

# Genetic Testing and Results in a Population-Based Cohort of Breast Cancer Patients and Ovarian Cancer Patients

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**PURPOSE** Genetic testing for cancer risk has expanded rapidly. We examined clinical genetic testing and results among population-based patients with breast and ovarian cancer.

**METHODS** The study included all women 20 years of age or older diagnosed with breast or ovarian cancer in California and Georgia between 2013 and 2014 and reported to the SEER registries covering the entire state populations. SEER data were linked to results from four laboratories that performed nearly all germline cancer genetic testing. Testing use and results were analyzed at the gene level.

**RESULTS** There were 77,085 patients with breast cancer and 6,001 with ovarian cancer. Nearly one quarter of those with breast cancer (24.1%) and one third of those with ovarian cancer (30.9%) had genetic test results. Among patients with ovarian cancer, testing was lower in blacks (21.6%; 95% CI, 18.1% to 25.4%; v whites, 33.8%; 95% CI, 32.3% to 35.3%) and uninsured patients (20.8%; 95% CI, 15.5% to 26.9%; v insured patients, 35.3%; 95% CI, 33.8% to 36.9%). Prevalent pathogenic variants in patients with breast cancer were *BRCA1* (3.2%), *BRCA2* (3.1%), *CHEK2* (1.6%), *PALB2* (1.0%), *ATM* (0.7%), and *NBN* (0.4%); in patients with ovarian cancer, prevalent pathogenic variants were *BRCA1* (8.7%), *BRCA2* (5.8%), *CHEK2* (1.4%), *BRIP1* (0.9%), *MSH2* (0.8%), and *ATM* (0.6%). Racial/ethnic differences in pathogenic variants included *BRCA1* (ovarian cancer: whites, 7.2%; 95% CI, 5.9% to 8.8%; v Hispanics, 16.1%; 95% CI, 11.8% to 21.2%) and *CHEK2* (breast cancer: whites, 2.3%; 95% CI, 1.8% to 2.8%; v blacks, 0.1%; 95% CI, 0% to 0.8%). When tested for all genes that current guidelines designate as associated with their cancer type, 7.8% of patients with breast cancer and 14.5% of patients with ovarian cancer had pathogenic variants.

**CONCLUSION** Clinically-tested patients with breast and ovarian cancer in two large, diverse states had 8% to 15% prevalence of actionable pathogenic variants. Substantial testing gaps and disparities among patients with ovarian cancer are targets for improvement.

J Clin Oncol 37:1305-1315. © 2019 by American Society of Clinical Oncology

## INTRODUCTION

Germline genetic testing has become an integral part of the care of patients with breast and ovarian cancer and their families since *BRCA1* and *BRCA2* (*BRCA1/2*) were identified in 1994 to 1995.<sup>1,2</sup> Epidemiologic studies have defined the prevalence of *BRCA1/2* pathogenic variants in patient subgroups such as triple-negative breast cancer (TNBC), pancreatic cancer, and prostate cancer,<sup>3-5</sup> and testing guidelines have evolved.<sup>6</sup> Recent advances in next-generation technology and regulatory changes have enabled sequencing of more genes at a lower cost using multiple-gene panels.<sup>7-9</sup>

Studies in clinic-based samples suggest that multiple-gene sequencing panels may double the prevalence of pathogenic variants detected by testing *BRCA1/2* alone.<sup>10-16</sup> However, such studies often used convenience

samples limited to a single institution or laboratory. Almost nothing is known about the prevalence of pathogenic variants on multiple-gene panels among clinically tested, population-based patients with breast cancer and patients with ovarian cancer. Yet, such knowledge is essential to inform population-wide health policy, resource planning, and development of testing guidelines.

We established the Georgia-California Surveillance, Epidemiology and End Results (SEER) Genetic Testing Linkage Initiative with the SEER registries of Georgia and California and the four laboratories that performed nearly all cancer susceptibility testing in these regions during the study period. In this article, we examine testing use and results among all patients with breast cancer (N = 77,085) and all patients with ovarian cancer (N = 6,001) diagnosed in California and Georgia between 2013 and 2014.

## ASSOCIATED CONTENT

Data Supplement

Podcast by Dr Boubberhan

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

Accepted on January 16, 2019 and published at [jco.org](http://jco.org) on April 9, 2019; DOI <https://doi.org/10.1200/JCO.18.01854>

## METHODS

### Creation of Study Cohort and Analytic Data Set

Using a third-party honest broker (Information Management Services, Rockville, MD), all female patients with breast and ovarian cancer diagnosed between 2013 and 2014 from the Georgia Cancer Registry and the California Cancer Registry were linked with germline genetic testing information from four laboratories (Ambry Genetics, Aliso Viejo, CA; GeneDx, Gaithersburg, MD; Invitae, San Francisco, CA; Myriad Genetics, Salt Lake City, UT) that performed the majority of clinical testing. Probabilistic methods were implemented to optimize linkage in the presence of uncertainty or errors in any individual linkage covariable.

The analytic data set combined testing data from all laboratories; all variables other than genetic tests and results were from SEER registries. Second or later breast or ovarian cancers in the same patient were excluded (6.1% for breast cancer; 4.3% for ovarian cancer). Patients diagnosed before 20 years of age, at death, or with unknown race were excluded (Fig 1). Breast tumor biomarker subtype was defined by combinations of hormone receptor (HR) and human epidermal growth factor receptor 2 (HER2) expression. Genetic test use and results were captured through the first quarter of 2016. If a patient was tested more than once, results were merged, keeping the most recent result for each gene. The combined 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 the risk of reidentification. This study was approved by the institutional review boards associated with the SEER registries.

### Testing Variables From Laboratories

Each laboratory provided results at the gene level for 139 genes, including the interpretation, according to American College of Medical Genetics criteria,<sup>18</sup> and sent to the ordering clinician: pathogenic or likely pathogenic (combined for analysis as pathogenic); variant of uncertain significance (VUS); and benign or likely benign (combined for analysis as normal). We categorized a test as a multiple-gene panel if it included other genes in addition to *BRCA1/2*, versus *BRCA1/2* only. To ensure anonymity of laboratories, results from all laboratories were combined, and gene-specific results were retained in the analytic data set only for genes tested by two or more laboratories ( $n = 53$ ). Results for the remaining 86 genes tested by only one laboratory were categorized collectively: pathogenic variants were rare (0% for ovarian cancer and 0.09% for breast cancer), whereas VUSs were more common (3.6% for ovarian and 2.1% for breast cancer).

### Statistical Methods

We examined testing use by patient characteristics among all patients with breast cancer and all patients with ovarian cancer in Georgia and California. Gene-specific results by cancer type for a subset of genes were presented using binomial proportions with exact confidence limits. This subset included 11 genes designated by the current National Comprehensive Cancer Network guidelines as breast cancer susceptibility genes (*ATM*, *BRCA1*, *BRCA2*, *CDH1*, *CHEK2*, *NBN*, *NF1*, *PALB2*, *PTEN*, *STK11*, and *TP53*), one gene designated as potentially associated with breast cancer (*BARD1*), and 11 genes designated as ovarian cancer susceptibility genes (*BRCA1*, *BRCA2*, *BRIP1*, *EPCAM*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, *RAD51C*, *RAD51D*, and *STK11*).<sup>6</sup> Pathogenic variants in these genes should prompt a change in care per guidelines.<sup>6</sup> Results were stratified by biomarker subtype (breast) and race/ethnicity (breast and ovarian). Pathogenic variant and VUS prevalence among patients tested for all 11 guideline-designated genes were examined by cancer type and race/ethnicity and tested for homogeneity by a  $\chi^2$  statistic.

## RESULTS

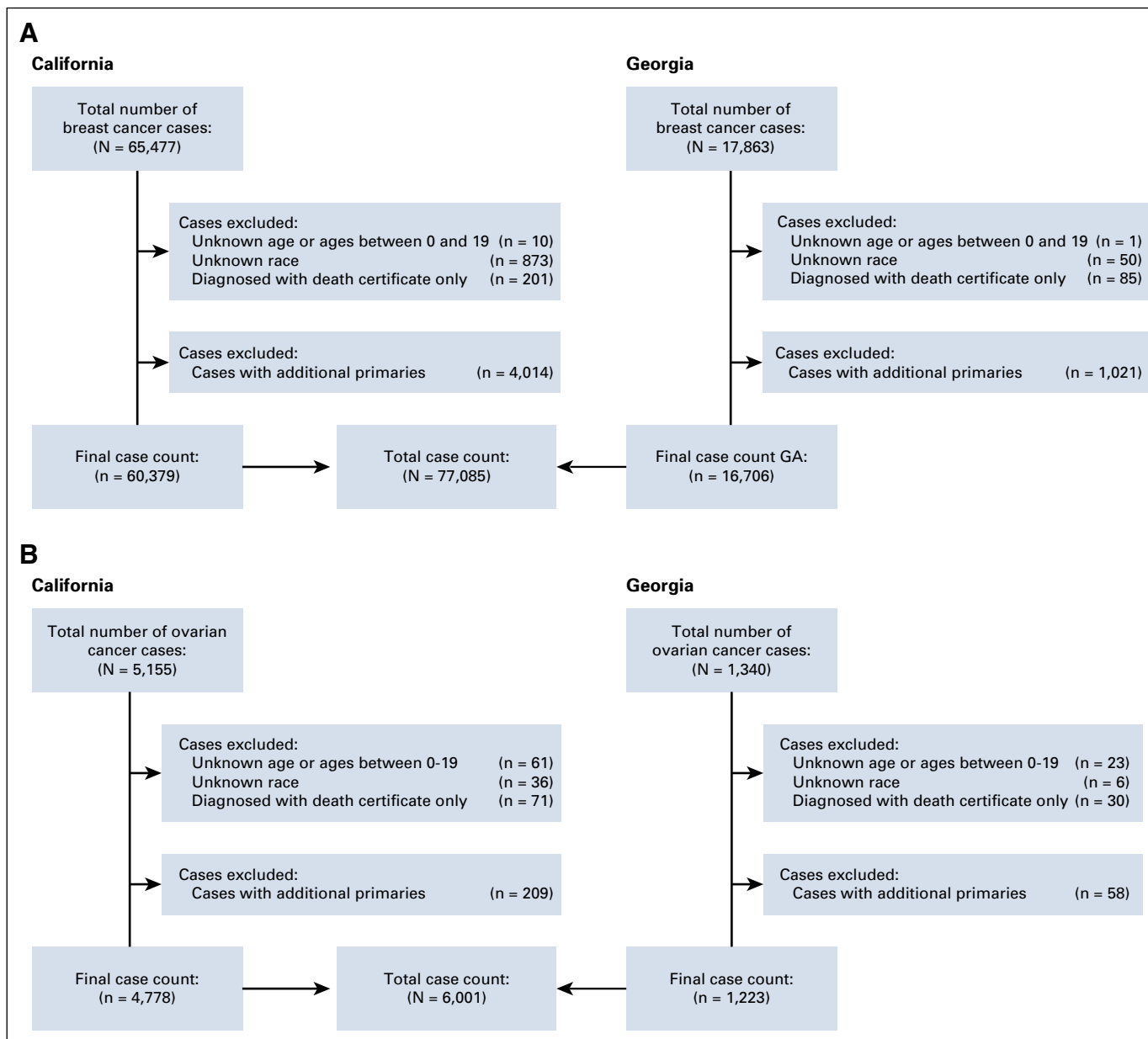
### Patient Characteristics

Figure 1 shows inclusion and exclusion criteria, yielding 77,085 women with breast cancer and 6,001 women with ovarian cancer. Approximately one quarter of patients with breast cancer (24.1%) and one third of patients with ovarian cancer (30.9%) had testing results linked from any laboratory. Testing rates were similar in both states and unchanged over time (Table 1).

### Genetic Testing Rates by Demographic and Clinical Factors

Among patients with breast cancer, testing decreased with increasing age at diagnosis (72.1% among those 20 to 29 years of age; 3.9% among those  $\geq 80$  years of age) and increasing area-based residential poverty at the census tract level (where poverty was less than 10%: 26.8%; 95% CI, 26.4% to 27.3%; where poverty was  $\geq 20$ %: 20.4%; 95% CI, 19.8% to 21.0%; Table 1). Testing did not vary substantially by race/ethnicity; this finding was largely consistent across age and subtypes, with some evidence for disparities in younger patients (Data Supplement). Testing rates were higher among women with the HR-negative, HER2-negative subtype (TNBC: 39.8%; 95% CI, 38.7% to 41.0%) than for the HR-positive, HER2-negative subtype (23.0%, 95% CI, 22.6% to 23.4%) and increased as both stage and grade increased, but decreased for stage IV.

Among patients with ovarian cancer, testing was highest in middle-age groups (39.7% ages 40 to 59; 95% CI, 37.6% to 41.8%; Table 1). Testing decreased with increasing area-based residential poverty (where poverty was less than 10%: 37.8%; 95% CI, 35.9% to 39.7%; where poverty was  $\geq 20$ %: 20.1%; 95% CI, 18.1% to 22.2%).



**FIG 1.** Inclusion and exclusion counts from California and Georgia SEER registries, 2013 to 2014, for (A) breast cancer and (B) ovarian cancer.

Considerable variation in testing existed by race/ethnicity (non-Hispanic white: 33.8%; 95% CI, 32.3% to 35.3%; black: 21.6%; 95% CI, 18.1% to 25.4%; Hispanic: 24.9%; 95% CI, 22.2% to 27.6%), marital status (married: 37.4%; 95% CI, 35.6% to 39.2%; single: 27.0%; 95% CI, 24.7% to 29.5%), and insurance (Medicaid: 20.3%; 95% CI, 17.8% to 22.9%; other insurance: 33.9%; 95% CI, 32.6% to 35.3%). Testing rates increased with both stage and grade, but decreased for stage IV.

### Genetic Testing Results Among Patients With Breast Cancer

The Data Supplement lists 53 genes tested by at least two laboratories, of which 11 are currently guideline-designated

as breast cancer susceptibility genes and 11 as ovarian cancer susceptibility genes.<sup>6</sup> Among patients with breast cancer, three times more were tested for *BRCA1* (18,506) and *BRCA2* (18,522) than any other breast cancer gene (6,842 for *TP53*, fewer for others; Table 2). Pathogenic variants were most frequently detected in *BRCA1* (3.2%) and *BRCA2* (3.1%), followed by *CHEK2* (1.6%), *PALB2* (0.96%), and *ATM* (0.73%; Fig 2A). Pathogenic variants were detected in *BARD1*, *CDH1*, *NBN*, *NF1*, and *TP53*, and ranged from 0.14% to 0.35%. Few patients with breast cancer (n = 1,464; 1.9%) were tested for all 11 genes designated by current guidelines<sup>6</sup> as breast cancer susceptibility genes (Table 3). Among patients tested for all 11 guideline-designated breast cancer genes, 7.8% had a

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

Characteristic	Breast Cancer			Ovarian Cancer		
	Total Patients	Tested Patients*	Proportion Tested, % (95% CI)*	Total Patients	Tested Patients*	Proportion Tested, % (95% CI)*
State and year of cancer diagnosis						
California†						
2013	30,367	7,314	24.1 (23.6 to 24.6)	2,388	707	29.6 (27.8 to 31.5)
2014	30,012	6,951	23.2 (22.7 to 23.6)	2,390	732	30.6 (28.8 to 32.5)
2013-2014	60,379	14,265	23.6 (23.3 to 24.0)	4,778	1,439	30.1 (28.8 to 31.4)
Georgia						
2013	8,296	2,066	24.9 (24.0 to 25.9)	618	206	33.3 (29.6 to 37.2)
2014	8,410	2,270	27.0 (26.0 to 28.0)	605	209	34.5 (30.8 to 38.5)
2013-2014	16,706	4,336	26.0 (25.3 to 26.6)	1,223	415	33.9 (31.3 to 36.7)
Age at cancer diagnosis, years						
20-29	409	295	72.1 (67.5 to 76.4)	147	33	22.5 (16.0 to 30.1)
30-39	3,003	2,236	74.5 (72.9 to 76.0)	279	96	34.4 (28.9 to 40.3)
40-44	5,013	3,360	67.0 (65.7 to 68.3)	303	122	40.3 (34.7 to 46.0)
45-49	7,452	3,567	47.9 (46.7 to 49.0)	470	187	39.8 (34.3 to 44.4)
50-59	18,829	4,517	24.0 (23.5 to 24.6)	1,429	565	39.5 (37.0 to 42.1)
60-69	21,307	3,100	14.5 (14.1 to 15.0)	1,474	495	33.6 (31.2 to 36.1)
70-79	13,765	1,244	9.0 (8.6 to 9.5)	1,101	282	25.6 (23.1 to 28.3)
≥ 80	7,307	282	3.9 (3.4 to 4.3)	798	74	9.3 (7.3 to 11.5)
Race/ethnicity						
Non-Hispanic white	48,063	11,635	24.2 (23.8 to 24.6)	3,701	1,251	33.8 (32.3 to 35.3)
Black	9,039	2,095	23.2 (22.3 to 24.1)	523	113	21.6 (18.1 to 25.4)
American Indian	207	51	24.6 (18.9 to 31.1)	19	5	26.3 (9.1 to 51.2)
Asian	9,061	2,034	22.5 (21.5 to 23.3)	728	229	31.5 (28.1 to 35.0)
Hispanic	10,715	2,786	26.0 (25.2 to 26.8)	1,030	256	24.9 (22.2 to 27.6)
Poverty level 2010 (census tract-level SES)						
High (poverty < 10%)	34,928	9,372	26.8 (26.4 to 27.3)	2,499	944	37.8 (35.9 to 39.7)
Medium (10%-19.9%)	24,941	5,724	22.9 (22.4 to 23.5)	1,970	600	30.5 (28.4 to 32.5)
Low (poverty ≥ 20%)	17,136	3,491	20.4 (19.8 to 21.0)	1,525	307	20.1 (18.1 to 22.2)
Marital status‡						
Single	12,007	3,289	27.4 (26.6 to 28.2)	1,324	358	27.0 (24.7 to 29.5)
Married	42,121	11,878	28.2 (27.8 to 28.6)	2,809	1,051	37.4 (35.6 to 39.2)
Separated	990	244	24.6 (22.0 to 27.4)	78	19	24.4 (15.3 to 35.4)
Divorced	8,393	1,736	20.7 (19.8 to 21.6)	588	175	29.8 (26.1 to 33.6)
Widowed	9,857	834	8.5 (7.9 to 9.0)	929	172	18.5 (16.1 to 21.2)
Insurance‡						
Uninsured	1,074	309	28.8 (26.1 to 31.6)	207	43	20.8 (15.5 to 26.9)
Any Medicaid	10,254	2,193	21.4 (20.6 to 22.2)	976	198	20.3 (17.8 to 22.9)
Insured	54,870	14,136	25.8 (25.4 to 26.1)	3,894	1,376	35.3 (33.8 to 36.9)
Insured/no specifics	9,560	1,751	18.3 (17.5 to 19.1)	793	216	27.2 (24.2 to 30.5)
Molecular subtypes, breast cancer‡§						
HR positive, HER2 negative	42,314	9,740	23.0 (22.6 to 23.4)	—	—	—
Triple negative	6,486	2,584	39.8 (38.7 to 41.0)	—	—	—
HR positive/HER2 positive	6,363	1,902	29.9 (28.8 to 31.0)	—	—	—
HR negative/HER2 positive	2,714	739	27.2 (25.6 to 28.9)	—	—	—

(continued on following page)

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

Characteristic	Breast Cancer			Ovarian Cancer		
	Total Patients	Tested Patients*	Proportion Tested, % (95% CI)*	Total Patients	Tested Patients*	Proportion Tested, % (95% CI)*
Stage (American Joint Committee on Cancer, 7 <sup>th</sup> edition)‡						
0	14,462	2,848	19.7 (19.1 to 20.3)	—	—	—
I	29,956	7,033	23.5 (23.0 to 24.0)	1,335	387	29.0 (26.6 to 31.5)
II	20,638	5,902	28.6 (28.0 to 29.2)	498	176	35.3 (31.1 to 39.7)
III	6,695	1,970	29.4 (28.3 to 30.5)	2,052	817	39.8 (37.7 to 42.0)
IV	3,444	558	16.2 (15.0 to 17.5)	1,688	443	26.2 (24.2 to 28.4)
Grade (Bloom-Richardson for breast cancer)‡						
I	15,366	3,004	19.5 (18.9 to 20.2)	430	118	27.4 (23.3 to 31.9)
II	31,336	7,206	23.0 (22.5 to 23.5)	553	184	33.3 (29.3 to 37.4)
III	24,603	7,350	29.9 (29.3 to 30.5)	1,455	587	40.3 (37.8 to 42.9)
IV	—	—	—	1,231	577	46.9 (44.0 to 49.7)
Histology, breast cancer‡						
Ductal or lobular	70,797	17,515	24.7 (24.4 to 25.1)	—	—	—
Other	6,288	1,086	17.3 (16.3 to 18.2)	—	—	—
Histology, ovarian cancer‡						
Cystic, mucinous, or serous	—	—	—	2,995	1,175	39.2 (37.5 to 41.0)
Adenoma/adenocarcinoma	—	—	—	1,816	546	30.1 (28.0 to 32.2)
Germ cell neoplasms	—	—	—	103	6	5.8 (2.2 to 12.3)
Other	—	—	—	1,087	127	11.7 (9.8 to 13.7)

Abbreviations: HER2, human epidermal growth factor receptor 2; HR, hormone receptor; SES, socioeconomic status.

\*Tested for any of 139 genes for which participating genetic testing laboratories provided results.

‡In California, three SEER registries (Cancer Registry of Greater California, Greater Bay Area Cancer Registry, Los Angeles Cancer Surveillance Program) comprise the California Cancer Registry of the California Department of Public Health.

‡Unknown values not shown.

§Restricted to invasive cancers only.

pathogenic variant, and 17.6% had VUSs in any of these genes (Table 3). Significant variation of both proportions (pathogenic variant and VUS) existed by race/ethnicity.

### Genetic Testing Results Among Patients With Ovarian Cancer

Among tested patients with ovarian cancer, almost twice as many were tested for *BRCA1* (1,844) and *BRCA2* (1,841) as for any other National Comprehensive Cancer Network–designated ovarian cancer gene (1,007 for *MSH2*, fewer for others; Table 2). Pathogenic variants were most prevalent in *BRCA1* (8.7%) and *BRCA2* (5.8%). After *BRCA1/2*, pathogenic variants in ovarian cancer genes were most prevalent in *BRIP1* (0.92%), *MSH2* (0.79%), and *RAD51C* (0.58%). However, pathogenic variants were similarly prevalent among patients with ovarian cancer as among patients with breast cancer in *CHEK2* (1.4%) and *ATM* (0.64%), genes not known to confer elevated ovarian cancer risk (Fig 2B; Table 2). Overall, 13.7% of patients with ovarian cancer were tested for all 11 genes currently guideline-designated as ovarian cancer susceptibility genes (Table 3). Among patients tested for all 11 guideline-designated ovarian cancer genes, 14.5% had a pathogenic variant, and 15.6% had VUSs in any of them.

### Genetic Testing Results by Breast Cancer Subtype

Breast cancer subtype-specific differences in pathogenic variant prevalence were observed in various genes (Data Supplement). Statistically significant examples include *BRCA1* (HR positive, HER2 negative: 2.1%; 95% CI, 1.8% to 2.3%; TNBC: 11.4%; 95% CI, 10.2% to 12.7%) and *CHEK2* (HR positive, HER2 negative: 1.7%; 95% CI, 1.3% to 2.3%; TNBC: 0.25%; 95% CI, 0.03% to 0.90%).

### Genetic Testing Results by Race/Ethnicity

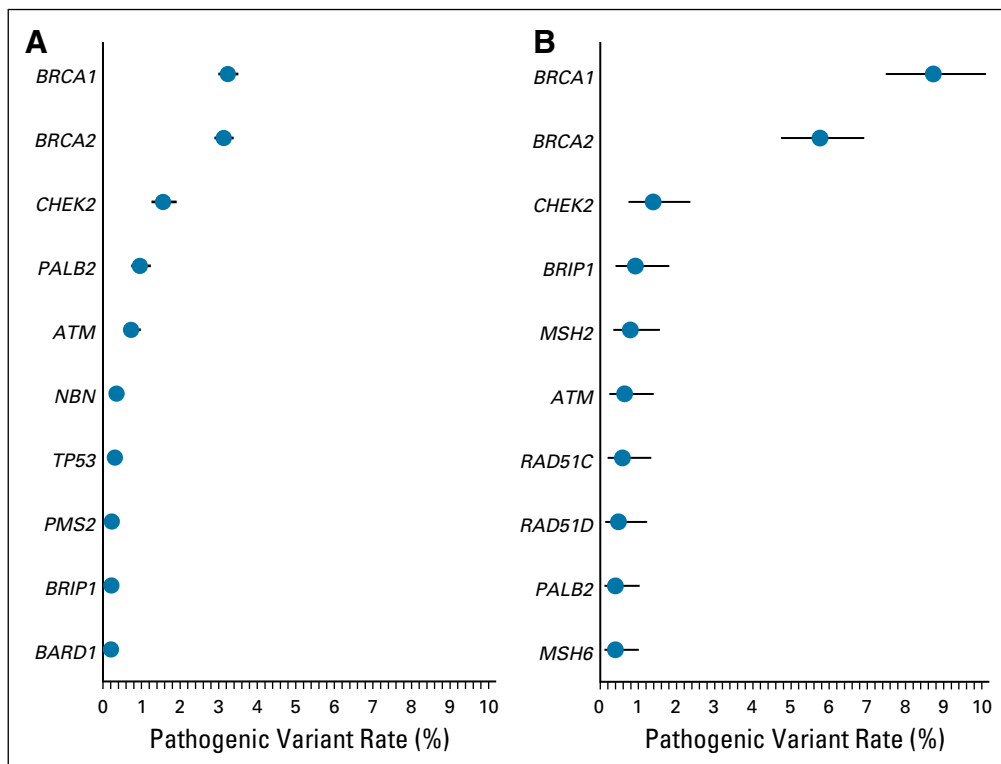
There were racial/ethnic differences in pathogenic variant prevalence in various genes (Data Supplement). Statistically significant examples include *BRCA1* in patients with breast cancer (whites: 2.5%; 95% CI, 2.2% to 2.8%; blacks: 4.0%; 95% CI, 3.2% to 5.0%; Asians: 3.1%; 95% CI, 2.4% to 4.0%; Hispanics: 5.8%; 95% CI, 4.9% to 6.7%) and in patients with ovarian cancer (whites: 7.2%; 95% CI, 5.9% to 8.8%; blacks: 13.4%; 95% CI, 7.7% to 21.1%; Asians: 6.2%; 95% CI, 3.4% to 10.1%; Hispanics: 16.1%; 95% CI, 11.8% to 21.2%), and *CHEK2* in patients with breast cancer (whites: 2.3%; 95% CI, 1.8% to 2.8%; blacks: 0.15%; 95% CI, 0% to 0.82%; Asians: 0.45%; 95% CI, 0.09% to 1.3%; Hispanics: 0.46%; 95% CI 0.13% to 1.2%).

**TABLE 2.** Genetic Test Results Among Tested Patients With Breast and Ovarian Cancer

Patients With Breast Cancer				
Gene	Number of Patients Tested for Gene	% of All Testers Tested for Gene	Pathogenic Variant, % (95% CI)	Variant of Uncertain Significance, % (95% CI)
<i>BRCA2</i> *†	18,522	99.6	3.1 (2.9 to 3.4)	1.9 (1.8 to 2.2)
<i>BRCA1</i> *†	18,506	99.5	3.2 (3.0 to 3.5)	0.76 (0.64 to 0.90)
<i>TP53</i> *	6,842	36.8	0.31 (0.19 to 0.47)	1.1 (0.86 to 1.4)
<i>PTEN</i> *	6,833	36.7	0.06 (0.02 to 0.15)	1.2 (0.92 to 1.5)
<i>PALB2</i> *	6,040	32.5	0.96 (0.73 to 1.2)	2.6 (2.2 to 3.0)
<i>STK11</i> *†	5,926	31.9	0.03 (0.00 to 0.12)	0.73 (0.53 to 0.98)
<i>ATM</i> *	5,901	31.7	0.73 (0.53 to 0.98)	7.4 (6.8 to 8.1)
<i>CHEK2</i> *	5,900	31.7	1.6 (1.3 to 1.9)	3.0 (2.6 to 3.4)
<i>CDH1</i> *	5,681	30.5	0.14 (0.06 to 0.28)	1.8 (1.5 to 2.2)
<i>BRIP1</i>	5,437	29.2	0.22 (0.11 to 0.39)	2.5 (2.1 to 2.9)
<i>NBN</i> *	5,436	29.2	0.35 (0.21 to 0.55)	2.8 (2.4 to 3.3)
<i>RAD51C</i>	5,430	29.2	0.18 (0.09 to 0.34)	1.5 (1.2 to 1.9)
<i>BARD1</i>	5,345	28.7	0.21 (0.10 to 0.37)	2.0 (1.6 to 2.4)
<i>RAD51D</i>	5,067	27.2	0.12 (0.04 to 0.26)	1.3 (1.0 to 1.7)
<i>MLH1</i>	4,883	26.3	0.04 (0.00 to 0.15)	1.2 (0.9 to 1.5)
<i>MSH2</i>	4,883	26.3	0.16 (0.07 to 0.32)	1.7 (1.1 to 2.1)
<i>MSH6</i>	4,883	26.3	0.18 (0.08 to 0.35)	2.3 (1.9 to 2.7)
<i>EPCAM</i>	4,882	26.2	0	0.02 (0.00 to 0.11)
<i>PMS2</i>	4,879	26.2	0.23 (0.11 to 0.40)	2.1 (1.7 to 2.5)
<i>NF1</i> *	2,082	11.2	0.19 (0.05 to 0.49)	1.8 (1.3 to 2.4)
Patients With Ovarian Cancer				
Gene	Number of Patients Tested for Gene	% of All Testers Tested for Gene	Pathogenic Variant, % (95% CI)	Variant of Uncertain Significance, % (95% CI)
<i>BRCA1</i> *†	1,844	99.5	8.7 (7.5 to 10.1)	1.5 (0.97 to 2.1)
<i>BRCA2</i> *†	1,841	99.3	5.8 (4.7 to 6.9)	1.4 (0.92 to 2.1)
<i>TP53</i>	1,011	54.5	0.20 (0.02 to 0.71)	0.69 (0.28 to 1.4)
<i>PTEN</i>	1,008	54.4	0	1.2 (0.62 to 2.1)
<i>MLH1</i> †	1,007	54.3	0.10 (0.00 to 0.55)	1.2 (0.62 to 2.1)
<i>MSH2</i> †	1,007	54.3	0.79 (0.34 to 1.6)	2.0 (1.2 to 3.1)
<i>MSH6</i> †	1,007	54.3	0.40 (0.11 to 1.0)	2.6 (1.7 to 3.8)
<i>EPCAM</i> †	1,006	54.3	0.10 (0.00 to 0.55)	0
<i>PMS2</i> †	1,006	54.3	0.30 (0.06 to 0.87)	1.4 (0.76 to 2.3)
<i>PALB2</i>	995	53.7	0.40 (0.11 to 1.0)	1.7 (1.0 to 2.7)
<i>STK11</i> *†	940	50.7	0	0.64 (0.23 to 1.4)
<i>CHEK2</i>	937	50.5	1.4 (0.74 to 2.4)	3.0 (2.0 to 4.3)
<i>ATM</i>	931	50.2	0.64 (0.2 to 1.4)	6.2 (4.8 to 8.0)
<i>BRIP1</i> †	869	46.9	0.92 (0.40 to 1.8)	2.7 (1.7 to 4.0)
<i>RAD51C</i> †	869	46.9	0.58 (0.19 to 1.3)	2.0 (1.1 to 3.1)
<i>NBN</i>	868	46.8	0.35 (0.07 to 1.0)	2.2 (1.3 to 3.4)
<i>BARD1</i>	858	46.3	0.12 (0.0 to 0.65)	2.2 (1.3 to 3.4)
<i>RAD51D</i> †	827	44.6	0.48 (0.13 to 1.2)	1.7 (0.93 to 2.8)
<i>CDH1</i>	774	41.7	0	1.2 (0.53 to 2.2)
<i>NF1</i>	335	18.1	0	0.90 (0.19 to 2.6)

\*Designated as a breast cancer susceptibility gene by National Comprehensive Cancer Network guidelines.

†Designated as an ovarian cancer susceptibility gene by National Comprehensive Cancer Network guidelines.



**FIG 2.** The 10 most prevalent pathogenic variants from genetic test results of genes related to (A) breast cancer and (B) ovarian cancer. The lines represent the 95% confidence intervals around the point estimates.

## DISCUSSION

To our knowledge, this is the first US study of hereditary cancer genetic testing at the population level with laboratory-confirmed testing results. We took advantage of SEER registries that cover the entire populations of California and Georgia, two regions of racial/ethnic and socioeconomic diversity that together comprise approximately 50 million people. We investigated the clinical use of genetic testing from the four major laboratories that provide it in the regions under study. We found that nearly one quarter of patients with breast cancer and fewer than one third of patients with ovarian cancer diagnosed between 2013 and 2014 had germline genetic testing. Among those tested for all genes designated by current guidelines as associated with their cancer type, 7.8% of patients with breast cancer and 14.5% of patients with ovarian cancer carried a pathogenic variant that warrants a potential change in care, such as secondary breast cancer screening incorporating magnetic resonance imaging, earlier colonoscopy, or risk-reducing surgery.<sup>6</sup>

Few population-level studies have evaluated trends, patterns, and correlates of genetic testing, and most focused on *BRCA1/2* testing only.<sup>19,20</sup> We previously published articles from a survey, the iCanCare study, of more than 5,000 patients diagnosed with breast cancer in 2013 to 2015 from Georgia and Los Angeles County.<sup>9,21-24</sup> However, that sample of testers was far too small to evaluate correlates of variants in specific genes. Furthermore, that previous study did not include patients with ovarian cancer.

In this study, our expanded population-level focus on more than 83,000 patients with breast cancer or ovarian cancer offers granular detail on testing gaps, disparities, and gene-specific results at a major inflection point in the implementation of precision oncology.

The context of cancer genetic testing changed in mid-2013, after a US Supreme Court decision on gene patenting, decreasing costs, and growing public awareness.<sup>25-28</sup> A study of medically underserved patients with breast and ovarian cancer who met criteria for Medicare coverage of *BRCA1/2* testing from 2002 to 2014 reported a testing rate of 9%.<sup>29</sup> Our study evaluated testing from 2012 to 2016 for all California and Georgia patients with breast and ovarian cancer diagnosed in 2013 to 2014. The observed testing rate of 24% among unselected patients with breast cancer demonstrates the broad penetration of testing into community practice. We found little regional variation, suggesting that these results are broadly generalizable. We also found little racial/ethnic variability in testing of patients with breast cancer, although there was an access gradient by poverty level. Higher testing rates among patients with TNBC reflect guideline recommendations to test nearly all such patients, whereas more restrictive criteria on the basis of family history are advised for other subtypes.<sup>6,30,31</sup> Although testing rates were higher among younger women, rates lower than 100% for women diagnosed with breast cancer younger than 45 years of age are suboptimal.

A 30% genetic testing rate for patients with ovarian cancer is inadequate, because guidelines have recommended

**TABLE 3.** Prevalence of Pathogenic Variants and VUSs in Guideline-Designated Genes by Cancer Type and Race/Ethnicity

Cancer Type and Race/Ethnicity	Patient Sample, No.	Tested for All 11 Guideline-Designated Genes for Cancer Type, No. (%)*	Pathogenic Variant in Any of 11 Guideline-Designated Genes for Cancer Type, No. (%)*†	VUS in any of 11 Guideline-Designated Genes for Cancer Type, No. (%)*†
Breast cancer				
All patients	77,085	1,464 (1.9)	114 (7.8)	258 (17.6)
NH whites	48,063	1,036 (2.2)	73 (7.0)	150 (14.5)
Blacks	9,039	137 (1.5)	8 (5.8)	39 (28.5)
American Indians	207	3 (1.4)	0 (0.0)	1 (33.3)
Asians	9,061	169 (1.9)	17 (10.1)	45 (26.6)
Hispanics	10,715	119 (1.1)	16 (13.4)	23 (19.3)
Ovarian cancer				
All patients	6,001	821 (13.7)	119 (14.5)	128 (15.6)
NH whites	3,701	555 (15.0)	68 (12.3)	76 (13.7)
Blacks	523	53 (10.1)	7 (13.2)	10 (18.9)
American Indians	19	3 (15.8)	1 (33.3)	0 (0.0)
Asians	728	105 (14.4)	14 (13.3)	30 (28.6)
Hispanics	1,030	105 (10.2)	29 (27.6)	12 (11.4)

Abbreviations: NH, non-Hispanic; VUS, variant of uncertain significance.

\*National Comprehensive Cancer Network guidelines-designated breast and/or ovarian cancer susceptibility genes include the following: breast cancer: *ATM*, *BRCA1*, *BRCA2*, *CDH1*, *CHEK2*, *NBN*, *NF1*, *PALB2*, *PTEN*, *STK11*, and *TP53*; ovarian cancer: *BRCA1*, *BRCA2*, *BRIP1*, *EPCAM*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, *RAD51C*, *RAD51D*, and *STK11*.

†Significant variation existed in pathogenic variant ( $\chi^2 P < .05$  for breast;  $P < .001$  for ovary) and VUS prevalence by race/ethnicity ( $\chi^2 P < .001$  for both). American Indians were excluded from the assessment because of small sample size.

testing all patients with high-grade, serous ovarian cancer for a decade.<sup>6,32,33</sup> We could not isolate high-grade serous cancers within this data set, but 39.2% testing among patients with tumors in the combined categories of cystic, mucinous, and serous suggests a major shortfall. Furthermore, large differences in testing rates across stage and grade subgroups suggest inappropriate targeting of testing that is indicated for all. Low testing rates among patients with earlier-stage ovarian cancer, who may survive this diagnosis, reflect a missed opportunity to provide risk-adapted screening for second cancers, such as breast, colon, and melanoma associated with pathogenic variants in specific ovarian cancer susceptibility genes. Substantial undertesting of patients with ovarian cancer may reflect their high morbidity and/or a relatively low public awareness of and advocacy for ovarian cancer. We report on a period just before US Food and Drug Administration approval of the first *BRCA1/2*-targeted therapy for ovarian cancer, the poly (ADP-ribose) polymerase inhibitor olaparib, in December 2014.<sup>34</sup> With three poly (ADP-ribose) polymerase inhibitors now approved for *BRCA1/2*-associated ovarian cancer,<sup>34-36</sup> two for *BRCA1/2*-associated metastatic breast cancer,<sup>37,38</sup> and other targeted agents in development,<sup>39</sup> appropriate testing of patients with metastatic breast and/or ovarian cancer is increasingly critical both for them and to inform their at-risk relatives. Finally, the large socioeconomic disparities in test receipt after ovarian

cancer diagnosis highlight the challenges of ensuring universal testing access.

Among patients tested for all genes that current guidelines designate for their cancer type, 7.8% of patients with breast cancer and 14.5% of patients with ovarian cancer carried at least one pathogenic variant that warrants a potential change in care.<sup>6</sup> These results do not constitute a true population prevalence among all patients with breast and ovarian cancer: patients were undoubtedly selected for testing according to clinician knowledge, patient preferences, and access factors.<sup>8,23,24,28,40,41</sup> Instead, these prevalence estimates apply to the average patient with breast or ovarian cancer who undergoes testing as implemented in community practice; thus, they are highly relevant for genetic counseling. Notably, only a small minority of 2013 to 2014 patients were tested for all genes designated by current guidelines as associated with their cancer type, reflecting the fact that testing and guidelines have rapidly evolved. Moreover, guidelines do not definitively endorse multiple-gene testing for all patients for whom *BRCA1/2* testing is advised. We previously reported rapid replacement of *BRCA1/2*-only with multiple-gene panel testing in a subsample of patients,<sup>9</sup> concurrent with the falling costs of sequencing. Thus, our prevalence estimates for non-*BRCA1/2* genes have a smaller denominator of tested patients than we would expect today. As the population of tested patients changes over time



(eg, if patients with less family history of breast and/or ovarian cancers are increasingly tested for more genes), prevalence estimates for both higher-risk genes (eg, *PALB2*) and lower-risk genes (eg, *ATM*) may shift.

Testing guidelines were developed to identify carriers of *BRCA1/2* pathogenic variants.<sup>6</sup> As data emerge about the clinical presentation of other pathogenic variants, guidelines should evolve. For example, although current guidelines state that *BARD1* pathogenic variants (found here in 0.2% of patients with breast cancer) have insufficient evidence to guide management,<sup>6</sup> recent results showing a four- to five-fold associated increase in TNBC risk may inform future guidelines.<sup>3</sup> Among patients with breast cancer, pathogenic variants in *ATM*, *CHEK2*, and *PALB2* were relatively common, with prevalence approximately 1% each; these results resemble those of prior studies.<sup>11,12,15,16,30</sup> However, we observed similar frequencies of *ATM*, *CHEK2*, and *PALB2* pathogenic variants among patients with ovarian cancer, although most studies have not reported an ovarian cancer risk association with these genes.<sup>16,42,43</sup> The prevalence of *ATM*, *CHEK2*, and *PALB2* pathogenic variants among patients with ovarian cancer may merely reflect their relatively high population carrier frequency, but additional study of their ovarian cancer risk association is warranted. Pathogenic variants in *BRIP1*, *MSH2*, and *RAD51C* also approached 1% prevalence each among patients with ovarian cancer, consistent with their guideline designation as ovarian cancer susceptibility genes.<sup>6</sup>

We observed little racial/ethnic variation in overall pathogenic variant prevalence, but did see differences by specific gene: significantly more *CHEK2* pathogenic variants among whites than blacks, and more *BRCA1* pathogenic variants among Hispanics. The prevalence of *CHEK2* pathogenic variants among whites likely reflects the Central European1100delC founder variant.<sup>44,45</sup> Others have noted a high *BRCA1* pathogenic variant prevalence in Hispanic and black patients with breast cancer.<sup>46</sup> Another racial/ethnic difference is VUS rates, more common in blacks, Asians, and Hispanics than whites. We and others previously reported that this VUS difference likely reflects racial bias in the definition of the normal gene sequence along with less clinical testing of minority patients,<sup>9,47-50</sup>

because an access disparity perpetuates a genetic information disparity. Ongoing efforts in germline VUS reclassification<sup>51,52</sup> are essential to promoting equity in cancer care.

Our study has limitations. Results are from two states only and may not be fully generalizable elsewhere, although the scant regional variation we observed is reassuring. The time period is limited (patients diagnosed in 2013 to 2014, with results complete through March 2016), with ongoing linkage under way. Some tests may have been missed because of incomplete ascertainment or uncertainty in the linkage process. However, we surveyed genetic counselors in both states who responded that the collaborating laboratories performed nearly all relevant testing in 2013 to 2014. Furthermore, testing rates from data linkage closely approximate those of patient self-report in our prior work.<sup>23,24</sup> We did not include laboratories that offer direct-to-consumer testing with an out-of-pocket charge; had we done so, we might have observed a magnification of the reported socioeconomic testing disparities. Finally, SEER registries do not collect data on family cancer history, which influences receipt of testing.

Clinical practice and health policy on germline genetic testing of patients with cancer are evolving rapidly as studies on the utility of genetic surveillance continue to emerge.<sup>3,37-39,51,53-57</sup> Some have called for population-based testing, either of all people or of all patients with breast cancer.<sup>57-59</sup> Although it is possible that universal testing guidelines might reduce disparities, our results demonstrate the challenges of adhering to such inclusive guidelines in the case of ovarian cancer. Many factors conspire to limit genetic testing in those with clinical indications, including patients' and clinicians' attitudes about the value of genetic testing and the challenges of integrating genetic testing into the cancer treatment workflow. In particular, the surge in multiple-gene panel testing has markedly increased the demand for timely genetic expertise in the face of a limited supply of genetic counselors. More research is needed to identify optimal approaches to genetic testing delivery and results management and determine the impact of the rapidly changing landscape of genetic risk evaluation on patients with cancer and their families.

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## SUPPORT

Supported by the National Cancer Institute (NCI) of the National Institutes of Health under award Nos. P01 CA163233 to the University of Michigan and R01 CA225697 to Stanford University. 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; the Centers for Disease Control and Prevention's National Program of Cancer Registries, under cooperative agreement 5NU58DP006344; the NCI's SEER Program under contract HHSN2612018000321 awarded to the University of California, San Francisco, contract HHSN261201800015I awarded to the University of Southern California, and contract HHSN261201800009I awarded to the Public Health Institute, Cancer Registry of Greater California. The ideas and opinions expressed herein are those of the authors and do not necessarily reflect the opinions of the State of California, the Department of Public Health, the NCI, and the Centers for Disease Control and Prevention or their Contractors and Subcontractors. Research funding to her institution for an unrelated project was provided to A.W.K. by Myriad Genetics. The authors have no conflicts of interest to declare.

#### AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI <https://doi.org/10.1200/JCO.18.01854>.

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#### ACKNOWLEDGMENT

We thank Jill S. Dolinsky, MS, CGC, and Melissa Pronold, PhD, at Ambry Genetics; Rachel Klein, PhD, Delores Bowman, BSN, and Benjamin Solomon, MD, PhD, 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 SEER data. Written permission was obtained to include the names of all acknowledged individuals.

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

##### **Genetic Testing and Results in a Population-Based Cohort of Breast Cancer Patients and Ovarian Cancer Patients**

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to [www.asco.org/rwc](http://www.asco.org/rwc) or [ascopubs.org/jco/site/fc](http://ascopubs.org/jco/site/fc).

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**Research Funding:** Myriad Genetics (Inst)

**Other Relationship:** Ambry Genetics, Color Genomics, GeneDx/BioReference, Invitae, Genentech

No other potential conflicts of interest were reported.