



# Time Trends in Receipt of Germline Genetic Testing and Results for Women Diagnosed With Breast Cancer or Ovarian Cancer, 2012-2019

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**PURPOSE** Genetic testing is important for breast and ovarian cancer risk reduction and treatment, yet little is known about its evolving use.

**METHODS** SEER records of women of age  $\geq 20$  years diagnosed with breast or ovarian cancer from 2013 to 2017 in California or Georgia were linked to the results of clinical germline testing through 2019. We measured testing trends, rates of variants of uncertain significance (VUS), and pathogenic variants (PVs).

**RESULTS** One quarter (25.2%) of 187,535 patients with breast cancer and one third (34.3%) of 14,689 patients with ovarian cancer were tested; annually, testing increased by 2%, whereas the number of genes tested increased by 28%. The prevalence of test results by gene category for breast cancer cases in 2017 were *BRCA1/2*, PVs 5.2%, and VUS 0.8%; breast cancer–associated genes or ovarian cancer–associated genes (*ATM*, *BARD1*, *BRIP1*, *CDH1*, *CHEK2*, *EPCAM*, *MLH1*, *MSH2*, *MSH6*, *NBN*, *NF1*, *PALB2*, *PMS2*, *PTEN*, *RAD51C*, *RAD51D*, *STK11*, and *TP53*), PVs 3.7%, and VUS 12.0%; other actionable genes (*APC*, *BMP1A*, *MEN1*, *MUTYH*, *NF2*, *RB1*, *RET*, *SDHAF2*, *SDHB*, *SDHC*, *SDHD*, *SMAD4*, *TSC1*, *TSC2*, and *VHL*) PVs 0.6%, and VUS 0.5%; and other genes, PVs 0.3%, and VUS 2.6%. For ovarian cancer cases in 2017, the prevalence of test results were *BRCA1/2*, PVs 11.0%, and VUS 0.9%; breast or ovarian genes, PVs 4.0%, and VUS 12.6%; other actionable genes, PVs 0.7%, and VUS 0.4%; and other genes, PVs 0.3%, and VUS 0.6%. VUS rates doubled over time (2013 diagnoses: 11.2%; 2017 diagnoses: 26.8%), particularly for racial or ethnic minorities (47.8% Asian and 46.0% Black, v 24.6% non-Hispanic White patients;  $P < .001$ ).

**CONCLUSION** A testing gap persists for patients with ovarian cancer (34.3% tested v nearly all recommended), whereas adding more genes widened a racial or ethnic gap in VUS results. Most PVs were in 20 breast cancer–associated genes or ovarian cancer–associated genes; testing other genes yielded mostly VUS. Quality improvement should focus on testing indicated patients rather than adding more genes.

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## INTRODUCTION

Genetic testing is increasingly valuable for cancer risk assessment, screening, risk reduction, and treatment. Innovation in sequencing technology and declining costs have facilitated the progress of genetic testing into the mainstream of cancer care.<sup>1</sup> Epidemiologic studies are defining cancer risks associated with many genes, and guidelines offer screening and prevention protocols for pathogenic variants (PVs) in more than 40 genes.<sup>2-4</sup> There is growing evidence for using germline results to guide therapy, with poly(ADP-ribose) polymerase (PARP) inhibitors approved to treat breast, pancreatic, prostate, and ovarian cancers in carriers of PVs in *BRCA1* and *BRCA2* (*BRCA1/2*).<sup>5-8</sup>

The expanding role of genetic testing in cancer care motivates research about how testing is deployed in the community and the implications of results for

patients and their families.<sup>9</sup> In particular, there is concern about gaps and disparities in testing and how results influence cancer risk reduction and treatment decisions.<sup>10-14</sup> However, most prior studies have been limited to small, clinic-based samples or predate the modern era of multiple-gene panels (MGPs). The Georgia-California SEER Genetic Testing Linkage Demonstration Project enabled a population-based assessment of genetic testing for cancer risk. In prior work, we reported on patterns and correlates of genetic testing among women diagnosed with breast or ovarian cancer in 2013 and 2014 and found underutilization of testing after diagnosis of ovarian cancer (only 31% tested v nearly 100% recommended) and racial or ethnic differences in receipt of variants of uncertain significance (VUS).<sup>15,16</sup>

In this article, we examine trends in germline testing over 7 years among all women diagnosed with breast

### ASSOCIATED CONTENT

#### Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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## CONTEXT

### Key Objective

To understand how the use and results of germline genetic testing are evolving over time among women diagnosed with breast cancer or ovarian cancer.

### Knowledge Generated

Most pathogenic variant results were found in 20 breast cancer–associated genes and/or ovarian cancer–associated genes.

There is persistent underuse of genetic testing among patients with ovarian cancer, whereas testing more genes per patient is associated with a growing racial or ethnic disparity in uncertain results.

### Relevance

Focused testing of a limited, clinically relevant subset of genes may optimize the yield of genetic testing for women diagnosed with breast cancer or ovarian cancer, particularly among racial or ethnic minorities.

cancer or ovarian cancer in Georgia or California from 2013 to 2017, followed for testing and result interpretation from 2012 to 2019. As interest in genetic risk evaluation has surged, our hypotheses were that (1) MGP would entirely replace testing *BRCA1/2* only, (2) testing underutilization in patients with ovarian cancer would improve, (3) more patients would be tested at lower levels of pretest risk for PVs, (4) sociodemographic differences in testing trends would not be observed, (5) detection of both PVs and VUS would increase, and (6) racial or ethnic disparities in rates of VUS would diminish.

## METHODS

### Study Cohort and Data Set

We linked all female patients with breast cancer or ovarian cancer diagnosed from January 1, 2013, to December 31, 2017, in Georgia and California and reported to one of the four SEER registries that provided statewide coverage (in Georgia, the Georgia Cancer Registry and in California, the Los Angeles Cancer Surveillance Program, the Greater Bay Area Cancer Registry, and the Cancer Registry of Greater California) to germline genetic testing results from four laboratories (Ambry Genetics, Aliso Viejo, CA; GeneDx, Gaithersburg, MD; Invitae, San Francisco, CA; and Myriad Genetics, Salt Lake City, UT) that performed the majority of clinical testing in the regions. We implemented probabilistic methods to maximize ascertainment and accuracy of the linkage. The analytic data set combined laboratory testing data (genetic tests and results from all laboratories) with variables from SEER registries. We obtained the genetic test use and results from reports dated 2012 through the first quarter of 2019. We excluded patients below 20 years old, missing race or ethnicity information, having more than one primary tumor, and diagnosed from death certificate only (Data Supplement, online only). For a patient who was tested more than once (12.7% of tested patients), we kept only the most recent result for each gene. Thus, the final status for each patient included any additional testing or reclassification of a prior finding reported by the laboratory

over 2012-2019. The analytic file containing both registry and laboratory information was stripped of protected health information (as defined by the Health Information Portability and Accountability Act Privacy Rule<sup>17</sup>), and some variables (age, race, marital status, poverty, insurance, histology, and test result) were collapsed to minimize re-identification risk. This study was approved by institutional review boards associated with the SEER registries.

### Test Results From Laboratories

Laboratories provided the results at the gene level, including the interpretation according to American College of Medical Genetics (ACMG) criteria<sup>18</sup> that were sent to the ordering clinician: PV or likely PV (combined for analysis as PV), VUS, and benign or likely benign (combined for analysis as normal). We combined the results from all laboratories to ensure anonymity of laboratories; gene-specific results were retained in the analytic data set only for genes tested by two or more laboratories ( $n = 86$ ). We grouped results for the remaining 252 genes tested by only one laboratory: PVs in these genes were rare (1.4% for ovarian and 0.5% for breast cancer), but VUS were more common (6.4% for ovarian and 5.4% for breast cancer).

### Measures

We categorized a test as MGP if it included other genes in addition to *BRCA1/2*. We grouped PVs according to the level of evidence that supported clinical testing, as follows: *BRCA1/2*; genes designated by National Comprehensive Cancer Network guidelines as associated with breast and/or ovarian cancer (*breast or ovarian genes*: *ATM*, *BARD1*, *BRIP1*, *CDH1*, *CHEK2*, *EPCAM*, *MLH1*, *MSH2*, *MSH6*, *NBN*, *NF1*, *PALB2*, *PMS2*, *PTEN*, *RAD51C*, *RAD51D*, *STK11*, and *TP53*)<sup>2</sup>; genes designated by ACMG guidelines as medically actionable, for which reporting is advised if a PV result is detected incidentally (*other actionable genes*: *APC*, *BMPR1A*, *MEN1*, *MUTYH*, *NF2*, *RB1*, *RET*, *SDHAF2*, *SDHB*, *SDHC*, *SDHD*, *SMAD4*, *TSC1*, *TSC2*, and *VHL*)<sup>19</sup>; and any other tested genes (*other genes*). Patients with VUS in any gene but no PVs were categorized as VUS. Patients with multiple VUS were categorized by the most

clinically significantly affected gene, as follows: *BRCA1/2*, breast or ovarian, other actionable, and other genes. SEER measures included diagnosis age, summary stage, bilateral disease (breast cancer only), triple-negative biologic subtype (breast cancer only), percent poverty at the census level (< 10%, 10%-19%, and  $\geq$  20%), and race or ethnicity (non-Hispanic White, Black, Hispanic, Asian, and Others).

### Analysis Plan

We evaluated clinical and sociodemographic correlates of testing over time for breast cancer and ovarian cancer separately. We tested for differences in trends in receipt of any test and in type of test using logistic regression, with race, age, and geographic site as covariates. Among testers, we described trends in the number of genes tested and used multivariate Poisson models to examine the association between sociodemographic factors and the number of genes tested. We then examined trends in test results (grouped by clinical testing evidence as defined above) among testers and whether these trends differed by race or ethnicity. To display trends in the patterns and results of testing, we used a nonparametric technique of local weighted regression, choosing a smoothing parameter using the Akaike Information Criterion.

## RESULTS

### Study Population

The study cohort included 187,535 patients with breast cancer and 14,689 patients with ovarian cancer, who were diagnosed in Georgia or California in 2013-2017. The Data Supplement shows the flow of patients into the study. California represented 78.1% and 79.6% of the breast and ovarian cancer cases, respectively (Table 1).

### Testing Receipt

Overall, 25.2% of patients with breast cancer and 34.3% of patients with ovarian cancer linked to one or more tests. There were differences in testing rates between states: Georgia linked 31.9% and 42.8% versus California 23.4% and 32.1% for breast and ovarian cancer, respectively ( $P < .001$ ). Among tested patients, 87.3% had one test, 10.7% had two, and 2.0% three or more. Most patients (71.8%) were first tested within 6 months after diagnosis, 24.2% more than 6 months after diagnosis, and 4.0% before diagnosis.

### Trends in Testing Receipt

Figure 1 shows that rates of receiving any genetic test increased little over time. On average, testing rates increased 2% per year. By contrast, there was a marked increase in the number of genes tested: about one quarter of tested patients with breast cancer diagnosed in early 2013 received MGP versus > 80% of those diagnosed in late 2017. Most patients diagnosed in late 2017 who had *BRCA1/2*-only testing were tested before cancer diagnosis. The trend for ovarian cancer was similar: about 40% of

patients diagnosed in early 2013 received MGP versus > 90% diagnosed in late 2017. These findings were similar between states. The Data Supplement shows testing trends by age: older patients were more likely to be tested in later years. In patients of age > 60 years (who accounted for > 50% of both cancer cohorts), testing rates increased from 11.1% in 2013 to 14.9% for breast cancer and 25.3% to 31.4% for ovarian cancer. By contrast, patients of age < 45 years (< 15% of the sample) had lower testing rates over time. We did not observe substantial changes in testing rates by other sociodemographic or clinical variables over time.

The Data Supplement shows trends in the number of genes tested: from 1 to 82 for breast cancer (mean, 19) and 1 to 81 for ovarian cancer (mean, 21). There was a consistent upward trend in gene number for patients with both breast and ovarian cancer, from approximately 10 to 35 genes. The increase in tested gene number for patients with breast cancer was 28.0% (95% CI, 27.5 to 28.8) annually, after adjusting for geographic site, race, and age.

### Trends in Test Results

Figure 2 shows results of trends for patients with breast cancer by clinical categories of genes. In early 2013, 18.3% of testers had a PV or VUS-only result, which increased to 37.2% in late 2017. The proportion of tested patients with breast cancer with PVs in *BRCA1/2* decreased from 7.5% to 5.0% ( $P < .001$ ), whereas PV yield for the two other clinically salient categories (breast or ovarian and other actionable genes) increased: in any breast or ovarian gene from 1.3% to 4.6% and in any other actionable gene from 0.3% to 1.3%. Breast or ovarian genes in which PVs were found included *ATM*, *BARD1*, *BRIP1*, *CDH1*, *CHEK2*, *EPCAM*, *MLH1*, *MSH2*, *MSH6*, *NBN*, *NF1*, *PMS2*, *PALB2*, *PTEN*, *RAD51C*, *RAD51D*, *STK11*, and *TP53*; other actionable genes in which PVs were found were *APC*, *MUTYH*, *RB1*, *RET*, *SDHB*, *SDHC*, *SDHD*, *SMAD4*, and *VHL*. PVs in any of the other 51 genes were generally < 1% per gene (Data Supplement). In contrast to PVs, VUS-only rates increased markedly: from 8.5% in patients diagnosed in early 2013 to 22.4% in patients diagnosed in late 2017.

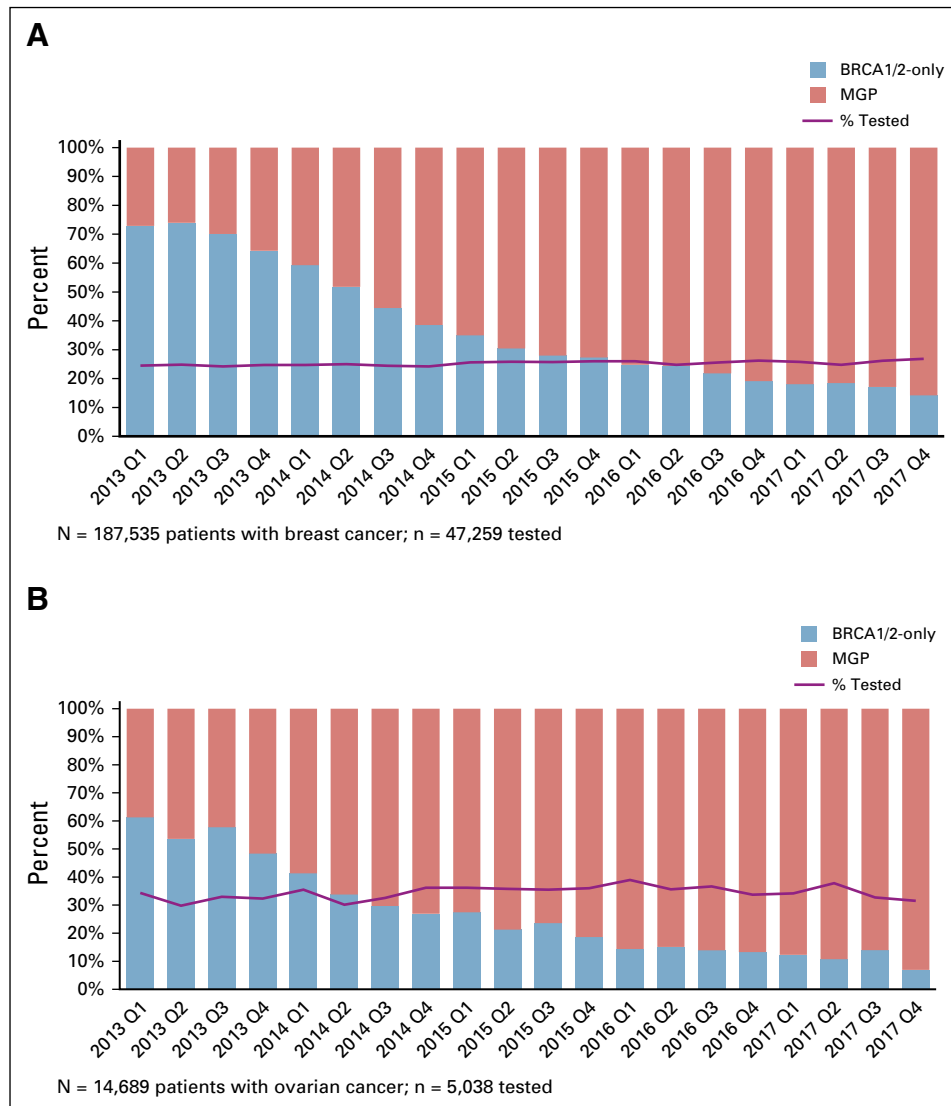
Figure 3 shows results of trends for patients with ovarian cancer by clinical categories of genes. In early 2013, 30.8% of testers had a PV or VUS-only result, which increased to 43.0% in late 2017: this was entirely due to the increase in VUS-only rates. The yield of PVs in *BRCA1/2* decreased from 15.7% to 12.4% ( $P < .001$ ), whereas the PV yield for breast or ovarian genes changed from 3.9% to 4.3% and for other actionable genes from 0.3% to 2.0% (Data Supplement). Breast or ovarian genes in which PVs were found were *ATM*, *BARD1*, *BRIP1*, *CHEK2*, *EPCAM*, *MLH1*, *MSH2*, *MSH6*, *NBN*, *NF1*, *PALB2*, *PMS2*, *PTEN*, *RAD51C*, *RAD51D*, *STK11*, and *TP53*; other actionable genes in which PVs were found were *APC*, *MUTYH*, and *SDHC*. VUS-only rates increased markedly, from 8.1% in patients diagnosed in early 2013 to 28.3% in patients diagnosed in late 2017.

**TABLE 1.** Characteristics of Patients With Breast Cancer and Ovarian Cancer by Genetic Testing Status

Characteristic	Breast Cancer				Ovarian Cancer			
	Patients				Patients			
	Total	Tested	% Tested	95% CI	Total	Tested	% Tested	95% CI
State								
California	146,431	34,189	23.3	23.1 to 23.6	11,694	3,759	32.1	31.3 to 33.0
Georgia	41,104	13,122	31.9	31.5 to 32.4	2,995	1,283	42.8	41.1 to 44.6
Age at diagnosis, years								
20-29	1,004	673	67.0	64.1 to 69.9	368	95	25.8	21.3 to 30.3
30-39	7,655	5,053	66.0	64.9 to 67.1	736	264	35.9	32.4 to 39.3
40-49	29,102	15,842	54.4	53.9 to 55.0	1,809	752	41.6	39.3 to 43.8
50-59	44,931	11,761	26.2	25.8 to 26.6	3,406	1,426	41.9	40.2 to 43.5
60-69	52,721	9,077	17.2	16.9 to 17.5	3,705	1,412	38.1	36.5 to 39.7
70-79	34,606	4,005	11.6	11.2 to 11.9	2,716	832	30.6	28.9 to 32.4
≥ 80	17,516	900	5.1	4.8 to 5.5	1,949	261	13.4	11.9 to 14.9
Race or ethnicity								
Non-Hispanic White	113,906	29,943	26.3	26.0 to 26.5	8,808	3,341	37.9	36.9 to 38.9
Black	22,040	5,512	25.0	24.4 to 25.6	1,347	345	25.6	23.3 to 27.9
Native American	526	136	25.9	22.1 to 29.6	38	12	31.6	16.8 to 46.4
Asian	23,180	5,008	21.6	21.1 to 22.1	1,772	579	32.7	30.5 to 34.9
Hispanic	27,883	6,712	24.1	23.6 to 24.6	2,724	765	28.1	26.4 to 29.8
Poverty level								
Low (poverty < 10%)	84,630	23,206	27.4	27.1 to 27.7	6,062	2,357	38.9	37.7 to 40.1
Medium (10%-19%)	60,861	14,859	24.4	24.1 to 24.8	4,811	1,618	33.6	32.3 to 35.0
High (poverty ≥ 20%)	41,737	9,168	22.0	21.6 to 22.4	3,785	1,056	27.9	26.5 to 29.3
Insurance								
Uninsured	1,448	443	30.6	28.2 to 33	290	80	27.6	22.4 to 32.7
Any Medicaid	10,626	3,319	31.2	30.4 to 32.1	955	255	26.7	23.9 to 29.5
Any other insurance (private, Medicare)	96,453	24,550	25.5	25.2 to 25.7	7,076	2,747	38.8	37.7 to 40.0
Insurance, not otherwise specified	4,509	1,614	35.8	34.4 to 37.2	307	141	45.9	40.4 to 51.5
Stage								
0	33,489	7,138	21.3	20.9 to 21.8	—	—	—	—
I	72,877	17,898	24.6	24.2 to 24.9	2,110	1,065	50.5	48.3 to 52.6
II	51,255	14,842	29.0	28.6 to 29.3	715	486	68.0	64.6 to 71.4
III	16,203	4,820	29.7	29.0 to 30.5	2,761	2,057	74.5	72.9 to 76.1
IV	8,417	1,554	18.5	17.6 to 19.3	3,001	1,260	42.0	40.2 to 43.8
Grade								
1	37,583	7,967	21.2	20.8 to 21.6	779	351	45.1	41.6 to 48.6
2	77,625	18,675	24.1	23.8 to 24.4	755	528	69.9	66.7 to 73.2
3	40,956	18,120	44.2	43.8 to 44.7	2,061	1,503	72.9	71.0 to 74.8
4 (ovarian only)	—	—	—	—	1,617	1,503	92.9	91.7 to 94.2

Figure 4 shows trends in PV and VUS-only rates among testers with breast cancer and with ovarian cancer by race or ethnicity. Among patients with breast cancer, racial or ethnic differences in PV rates were small and did not change over time. However, large differences in VUS-only

rates across race or ethnicity persisted: in 2017, VUS-only rates were substantially higher in Asian (42.4%), Black (36.6%), and Hispanic (27.7%) than non-Hispanic White patients with breast cancer (24.5%,  $P < .001$ ). Among patients with ovarian cancer, PV rates across racial or



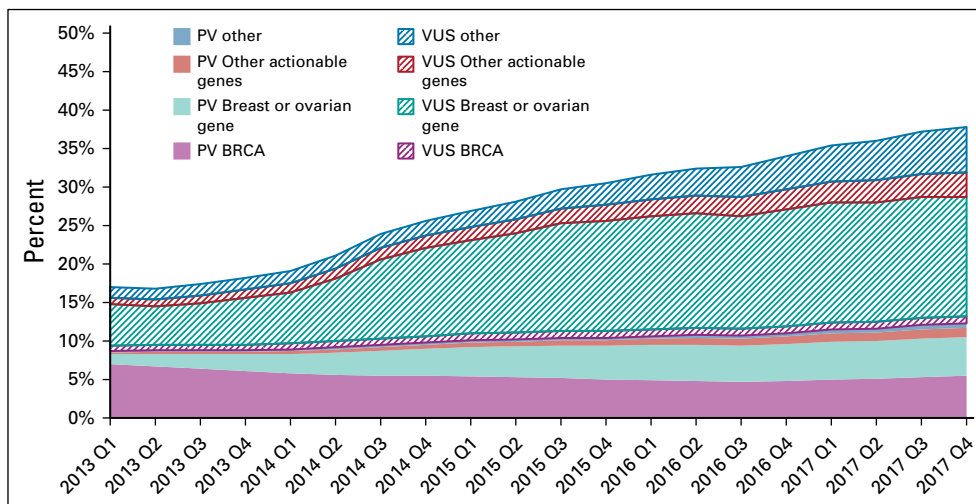
**FIG 1.** (A) Trends in test rates and test type for patients with breast cancer and (B) patients with ovarian cancer. The solid line indicates the proportion of patients who received any genetic test over the observation period by quarter (Q) and year of diagnosis. The bars indicate the percent of testers in each time period who received *BRCA1/2*-only testing (blue) or MGP testing (orange). MGP, multiple-gene panel.

ethnic groups diminished over time. By contrast, large racial or ethnic differences in VUS-only rates persisted throughout the study period: in 2017, VUS-only rates were substantially higher in Asian (47.8%), Black (46.0%), and Hispanic (36.8%) than non-Hispanic White patients with ovarian cancer (24.6%,  $P < .001$ ).

Multivariable logistic regressions were performed separately for tested patients with breast cancer and ovarian cancer, regressing the VUS-only result against date of diagnosis, race or ethnicity, age, stage, and geographic site. In both models, date of diagnosis and race or ethnicity were significant predictors of VUS-only results (all  $P < .001$ ). There was no significant interaction between race or ethnicity and date, confirming no significant change in racial or ethnic differences across the study period (Data Supplement).

## DISCUSSION

We studied receipt of genetic testing and outcomes for nearly 200,000 patients with breast cancer and 15,000 patients with ovarian cancer diagnosed from 2013 to 2017. We examined test trends over time that integrated information from repeat testing and reinterpretation of VUS results in individual patients through 2019. Consistent with our hypotheses, we observed marked expansion in the number of genes sequenced; a modest trend in selection toward patients with lower pretest risk; no sociodemographic differences in testing trends; a small increase in PV rates; and a substantial increase in VUS-only rates. Contrary to our hypotheses, we observed a major, sustained deficit in testing of patients with ovarian cancer (only 34.3% v nearly 100% recommended) and no evidence of

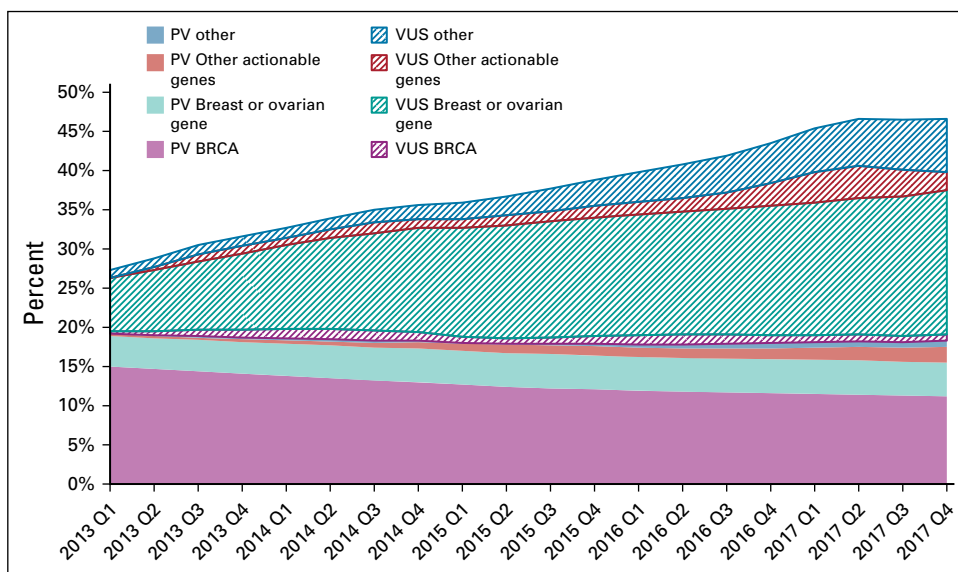


**FIG 2.** Trends by diagnosis year and quarter (Q) in PV and VUS results for patients with breast cancer by gene categories: *BRCA1/2* (n = 2); breast cancer–associated genes or ovarian cancer–associated genes: *ATM, BARD1, BRIP1, CDH1, CHEK2, EPCAM, MLH1, MSH2, MSH6, NBN, NF1, PALB2, PMS2, PTEN, RAD51C, RAD51D, STK11, and TP53* (n = 18); other actionable genes: *APC, BMPR1A, MEN1, MUTYH, NF2, RB1, RET, SDHAF2, SDHB, SDHC, SDHD, SMAD4, TSC1, TSC2, and VHL* (n = 15); and other genes (n = 51). See the Data Supplement for the list of genes. PV, pathogenic variant; VUS, variant of unknown significance.

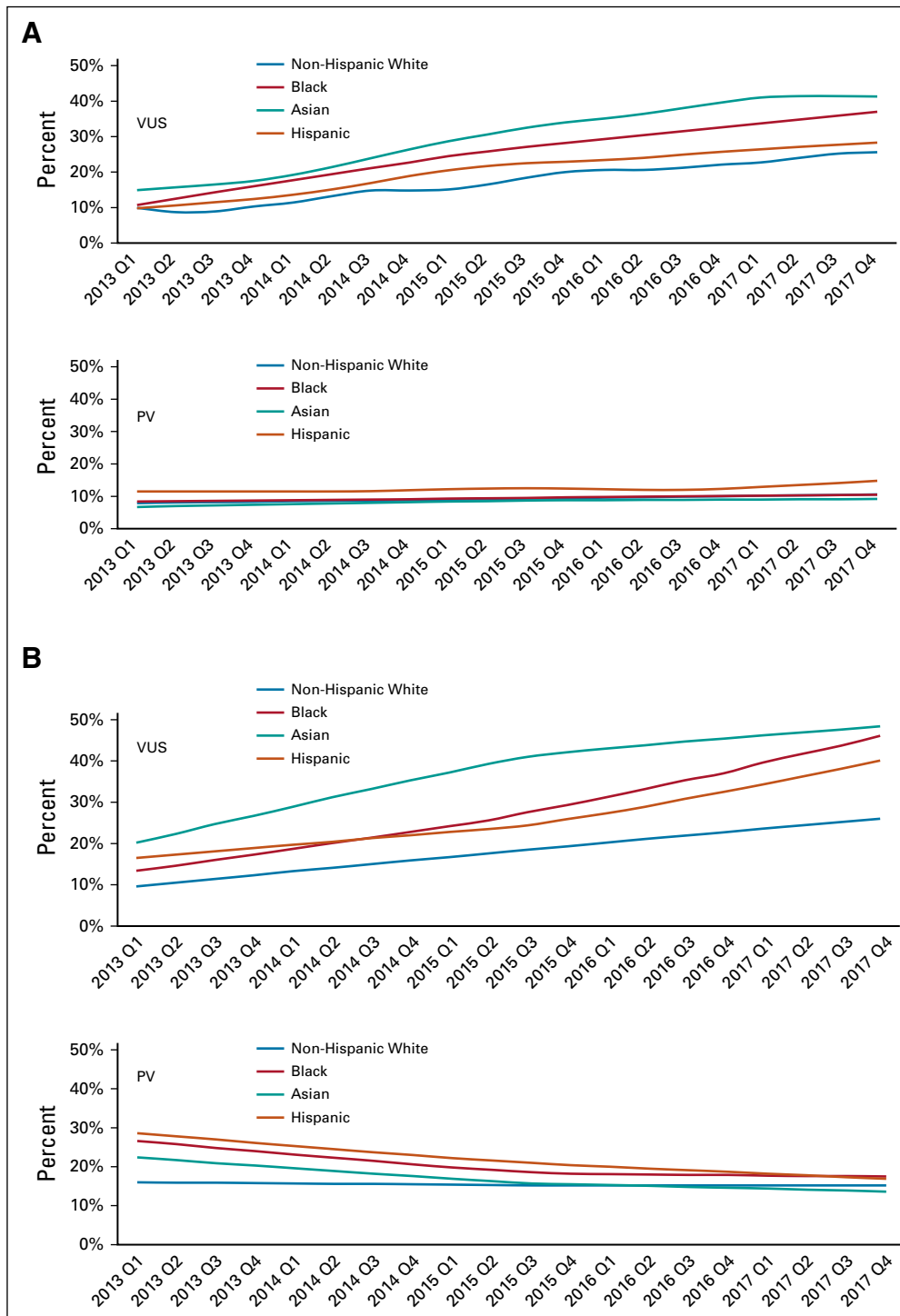
reduction in the racial or ethnic disparity in VUS: these persistent gaps are key targets for intervention.

We found that the trend toward sequencing more genes, which we observed in 2013-2014,<sup>15</sup> progressed to near-total replacement of *BRCA1/2*-only with MGP testing by 2019. The mean number of genes tested per patient increased over time

but did not vary meaningfully by race or ethnicity and other demographic or clinical factors. Receipt of testing increased in older versus younger patients, which suggested a decreasing pretest probability of PV carriage over time among those tested, potentially supported by emerging studies of PV prevalence and clinical utility.<sup>2,7,20-22</sup> Recent studies that found



**FIG 3.** Trends by diagnosis year and quarter (Q) in PV and VUS results for patients with ovarian cancer by gene categories: *BRCA1/2* (n = 2); breast cancer–associated genes or ovarian cancer–associated genes: *ATM, BARD1, BRIP1, CDH1, CHEK2, EPCAM, MLH1, MSH2, MSH6, NBN, NF1, PALB2, PMS2, PTEN, RAD51C, RAD51D, STK11, and TP53* (n = 18); other actionable genes: *APC, BMPR1A, MEN1, MUTYH, NF2, RB1, RET, SDHAF2, SDHB, SDHC, SDHD, SMAD4, TSC1, TSC2, and VHL* (n = 15); and other genes (n = 51). See the Data Supplement for the list of genes. PV, pathogenic variant; VUS, variant of unknown significance only.



**FIG 4.** Trends by diagnosis year and quarter (Q) in the percent of VUS-only and PV results in any gene among testers by selected racial or ethnic groups with (A) breast cancer and (B) ovarian cancer. PV, pathogenic variant; VUS, variant of unknown significance only.

little evidence for patient worry or other psychological harms of testing might have offered reassurance about sequencing more genes in lower-risk patients.<sup>23-25</sup>

Ovarian is the cancer for which genetic testing has been most unequivocally indicated for more than 10 years. The

prevalence of *BRCA1/2* PVs is higher in ovarian than in breast, prostate, pancreatic, or other cancers<sup>26,27</sup>; germline-targeted therapy with a PARP inhibitor was first approved for ovarian cancer<sup>28</sup>; guidelines have advised, and most insurance has covered testing all patients with

high-grade, serous epithelial carcinoma of the ovary, fallopian tube, and/or peritoneum since 2009.<sup>2,29</sup> Despite these very strong indications, we previously identified substantial undertesting of patients with ovarian cancer diagnosed in 2013-2014,<sup>16</sup> but we anticipated that mounting evidence for PARP inhibitors<sup>30-33</sup> and declining test costs would quickly close this gap. Strikingly and concerning, however, follow-up through early 2019 reveals virtually no improvement in testing rates, which remain at only 34.3% of patients with ovarian cancer. We previously identified characteristics associated with less testing, including Black race, greater poverty, and less insurance.<sup>16</sup> There is urgent need to further define the patient, clinician, and healthcare system factors that limit testing of patients with ovarian cancer and to develop interventions that surmount these barriers.

The yield of PVs changed over time. For patients with breast cancer, the proportion of all PVs that were in *BRCA1/2* fell substantially as adoption of MGP testing doubled the probability of detecting a PV in any tested gene. A lower pretest probability of *BRCA1/2* PV carriage might have also contributed. Most of the PV increase was in genes with an established breast or ovarian cancer association as noted by National Comprehensive Cancer Network guidelines<sup>2</sup>; fewer PVs were found in other genes designated by ACMG guidelines as actionable.<sup>19</sup> By contrast, very few tested patients had a PV in other tested genes. Our findings suggest that, based on current understanding of breast and ovarian cancer genetics, testing a panel of 20 breast cancer-associated and/or ovarian cancer-associated genes may optimize the signal-to-noise ratio of PVs to VUS.

We found that the increase in VUS-only results outpaced the increase in PVs, although VUS reclassification has accelerated over time.<sup>34</sup> Notably, these data incorporate VUS reclassification by laboratories through early 2019, so our findings offer a contemporary measure of the uncertainty that accompanies MGP testing. Our findings imply that population-based testing, which would include those with lower pretest PV probability than the clinically selected patients in this study, would exacerbate the proliferation of VUS over PVs.

We and others have previously reported that racial or ethnic minorities are more likely to receive a VUS-only result, much greater with MGP versus *BRCA1/2*-only testing.<sup>15,35-37</sup> This VUS gap arises from the substantially larger volume of clinical genetic testing data from non-Hispanic White patients, such that the spectrum of normal

variation is less well-defined in other racial or ethnic groups and they more often receive VUS results. Our findings now show that the racial or ethnic VUS gap did not close but rather widened over time, with Black and Asian patients having nearly twofold more VUS although they were not tested for more genes than non-Hispanic White patients. Questions remain about the impact of VUS on patients. Although some studies found little evidence of overtreatment because of VUS misinterpretation as PV, another study recently reported unwarranted risk-reducing salpingo-oophorectomy with VUS results.<sup>38,39</sup> Moreover, VUS may exacerbate the challenge of family result communication and cascade genetic testing of relatives. It is essential to accelerate approaches to VUS reclassification, particularly as VUS results are increasing more markedly in racial or ethnic minorities than non-Hispanic White patients.

Aspects of our study warrant comment. Strengths include a very large, diverse, contemporary population-based sample that is relevant to clinically tested patients with breast and ovarian cancer, with testing and result classification updated through early 2019. Limitations include the lack of detailed genetic sequence data, because of privacy concerns, and the lack of patient and physician-reported data about test selection and results management. We previously confirmed by survey of patients from the participating SEER registries and clinicians practicing in these regions that the four participating laboratories performed the great majority of tests in the regions and years under study<sup>15,16</sup>; however, it is possible that some tests from other laboratories were missed. We studied two states only, which may not represent the whole United States.

Our findings suggest that a more delimited panel composition could improve the clinical validity and utility of genetic testing for women with breast cancer or ovarian cancer. Most PVs were found in 20 genes among patients with breast and ovarian cancer (*ATM*, *BARD1*, *BRCA1*, *BRCA2*, *BRIP1*, *CDH1*, *CHEK2*, *EPCAM*, *MLH1*, *MSH2*, *MSH6*, *NBN*, *NF1*, *PMS2*, *PALB2*, *PTEN*, *RAD51C*, *RAD51D*, *STK11*, and *TP53*); testing only these genes could maximize clinically relevant PV yield while minimizing the VUS results, particularly for racial or ethnic minority patients. Since 2012, genetic testing rates have increased annually by 2%, whereas the number of tested genes has increased annually by 28%. Quality improvement efforts should focus on closing the genetic testing gap in indicated patients, notably those with ovarian cancer, rather than adding more genes per test.

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#### **AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

##### **Time Trends in Receipt of Germline Genetic Testing and Results for Women Diagnosed With Breast Cancer or Ovarian Cancer, 2012-2019**

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