Clinical management among individuals with variant of uncertain significance in hereditary cancer: A systematic review and meta-analysis. *Clin Genet*. 2021;100(2):119-131. doi:10.1111/cge.13966

37. Lai KN, Ho WK, Kang IN, et al. Characterization of BRCA1 and BRCA2 variants in multi-ethnic asian cohort from a malaysian case-control study. *BMC Cancer*. 2017;17(1):149. doi:10.1186/s12885-017-3099-6

38. Nanda R, Schumm LP, Cummings S, et al. Genetic testing in an ethnically diverse cohort of high-risk women: a comparative analysis of BRCA1 and BRCA2 mutations in american Families of european and african ancestry. *JAMA*. 2005;294(15):1925-1933. doi:10.1001/jama.294.15.1925

39. Bhaskaran SP, Chandratre K, Gupta H, et al. Germline variation in BRCA1/2 is highly ethnic-specific: evidence from over 30,000 chinese hereditary breast and ovarian cancer patients. *Int J Cancer*. 2019;145(4):962-973. doi:10.1002/ijc.32176

40. Caswell-Jin JL, Gupta T, Hall E, et al. Racial/ethnic differences in multiple-gene sequencing results for hereditary cancer risk. *Genet Med*. 2018;20(2):234-239. doi:10.1038/gim.2017.96

41. Yadav S, LaDuca H, Polley EC, et al. Racial and ethnic differences in multigene hereditary cancer panel test results for women with breast cancer. *J Natl Cancer Inst*. 2021;113(10):1429-1433. doi:10.1093/jnci/djaa167

42. John EM, Miron A, Gong G, et al. Prevalence of pathogenic BRCA1 mutation carriers in 5 US racial/ethnic Groups. *JAMA*. 2007;298(24):2869-2876. doi:10.1001/jama.298.24.2869

43. Li JY, Jing R, Wei H, et al. Germline mutations in 40 cancer susceptibility genes among Chinese patients with high hereditary risk breast cancer. *Int J Cancer*. 2019;144(2):281-289. doi:10.1002/ijc.31601

44. Momozawa Y, Iwasaki Y, Parsons MT, et al. Germline pathogenic variants of 11 breast cancer genes in 7,051 Japanese patients and 11,241 controls. *Nat Commun*. 2018;9(1):4083. doi:10.1038/s41467-018-06581-8

45. Kwong A, Shin VY, Ho JC, et al. Comprehensive spectrum of BRCA1 and BRCA2 deleterious mutations in breast cancer in asian countries. *J Med Genet*. 2016;53(1):15-23. doi:10.1136/jmedgenet-2015-103132

46. Cao W, Wang X, Li JC. Hereditary breast cancer in the han chinese population. *J Epidemiol*. 2013;23(2):75-84. doi:10.2188/jea.je20120043

47. Domchek SM, Friebel TM, Singer CF, et al. Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality. *JAMA*. 2010;304(9):967-975. doi:10.1001/jama.2010.1237

48. Meijers-Heijboer H, van Geel B, van Putten WL, et al. Breast cancer after prophylactic bilateral mastectomy in women with a BRCA1 or BRCA2 mutation. *N Engl J Med*. 2001;345(3):159-164. doi:10.1056/nejm200107193450301

49. Rebbeck TR, Friebel T, Lynch HT, et al. Bilateral prophylactic mastectomy reduces breast cancer risk in BRCA1 and BRCA2 mutation carriers: the PROSE Study Group. *J Clin Oncol*. 2004;22(6):1055-1062. doi:10.1200/jco.2004.04.188

50. Kuchenbaecker KB, Hopper JL, Barnes DR, et al. Risks of breast, ovarian, and contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. *JAMA*. 2017;317(23):2402-2416. doi:10.1001/jama.2017.7112

51. Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med*. 2002;347(16):1233-1241. doi:10.1056/NEJMoa022152

52. Veronesi U, Saccozzi R, Del Vecchio M, et al. Comparing radical mastectomy with quadrantectomy, axillary dissection, and radiotherapy in patients with small cancers of the breast. *N Engl J Med*. 1981;305(1):6-11. doi:10.1056/nejm198107023050102

53. Litière S, Werutsky G, Fentiman IS, et al. Breast conserving therapy versus mastectomy for stage I-II breast cancer: 20 year follow-up of the EORTC 10801 phase 3 randomised trial. *Lancet Oncol*. 2012;13(4):412-419. doi:10.1016/s1470-2045(12)70042-6

54. Sarrazin D, Lê M, Rouëssé J, et al. Conservative treatment versus mastectomy in breast cancer tumors with macroscopic diameter of 20 millimeters or less. The experience of the institut gustave-roussy. *Cancer*. 1984;53(5):1209-1213. https://doi.org/10.1002/1097-0142(19840301)53:5%3C1209::aid-cncr2820530531%3E3.0.co;2-y

55. Veronesi U, Banfi A, Salvadori B, et al. Breast conservation is the treatment of choice in small breast cancer: long-term results of a randomized trial. *Eur J Cancer*. 1990;26(6):668-670. doi:10.1016/0277-5379(90)90113-8

56. Fisher B, Bauer M, Margolese R, et al. Five-year results of a randomized clinical trial comparing total mastectomy and segmental mastectomy with or without radiation in the treatment of breast cancer. *N Engl J Med*. 1985;312(11):665-673. doi:10.1056/nejm198503143121101

57. Fisher B, Redmond C, Poisson R, et al. Eight-year results of a randomized clinical trial comparing total mastectomy and lumpectomy with or without irradiation in the treatment of breast cancer. *N Engl J Med*. 1989;320(13):822-828. doi:10.1056/nejm198903303201302

58. Straus K, Lichter A, Lippman M, et al. Results of the national cancer institute early breast cancer trial. *J Natl Cancer Inst Monogr*. 1992;(11):27-32.

59. van Dongen JA, Bartelink H, Fentiman IS, et al. Randomized clinical trial to assess the value of breast-conserving therapy in stage I and II breast cancer, EORTC 10801 trial. *J Natl Cancer Inst Monogr*. 1992;(11):15-18.

60. Blichert-Toft M, Rose C, Andersen JA, et al. Danish randomized trial comparing breast conservation therapy with mastectomy: six years of life-table analysis. Danish breast cancer cooperative group. *J Natl Cancer Inst Monogr*. 1992;(11):19-25.

61. Huang X, Cai XY, Liu JQ, et al. Breast-conserving therapy is safe both within BRCA1/2 mutation carriers and noncarriers with breast cancer in the Chinese population. *Gland Surg*. 2020;9(3):775-787. doi:10.21037/gs-20-531

62. Emiroglu S, Özkurt E, Cabıoglu N, et al. Is breast conserving surgery efficacious in breast cancer patients with BRCA1 or BRCA2 germline mutation? *Breast Cancer (Dove Med Press)*. 2023;15:163-173. doi:10.2147/bctt.S395054

63. Co M, Liu T, Leung J, et al. Breast conserving surgery for BRCA mutation carriers-a systematic review. *Clin Breast Cancer*. 2020;20(3):e244-e250. doi:10.1016/j.clbc.2019.07.014

64. Braun KL, Fong M, Gotay CC, Chong CD. Ethnic differences in breast cancer in Hawaiʻi: age, stage, hormone receptor status, and survival. *Pac Health Dialog*. 2004;11(2):146-153.

65. Wan Q, Su L, Ouyang T, et al. Comparison of survival after breast-conserving therapy vs mastectomy among patients with or without the BRCA1/2 variant in a large series of unselected chinese patients with breast cancer. *JAMA Netw Open*. 2021;4(4):e216259. doi:10.1001/jamanetworkopen.2021.6259