

Association of Germline Genetic Testing Results With Locoregional and Systemic Therapy in Patients With Breast Cancer

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 Supplemental content

IMPORTANCE The increasing use of germline genetic testing may have unintended consequences on treatment. Little is known about how women with pathogenic variants in cancer susceptibility genes are treated for breast cancer.

OBJECTIVE To determine the association of germline genetic testing results with locoregional and systemic therapy use in women diagnosed with breast cancer.

DESIGN, SETTING, AND PARTICIPANTS For this population-based cohort study, data from women aged 20 years or older who were diagnosed with stages 0 to III breast cancer between 2014 and 2016 were accrued from the Surveillance, Epidemiology and End Results (SEER) registries of Georgia and California. The women underwent genetic testing within 3 months after diagnosis and were reported to the Georgia and California SEER registries by December 1, 2017.

EXPOSURES Pathogenic variant status based on linked results of clinical germline genetic testing by 4 laboratories that did most such testing in the studied regions.

MAIN OUTCOMES AND MEASURES Potential deviation of treatment from practice guidelines was assessed in the following clinical scenarios: (1) surgery: receipt of bilateral mastectomy by women eligible for less extensive unilateral surgery (unilateral breast tumor); (2) radiotherapy: omission in women indicated for postlumpectomy radiotherapy (all lumpectomy recipients except age ≥ 70 with stage I, estrogen and/or progesterone receptor [ER/PR] positive, *ERBB2* [formerly *HER2*]-negative disease); and (3) chemotherapy: receipt by women eligible to consider chemotherapy omission (stages I-II, ER/PR-positive, *ERBB2*-negative, and 21-gene recurrence score of 0-30, which was the upper limit of the intermediate risk range during the study years). The adjusted percentage treated and adjusted odds ratio (OR) are reported based on multivariable modeling for each treatment-eligible group.

RESULTS A total of 20 568 women (17.3%) of 119 198 were eligible (mean [SD] age, 51.4 [12.2]). Compared with women whose test results were negative, those with *BRCA1/2* pathogenic variants were more likely to receive bilateral mastectomy for a unilateral tumor (61.7% vs 24.3%; OR, 5.52, 95% CI, 4.73-6.44), less likely to receive postlumpectomy radiotherapy (50.2% vs 81.5%; OR, 0.22, 95% CI, 0.15-0.32), and more likely to receive chemotherapy for early-stage, ER/PR-positive disease (38.0% vs 30.3%; OR, 1.76 [95% CI, 1.31-2.34]). Similar patterns were seen with pathogenic variants in other breast cancer-associated genes (*ATM*, *CDH1*, *CHEK2*, *NBN*, *NF1*, *PALB2*, *PTEN*, and *TP53*) but not with variants of uncertain significance.

CONCLUSIONS AND RELEVANCE Women with pathogenic variants in *BRCA1/2* and other breast cancer-associated genes were found to have distinct patterns of breast cancer treatment; these may be less concordant with practice guidelines, particularly for radiotherapy and chemotherapy.

JAMA Oncol. doi:10.1001/jamaoncol.2019.6400
Published online February 6, 2020.

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Breast cancer is the first common health condition to incorporate extensive germline testing for disease susceptibility genes.^{1,2} Guidelines are expanding, with debate over whether all breast cancer patients should be tested.^{1,2} The primary reason for testing breast cancer patients is to target prevention strategies for second cancers and for relatives who share an identified pathogenic variant.¹

Integrating genetic testing into breast cancer care has been complex and challenging. There is wide variability in which clinician orders testing and discloses results; in the clinical significance of results; and in how clinicians interpret results to patients.³⁻¹⁰ Little is known about the association between germline testing results and treatment. For surgical procedures, guidelines state that prophylactic bilateral mastectomy should be discussed with carriers of pathogenic variants in *BRCA1* (OMIM 113705) or *BRCA2* (OMIM 600185) (*BRCA1/2*), *PTEN* (OMIM 601728) and *TP53* (OMIM 191170),¹ but there is no evidence for use of bilateral mastectomy for other pathogenic variant carriers. For radiotherapy, guidelines advise that results should not inform decision-making except with *TP53* pathogenic variants.¹ For systemic therapy, poly(adipose phosphatase-ribose) polymerase inhibitors are approved for metastatic disease in *BRCA1/2* pathogenic variant carriers,^{11,12} but guidelines do not advise using results for systemic therapy decision-making in early-stage disease.¹

To investigate the potential consequences of the recent increases in genetic testing, we examined the association of testing results with treatment in patients drawn from a contemporary diverse population sample. We hypothesized that the association of genetic test results with treatment would be consistent with guidelines. Compared with negative results, a pathogenic variant would (1) be associated with more extensive surgical procedure among candidates for unilateral surgery; (2) not be associated with omitting postlumpectomy radiotherapy among those indicated for radiotherapy; and (3) not be associated with chemotherapy receipt among those eligible to consider omitting chemotherapy.

Methods

Creation of Cohort

Details of developing the Georgia and California Surveillance, Epidemiology and End Results (SEER) Genetic Testing Linkage Initiative were published previously.⁷ Briefly, all female patients with breast cancer aged 20 years or older diagnosed between 2014 and 2016 and reported to the Georgia and California Cancer Registries by December 1, 2017, were linked with germline testing data from 4 laboratories (Ambry Genetics, Aliso Viejo, California; GeneDx, Gaithersburg, Maryland; Invitae, San Francisco, California; Myriad Genetics, Salt Lake City, Utah) that did most clinical testing in these regions during those years. The SEER data for the linked cases were obtained in March 2019, providing more than 1 year of treatment follow-up for all patients. Waivers of informed consent and authorization were approved by institutional review boards of the states of California and Georgia given the use of a third-party honest broker to conduct the linkage and create a

Key Points

Question Is the increasing use of germline genetic testing associated with the treatment of women diagnosed with breast cancer?

Findings In this population-based cohort study of 20 568 women who were diagnosed with stages 0 to III breast cancer from 2014 to 2016 and received germline genetic testing, women with pathogenic variants in *BRCA1*, *BRCA2*, and other breast cancer-associated genes were more likely to receive bilateral mastectomy, less likely to receive radiotherapy after lumpectomy, and more likely to receive chemotherapy for early-stage hormone receptor-positive disease.

Meaning Women with germline pathogenic variants in breast cancer susceptibility genes have been found to have different patterns of breast cancer treatment, which may be less concordant with practice guidelines, particularly for radiotherapy and chemotherapy.

deidentified data set for analyses (hence not requiring informed written consent).

Participating laboratories provided gene-specific results as reported to the ordering clinician: pathogenic or likely pathogenic (combined for analysis as pathogenic variant), variant of uncertain significance (VUS), and benign or likely benign (combined for analysis as negative). For this study, we included results of testing *BRCA1/2* and other genes designated as breast cancer-associated by guidelines (*ATM* [OMIM 607585], *CDH1* [OMIM 192090], *CHEK2* [OMIM 604373], *NBN* [OMIM 602667], *NF1* [OMIM 613113], *PALB2* [OMIM 610355], *PTEN*, and *TP53*)¹; *STK11* is also so designated, but no patients had *STK11* pathogenic variants so it could not be included. Patients who had pathogenic variants in other genes were excluded. Genetic results were linked to SEER data; SEER was the source of all other variables except the 21-gene recurrence score (RS), which was obtained through linkage to the testing laboratory (Genomic Health, Redwood City, California) as previously reported.^{13,14} To ensure that patients in the analytic sample had test results available during the first few months after diagnosis when most treatment decisions are made, patients with genetic tests conducted more than 3 months after diagnosis were excluded from analysis. The 3 separate treatment subgroups were nonexclusive; many patients were eligible to receive all 3 treatments and are included in all 3 analyses.

Definition of Treatment-Eligible Subgroups

We assessed potential treatment deviation from guidelines in 3 clinical scenarios: potential overuse of bilateral mastectomy, underuse of radiotherapy, and overuse of chemotherapy. For each treatment, eligibility was defined according to guidelines of the National Comprehensive Cancer Network.¹⁵ For the bilateral mastectomy analysis, we selected patients who were eligible for a less extensive unilateral surgical procedure (had a unilateral tumor of stages 0-III). For the radiotherapy analysis, we selected all patients with tumors of stages 0 to III who were treated with lumpectomy, except those for whom radiotherapy may be omitted (diagnosed at age ≥ 70 years with stage I, estrogen receptor

Table 1. Rates of Treatment Receipt by Germline Genetic Test Results, Unadjusted and Adjusted^a

Genetic Testing Result	% (95% CI)					
	Bilateral Mastectomy (n = 15 126)		Radiation Therapy (n = 7248)		Chemotherapy (n = 8509)	
	Unadjusted	Adjusted ^a	Unadjusted	Adjusted ^a	Unadjusted	Adjusted ^a
Negative	24.0 (23.2-24.8)	24.3 (23.6-25.1)	81.5 (80.5-82.5)	81.5 (80.5-82.5)	29.1 (28.0-30.2)	30.3 (29.4-31.1)
VUS only	24.2 (22.5-25.9)	24.1 (22.5-25.8)	82.6 (80.4-84.7)	82.4 (80.2-84.5)	27.2 (27.2-32.0)	29.5 (27.7-31.4)
Pathogenic variant						
<i>BRCA1/2</i>	66.1 (62.9-69.3)	61.7 (58.4-65.0)	50.9 (41.3-60.5)	50.2 (41.0-59.4)	52.8 (52.8-63.4)	38.0 (34.0-42.1)
Other gene ^b	43.0 (37.7-48.4)	42.5 (37.3-47.7)	75.0 (67.5-82.5)	76.1 (69.0-83.1)	32.2 (32.2-46.0)	33.5 (28.3-38.6)

Abbreviation: VUS, variant of uncertain significance.

^a Adjusted rates are marginal effects from a multivariate logistic model including covariates for age and stage (all models) and additionally histologic grade and 21-gene recurrence score for the chemotherapy model.

^b Other genes analyzed were those designated by practice guidelines of the

National Comprehensive Cancer Network as associated with increased breast cancer risk: *ATM*, *CDH1*, *CHEK2*, *NBN*, *NF1*, *PALB2*, *PTEN*, and *TP53*. *STK11* is also designated as a breast cancer-associated gene by the National Comprehensive Cancer Network, but no patients in the sample had *STK11* pathogenic variants so it was not included in the analysis.

and/or progesterone receptor [ER/PR]-positive and *ERBB2* [formerly *HER2*]-negative breast cancer). For the chemotherapy analysis, we selected women eligible to omit chemotherapy: stages I to II, ER/PR-positive and *ERBB2*-negative breast cancer, with RS less than 31 if that testing was performed. The RS less than 31 was selected because it was the threshold value for the intermediate-risk category from 2014 to 2016, before publication of the TAILORx (Trial Assigning Individualized Options for Treatment) trial in 2018.¹⁶

Statistical Methods

We examined treatment receipt by test results for each results subgroup: negative (no pathogenic variant or VUS in any tested gene), VUS (in any gene, but no pathogenic variant), *BRCA1/2* pathogenic variant (with or without a VUS in any gene), and other breast cancer-associated pathogenic variant defined as *ATM*, *CDH1*, *CHEK2*, *NBN*, *NF1*, *PALB2*, *PTEN*, and *TP53* (with or without a VUS in any gene). We calculated treatment rates, both unadjusted and adjusted for selected clinical covariates that substantively improved model fit or addressed confounding by indication. All interactions between test result groups and clinical variables were evaluated in each model and no meaningful associations were observed. Significance was examined with χ^2 tests in bivariate comparisons and Wald F tests in multivariate models. In both cases, 2-sided tests were used with $\alpha = .05$.

Results

Patient Characteristics

Of the 119 198 women diagnosed with breast cancer in Georgia and California during the study period, 20 568 (17.3%) (mean [SD] age, 51.4 [12.2] years) linked to a genetic test performed within 3 months of diagnosis (eFigure in the Supplement). Among these patients, 15 126 met eligibility criteria for unilateral breast surgery; 7248 for postlumpectomy radiotherapy; and 8509 for consideration of omission of chemotherapy. The eTable in the Supplement shows patient characteristics for all variables included in each subgroup analysis.

Treatments by Genetic Results

Table 1 shows treatment use as proportions and 95% CIs, both unadjusted and adjusted for clinical and demographic factors. Unadjusted bilateral mastectomy analysis showed use rates of 66.1% (95% CI, 62.9%-69.3%) for *BRCA1/2* pathogenic variant carriers, 43.0% (95% CI, 37.7%-48.4%) for carriers of a pathogenic variant in any of the following genes, hereafter defined as other pathogenic variant carriers: *ATM*, *CDH1*, *CHEK2*, *NBN*, *NF1*, *PALB2*, *PTEN*, and *TP53*, 24.2% (95% CI, 22.5%-25.9%) with VUS, and 24.0% (95% CI, 23.2%-24.8%) for patients testing negative; results changed minimally after adjustment. Unadjusted radiotherapy analysis showed use rates of 50.9% (95% CI, 41.3%-60.5%) for *BRCA1/2* pathogenic variant carriers, 75.0% (95% CI, 67.5%-82.5%) for other pathogenic variant carriers, 82.6% (95% CI, 80.4%-84.7%) with VUS, and 81.5% (95% CI, 80.5%-82.5%) among patients testing negative, with minimal change after adjustment. Unadjusted chemotherapy analysis showed use rates of 52.8% (95% CI, 52.8%-63.4%) for *BRCA1/2* pathogenic variant carriers, 32.2% (95% CI, 32.2%-46.0%) for other pathogenic variant carriers, 27.2% (95% CI, 27.2%-32.0%) with VUS, and 29.1% (95% CI, 28.0%-30.2%) for patients testing negative. In contrast to surgery and radiotherapy, chemotherapy results changed substantially after adjustment: 38.0% (95% CI, 34.0%-42.1%) for *BRCA1/2* pathogenic variant carriers, 33.5% (95% CI, 28.3%-38.6%) for other pathogenic variant carriers, 29.5% (95% CI, 27.7%-31.4%) with VUS, and 30.3% (95% CI, 29.4%-31.1%) for patients testing negative. This reflected the strong confounding by indication with clinical factors well known to influence systemic treatment recommendations, such as stage, RS, and histologic grade. Time interval between breast cancer diagnosis and genetic testing was not significant in any model. Table 2 shows the results of the multivariate analyses for each subgroup that were used to calculate the adjusted treatment rates.

Discussion

To our knowledge, this is the first population-based study of cancer treatment according to germline genetic testing results. There were distinct patterns of surgical procedure,

Table 2. Multivariable Model of Treatment Receipt

Variable	OR (95% CI)		
	Bilateral Mastectomy	Radiation Therapy	Chemotherapy
Genetic testing result			
Negative	1 [Reference]	1 [Reference]	1 [Reference]
VUS only	0.99 (0.89-1.1)	1.06 (0.90-1.25)	0.95 (0.81-1.11)
Pathogenic variant			
<i>BRCA1/2</i>	5.52 (4.73-6.44)	0.22 (0.15-0.32)	1.76 (1.31-2.34)
Other gene ^a	2.41 (1.92-3.03)	0.71 (0.47-1.07)	1.27 (0.87-1.86)
Age (OR per 10-y increase)	0.69 (0.67-0.71)	0.95 (0.90-1.00)	0.61 (0.58-0.64)
Stage			
I	1 [Reference]	1 [Reference]	1 [Reference]
0	1.16 (1.03-1.31)	0.32 (0.28-0.38)	NA
II	1.25 (1.15-1.37)	0.81 (0.70-0.94)	7.05 (6.25-7.94)
III	1.85 (1.63-2.09)	0.51 (0.39-0.68)	NA
Grade			
1	NA	NA	1 [Reference]
2	NA	NA	2.34 (2.00-2.73)
3	NA	NA	10.17 (8.47-12.2)
21-Gene recurrence score			
Not tested	NA	NA	1 [Reference]
0-10	NA	NA	0.12 (0.07-0.19)
11-18	NA	NA	0.22 (0.17-0.29)
19-30	NA	NA	2.79 (2.20-3.54)

Abbreviations: NA, not applicable; OR, odds ratio; VUS, variant of uncertain significance.

^a Other genes analyzed were those designated by practice guidelines of the National Comprehensive Cancer Network as associated with increased breast cancer risk: *ATM*, *CDH1*, *CHEK2*, *NBN*, *NFI*, *PALB2*, *PTEN*, and *TP53*. *STK11* is also designated as a breast cancer-associated gene by the National Comprehensive Cancer Network, but no patients in the sample had *STK11* pathogenic variants so it was not included in the analysis.

radiotherapy, and chemotherapy receipt among carriers of pathogenic variants in *BRCA1/2* and other breast cancer-associated genes: notably, greater use of bilateral mastectomy in patients who were eligible for unilateral surgery; lower use of postlumpectomy radiotherapy among those indicated for radiotherapy; and greater use of chemotherapy in patients eligible to consider omitting chemotherapy (early-stage, ER/PR-positive disease). The results suggest that breast cancer treatment of pathogenic variant carriers is less concordant with practice guidelines, particularly for radiotherapy and chemotherapy.

Consistent with prior research, we found an association between testing results and the extensiveness of surgery.¹⁷⁻¹⁹ While no randomized trial to date has evaluated the efficacy of bilateral mastectomy compared with less extensive surgical procedures in *BRCA1/2* pathogenic variant carriers, observational studies and simulation modeling suggest a reduction in contralateral breast cancers and mortality; accordingly, practice guidelines advise discussing the option of bilateral mastectomy with *BRCA1/2*, *PTEN* and *TP53* pathogenic variant carriers.²⁰⁻²³ By contrast, studies of bilateral mastectomy are lacking among carriers of pathogenic variants in genes such as *ATM* and *CHEK2* (sometimes called moderate penetrance genes); accordingly, guidelines state that evidence is insufficient to support advising bilateral mastectomy for such patients.¹ Given the absence of data or guidelines for bilateral mastectomy among carriers of pathogenic variants in moderate penetrance genes, further study of the observed care patterns and their outcomes appears to be warranted.

Patients with a pathogenic variant were substantially less likely to receive radiotherapy after lumpectomy. One explanation

might be that some patients had subsequent mastectomy as an alternative to radiotherapy, which would constitute appropriate locoregional therapy. The SEER policy is to capture all data on the first course of treatment, so if a patient had mastectomy after lumpectomy, it should be documented in the SEER data that we used. However, a mastectomy occurring substantially later (>1 year) might not be captured. Thus, we cannot conclusively state that pathogenic variant carriers failed to receive appropriate locoregional therapy. We speculate, however, that lower postlumpectomy radiotherapy rates in pathogenic variant carriers might reflect concerns about whether radiotherapy is associated with increases in cancer risks or toxic effects in these patients. Case series of sarcomas arising in irradiated tissue of *TP53* pathogenic variant carriers have raised concern, as have reports of radiation sensitivity among patients with ataxia telangiectasia with biallelic *ATM* pathogenic variants.²⁴⁻²⁷ One study suggested an increased risk of contralateral breast cancers among carriers of monoallelic *ATM* pathogenic variants who received radiotherapy in the 1980s and 1990s,²⁸ but a meta-analysis and several recent studies found no increase in radiation-related toxic effects or second cancers.²⁹⁻³¹ Studies have demonstrated the safety of breast-conserving therapy among *BRCA1/2* pathogenic variant carriers, finding no excess toxic effects or risk of new cancers.^{32,33} Although questions remain about the safety of radiation treatment in *TP53* pathogenic variant carriers, *TP53* pathogenic variant carriers constituted only 0.1% of the sample. There is a need to understand the causes of this observed radiotherapy gap, which could have potential implications for breast cancer outcomes.

Women with pathogenic variants were significantly more likely to receive chemotherapy for favorable-prognosis breast

cancer. There is growing consensus that many women with stages I to II, ER/PR-positive, *ERBB2*-negative breast cancer may safely forego chemotherapy.^{14,16,34,35} We adjusted for factors associated with chemotherapy decision-making (age, stage, grade, and RS), and observed a reduction in the odds of chemotherapy receipt among pathogenic variant carriers. The observed reduction in chemotherapy receipt after adjustment suggests that clinicians appropriately consider factors other than genetic testing results in chemotherapy decision-making, as we and others have previously shown.^{14,36,37} Yet even after full adjustment, *BRCA1/2* pathogenic variant carriers (and to a lesser extent other pathogenic variant carriers) remained more likely to receive chemotherapy. While some studies have suggested that *BRCA1/2* pathogenic variant carriers may benefit more than noncarriers from chemotherapy,^{38,39} others have not.⁴⁰⁻⁴² A study of *CHEK2* pathogenic variant carriers found no greater chemotherapy benefit.⁴³ Accordingly, guidelines do not recommend using germline results to inform chemotherapy decision-making in ER/PR-positive, *ERBB2*-negative breast cancer.^{1,15} We do not know what other factors may have influenced chemotherapy decisions, such as patient preference. Studies of the long-term outcomes of chemotherapy in pathogenic variant carriers will be necessary to understand these treatment patterns.

Strengths and Limitations

Strengths of this study include a large diverse population-based sample and detailed information on genetic results obtained directly from testing laboratories. However, this study has limitations. It is difficult to ascertain the exact start date

of treatments using SEER data; therefore, we included only patients who were tested within 3 months of diagnosis, as most treatment decisions are made in this time frame. Additionally, the interval between diagnosis and testing was not statistically significant in multivariable models. However, it is possible that some genetic testing results arrived after treatment decision-making. As noted, it is possible that SEER did not capture some delayed treatments (>1 year after diagnosis). While we previously validated genetic testing linkage against self-report,^{6,44} we may have missed some tests. Patients were selected into clinical testing, and thus may not be representative of all breast cancer patients. The sample size limited assessment of treatment at the gene level for pathogenic variant other than *BRCA1/2*. We have no data on why physicians and patients chose treatments. Finally, we have not yet characterized the association of treatments with survival in pathogenic variant carriers.

Conclusions

Multiplex sequencing for germline cancer susceptibility genes has quickly been adopted in oncology practice, sometimes outpacing the evidence base.⁴⁵⁻⁴⁷ This study reported a distinct treatment pattern in pathogenic variant carriers that appeared less concordant with guidelines, particularly for radiotherapy and chemotherapy. We believe more research is needed to confirm our results and to evaluate long-term outcomes of pathogenic variant carriers to understand treatment decision-making and consequences.

ARTICLE INFORMATION

Accepted for Publication: November 7, 2019.

Published Online: February 6, 2020.
doi:10.1001/jamaoncol.2019.6400

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Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Kurian, Abrahamse, Deapen, Katz.

Critical revision of the manuscript for important intellectual content: Kurian, Ward, Abrahamse, Hamilton, Morrow, Jagsi, Katz.

Statistical analysis: Abrahamse, Katz.

Obtained funding: Kurian, Katz.

Administrative, technical, or material support: Ward, Hamilton, Deapen, Katz.

Supervision: Kurian, Hamilton, Deapen, Katz.

Conflict of Interest Disclosures: Dr Kurian reported receiving grants from Myriad Genetics outside the submitted work. Dr Hamilton reported receiving grants from the University of Michigan and the National Institutes of Health (NIH) during the conduct of the study. Dr Deapen reported receiving grants from the University of Michigan during the conduct of the study. Dr Morrow reported receiving honoraria from Genomic Health and Roche outside the submitted work. Dr Jagsi reported receiving grants from the National Cancer Institute (NCI) of the NIH, grants and honorarium from Greenwall Foundation, grants from Doris Duke Charitable Foundation, grants from Susan G. Komen Foundation, honoraria from Amgen and Vizient, and stock options for serving as an advisor to Equity Quotient outside the submitted work. No other disclosures were reported.

Funding/Support: Research reported in this publication was supported by the NCI/NIH (award No. P01 CA163233 to the University of Michigan and award No. R01 CA225697 to Stanford University). The collection of cancer incidence data in Georgia

was supported by contract HHSN2612018000031, Task Order HHSN26100001 from the NCI and cooperative agreement 5NU58DP006352-03-00 from the Centers for Disease Control and Prevention (CDC). The collection of cancer incidence data used in this study was supported by the California Department of Public Health pursuant to California Health and Safety Code Section 103885; CDC National Program of Cancer Registries, under cooperative agreement 5NU58DP006344; the NCI's Surveillance, Epidemiology and End Results Program under contract HHSN2612018000321 awarded to the University of California, San Francisco, contract HHSN2612018000151 awarded to the University of Southern California, and contract HHSN2612018000091 awarded to the Public Health Institute, Cancer Registry of Greater California.

Role of the Funder/Sponsor: The funders/sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: The ideas and opinions expressed herein are those of the authors and do not necessarily reflect the opinions of the State of California, Department of Public Health, the NCI, and the CDC, or their Contractors and Subcontractors.

Meeting Presentation: Preliminary results of this study were presented at the American Society of Clinical Oncology Annual Meeting; June 1, 2019; Chicago, IL; and at the North American Association of Central Cancer Registries Annual Meeting; June 9, 2019; Vancouver, British Columbia, Canada.

Disclaimer: Dr Morrow is Associate Editor for Reviews and CME for *JAMA Oncology*, but she was not involved in any of the decisions regarding review of the manuscript or its acceptance.

Additional Contributions: We thank Lynne S. Penberthy, MD, and Valentina I. Petkov, MD, at the National Cancer Institute; Nicola Schussler, BS, at Information Management Services; Jill S. Dolinsky, MS, CGC and Melissa Pronold, PhD, at Ambry Genetics; Delores Bowman, PhD, and Benjamin Solomon, MD, at GeneDx; Edward Esplin, MD, PhD, and Stephen Lincoln, PhD, at Invitae; and Johnathan Lancaster, MD, PhD, and Brian Dechairo, PhD, at Myriad Genetics for their collaboration on the genetic test data linkage to Surveillance, Epidemiology and End Results (SEER) data. These individuals received no compensation for this work.

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