Influence of Provider Factors and Race on Uptake of Breast Cancer Gene Expression Profiling

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BACKGROUND: Gene expression profiling (GEP) has been rapidly adopted for early breast cancer and can aid in chemotherapy decision making. Study results regarding racial disparities in testing are conflicting, and may reflect different care settings. To the authors' knowledge, data regarding the influence of provider factors on testing are scarce. **METHODS:** The authors used a statewide, multipayer, insurance claims database linked to cancer registry records to examine the impact of race and provider characteristics on GEP uptake in a cohort of patients newly diagnosed with breast cancer between 2005 and 2012. Incidence proportion models were used to examine the adjusted likelihood of testing. Models were stratified by lymph node status (N0 vs N1). **RESULTS:** Among 11,958 eligible patients, 23% of black and 26% of non-Hispanic white patients received GEP. Among patients with N0 disease, black individuals were 16% less likely to receive testing after adjustment for clinical factors and the provider's specialty and volume of patients with breast cancer (95% confidence interval, 0.77-0.93). Adjustment for provider characteristics did not attenuate the effect of race on testing. Patients of middle-volume providers were more likely to be tested compared with those with either high-volume or low-volume providers, whereas patients seeing a medical oncologist were more likely to be tested compared with those whose only providers were from surgical specialties. **CONCLUSIONS:** Provider volume and specialty were found to be significant predictors of GEP use, but did not explain racial disparities in testing. Further research concerning the key contributors to lagging test use among black women is needed to optimize the equitable use of GEPs and support personalized treatment decision making for all patients. ***Cancer* 2018;124:1743-51**.

KEYWORDS: breast cancer, gene profiling, health care disparities, minority health, provider factors.

INTRODUCTION

Over the past decade, gene expression profiles (GEPs) have been rapidly and widely adopted for early hormone receptor-positive (HR+) breast cancer. GEPs use genomic information from tumor samples to estimate the risk of breast cancer recurrence and the incremental survival benefit from chemotherapy to guide decisions regarding adjuvant chemotherapy treatment. The most widely used GEP in the United States, the 21-gene Recurrence Score assay,[1] has been demonstrated to add prognostic and predictive value compared with clinical and pathologic factors alone,[2] and studies of providers indicate that GEP information changes chemotherapy recommendations in approximately 25% to 33% of cases.[3-6]

The increased use of GEP testing has provoked concerns regarding possible disparities in test use and whether testing decisions are being driven by clinical or nonclinical factors. Several studies have reported that only approximately 25% to 50% of eligible patients receive testing, and that testing rates vary depending on nonclinical patient characteristics. In particular, lower adjusted rates of testing have been noted among eligible black patients in a variety of settings, including the National Comprehensive Cancer Network[7]; hospitals in the Atlanta, Georgia metropolitan area[8]; the National Cancer Database[9]; and the California Cancer Registry.[10] However, at least 1 recent population-based study from Surveillance, Epidemiology, and End Results (SEER) registries failed to find a racial disparity.[11] Institutional characteristics are known drivers of variation in testing rates,[12] and it is possible that observed racial disparities may be explained by the concentration of black patients within hospitals with lower overall rates of testing.[13]

One key factor missing from existing studies of GEP patterns of care and racial disparities is the influence and specialties of cancer care providers. GEP tests require the cooperation of treating providers in offering, explaining, ordering, and providing tissue for the assay, and breast cancer patients often receive care from providers in multiple specialties. One recent study suggested that patient-level differences in GEP use are partially explained by their oncologist's patterns of

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use.[14] Thus, apparent racial disparities in test use may be attributable to differences in the types of cancer care providers seen by white and black women. To the best of our knowledge, this hypothesis has not been explored in published studies of GEP use, possibly due to the complexity of determining provider-patient relationships within the context of multidisciplinary and occasionally fragmented oncology care and the limited availability of multipayer, population-based data sets that represent a broad spectrum of providers.

In the current study, we examined the use of breast cancer GEPs over time in a diverse population-based cohort of women with newly diagnosed breast cancer from the Cancer Information and Population Health Resource database, a statewide linkage of North Carolina Central Cancer Registry data to multipayer insurance claims and provider and demographic data.[15] In particular, we examined whether apparent racial disparities in the receipt of GEP testing can be explained by characteristics of oncology providers, including specialty and the volume of patients with breast cancer treated.

MATERIALS AND METHODS

The study cohort was assembled from the Cancer Information and Population Health Resource database and included women with newly diagnosed breast cancer who were eligible for GEP testing between 2005 and 2012 and who were insured by either Medicare or commercial health plans during the study period. Using national guidelines as a template, we included patients with T1-2, N0, and N1 disease and positive estrogen or progesterone receptors.[16] Patients with missing stage of disease or HR data were excluded. All patients were required to have undergone cancer-directed surgery (lumpectomy or mastectomy) within 6 months of diagnosis and to have no claims for chemotherapy before surgery. Because the North Carolina Medicaid program did not cover commercially available GEP assays during the study period, the cohort was limited to patients with Medicare or commercial health insurance. Patients were required to have continuous enrollment in an eligible insurance plan from 1 month before to 12 months after diagnosis, including parts A and B fee-for-service coverage for Medicare beneficiaries.

The primary outcome was the receipt of GEP testing, defined as an insurance claim for Healthcare Common Procedure Coding System (HCPCS) code S3854 or Current Procedural Terminology (CPT) code 81504, following previous methodology.[17] Providers for both tested and untested patients were analyzed to assign each patient a provider with the best opportunity to offer testing following a prespecified algorithm, as illustrated in Figure 1. Hereafter, this provider is referred to as the "assigned provider," whose specialty then was determined based on the provider specialty code on the relevant service claims within 12 months of diagnosis. Briefly, tested patients were assigned to the provider who ordered the test. Untested patients who received chemotherapy were assigned to the provider on the first chemotherapy claim, whereas untested patients not treated with chemotherapy were assigned to the first medical oncologist they saw after surgery or, if no medical oncologist was seen during the study period, to the surgical provider on their final surgery claim. Unique providers were identified across different insurance payers using a proprietary crosswalk between the National Provider Identification number and the unique provider identifiers used by the commercial payers. To quantify the volume of patients with breast cancer for each provider, providers were ranked by the total number of patients in the full study cohort for whom they provided care. The ranked providers then were divided into 6 volume groups from lowest to highest to produce approximately equal numbers of patients represented by providers in each group. Preliminary modeling included a hierarchical approach, in which patients were clustered within providers, but cluster sizes among lower-volume providers were not large enough to support this approach. Therefore patient-level models were performed using Poisson regression, with assigned provider volume included as a patient-level covariate.

In all models, the likelihood of receiving GEP testing was adjusted for patient age, race, year of diagnosis, tumor characteristics, comorbidity burden (represented by the Klabunde modification of the Charlson Comorbidity Score),[18] and insurance type (public vs private). The model then was adjusted for provider characteristics, including clinical specialty and volume of patients with breast cancer, of the provider with the best opportunity to offer testing to each patient (the "assigned provider") (Fig. 1). Based on prior literature and clinical reasoning that predictors of testing would differ between patients with lymph node-positive and lymph node-negative disease, all models were stratified by lymph node status (N0 vs N1). A priori models were not adjusted for socioeconomic variables in accordance with the approach to models of racial disparity suggested by the Institute of Medicine[19]; however, sensitivity analyses subsequently adjusted for census tract-level measures of poverty and education. All statistical modeling was performed using SAS Enterprise Guide V7.1 (SAS Institute Inc, Cary, North Carolina). This

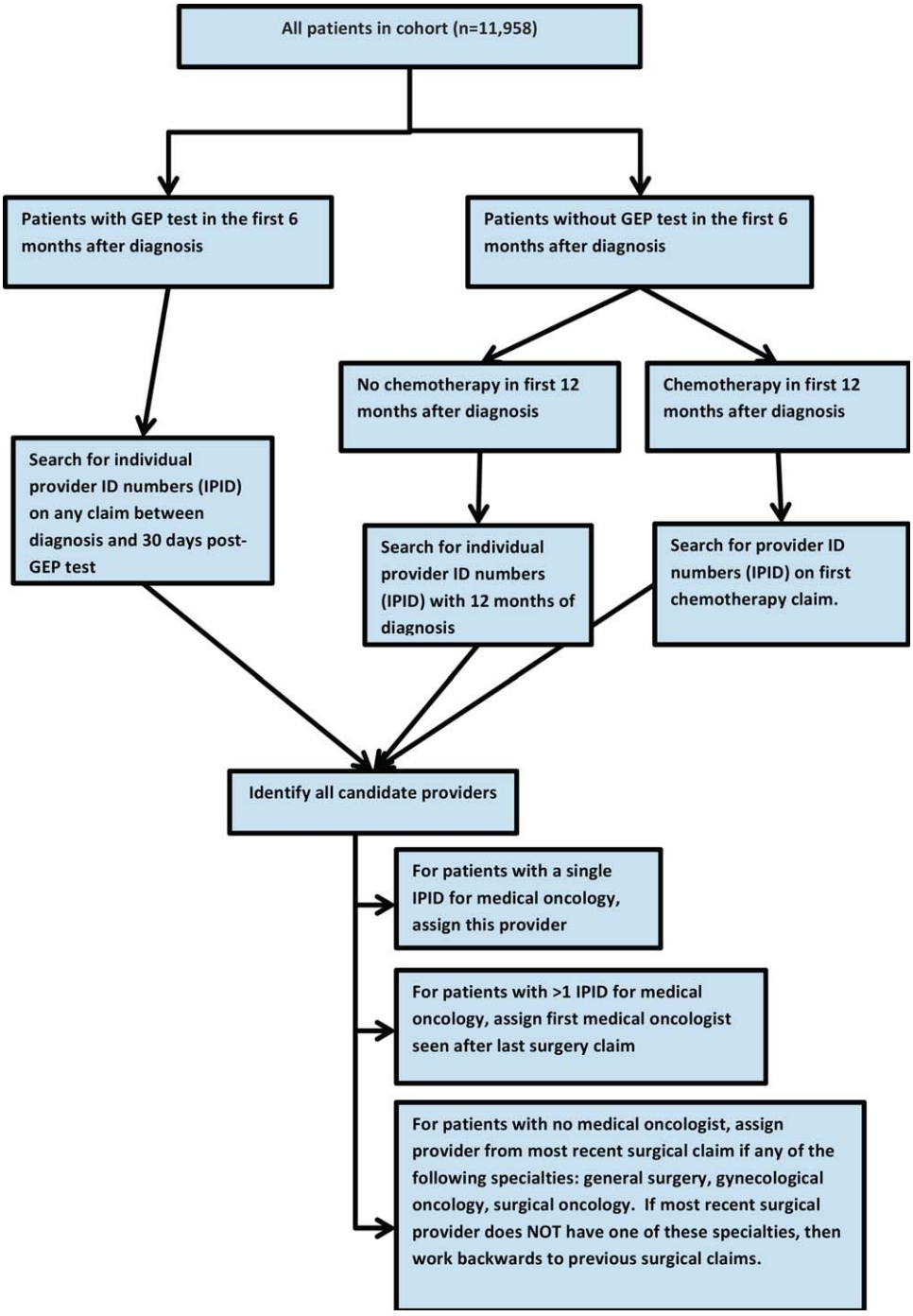

Figure 1. Algorithm for assignment of the provider with the best opportunity to offer gene expression profile (GEP) testing. IPID indicates individual provider identification number.

study was approved by the institutional review board of the University of North Carolina.

RESULTS

The final study cohort included 11,958 patients (Table 1), 1538 of whom (13%) were black and 10,109 of whom (85%) were non-Hispanic white. A small number of patients were Hispanic (<1%) or of other racial/ethnic minorities (2%). A Consolidated Standards Of Reporting Trials (CONSORT) diagram of study inclusion criteria is presented in Figure 2. Overall, 23% of black women and 26.2% of non-Hispanic white women received GEP

TABLE 1. Population Sample Characteristics by GEP Test Status

Variables	Levels	Total		GEP Testing		No GEP Testing		*P*
		N = 11,958	%	N = 3096	%	N = 8862	%	
Race/ethnicity	White	10,109	84.5	2651	85.6	7458	84.2	.0217
	Black	1538	12.9	354	11.4	1184	13.4	
	Hispanic	102	0.9	27	0.9	75	0.9	
	Other	209	1.8	64	2.1	145	1.6	
Age at diagnosis, y	<50	1312	11.0	533	17.2	779	8.8	<.0001
	50-69	5474	45.8	1858	60.0	3616	40.8	
	≥70	5172	43.3	705	22.8	4467	50.4	
N classification	N0	9671	80.9	2682	86.6	6989	78.9	<.0001
Tumor size	T1a-b	3837	32.1	660	21.3	3177	35.9	<.0001
	T1c	5192	43.4	1654	53.4	3538	39.9	
	T2	2929	24.5	782	25.3	2147	24.2	
Insurance type at time of diagnosis	Medicare only	7003	58.6	1248	40.3	5755	64.9	<.0001
	Any private	4955	41.4	1848	59.7	3107	35.1	
NCI Comorbidity Index	0	3600	30.1	1418	45.8	2182	24.6	<.0001
	≥1	761	6.4	227	7.3	534	6.0	
	Unable to assess	7597	63.5	1451	46.9	6146	69.4	
RT within 12 mo of diagnosis	No	4711	39.4	1044	33.7	3667	41.4	<.0001
	Yes	7247	60.6	2052	66.3	5195	58.6	
Surgery within 6 mo of diagnosis	Lumpectomy	7466	62.4	1978	63.9	5488	61.9	.0524
	Mastectomy	4492	37.6	1118	36.1	3374	38.1	
Stage of disease at diagnosis	I	7740	64.7	2035	65.7	5705	64.4	.1747
	II	4218	35.3	1061	34.3	3157	35.6	
Specialty of provider	Gynecological oncology	344	2.9	83	2.7	261	3.0	<.0001
	General surgery	2085	17.4	234	7.6	1851	20.9	
	Medical oncology	9341	78.1	2746	88.7	6595	74.4	
	Oncology surgery	73	0.6	13	0.4	60	0.7	
	Missing data	115	1.0	20	0.7	95	1.1	
Tumor grade	1	3641	30.5	815	26.3	2826	31.9	<.0001
	2	5633	47.1	1625	52.5	4008	45.2	
	3	2684	22.5	656	21.2	2028	22.9	
Volume of assigned provider	Top 10	1594	13.3	465	15.0	1129	12.7	<.0001
	11th-30th	1825	15.3	601	19.4	1224	13.8	
	31st-50th	1313	11.0	445	14.4	868	9.8	
	51st-100th	2254	18.9	629	20.3	1625	18.3	
	100th-200th	2374	19.9	518	16.7	1856	20.9	
	≤201st	2481	20.8	418	13.5	2063	23.3	
	Missing data	117	1.0	20	0.7	97	1.1	
Y of diagnosis	2005	1091	9.1	29	0.9	1062	12.0	<.0001
	2006	1229	10.3	144	4.7	1085	12.2	
	2007	1404	11.7	228	7.4	1176	13.3	
	2008	1455	12.2	381	12.3	1074	12.1	
	2009	1635	13.7	498	16.1	1137	12.8	
	2010	1610	13.5	552	17.8	1058	11.9	
	2011	1784	14.9	612	19.8	1172	13.2	
	2012	1750	14.6	652	21.1	1098	12.4	

Abbreviations: GEP, gene expression profile; NCI, National Cancer Institute; RT, radiotherapy; y, years.

testing, with rates rising significantly in both groups over time (Figs. 3 Top and Bottom).

Results of the primary multivariable analysis of predictors of testing are presented in Table 2. Provider specialty and volume of patients with breast cancer were found to be significant predictors of testing. Among patients with lymph node-negative disease, those whose assigned provider was a medical oncologist were more likely to be tested compared with those whose assigned provider was a general surgeon (adjusted risk ratio [aRR], 0.59; 95% confidence interval [95% CI], 0.52-0.67) or gynecologic oncologist (aRR, 0.82; 95% CI, 0.67-1.00). There was a nonsignificant trend toward a lower likelihood of testing for patients whose assigned provider was a surgical oncologist (aRR, 0.77; 95% CI, 0.46-1.31). Similar differences in testing percentages by specialty were observed for patients with N1 disease, but with larger decrements in patients seen by nonmedical oncology specialties. For patients with N0 disease, those with moderate-volume providers (11-100 patients) had a significantly higher percentage of testing compared with patients treated by the highest-volume providers, whereas patients

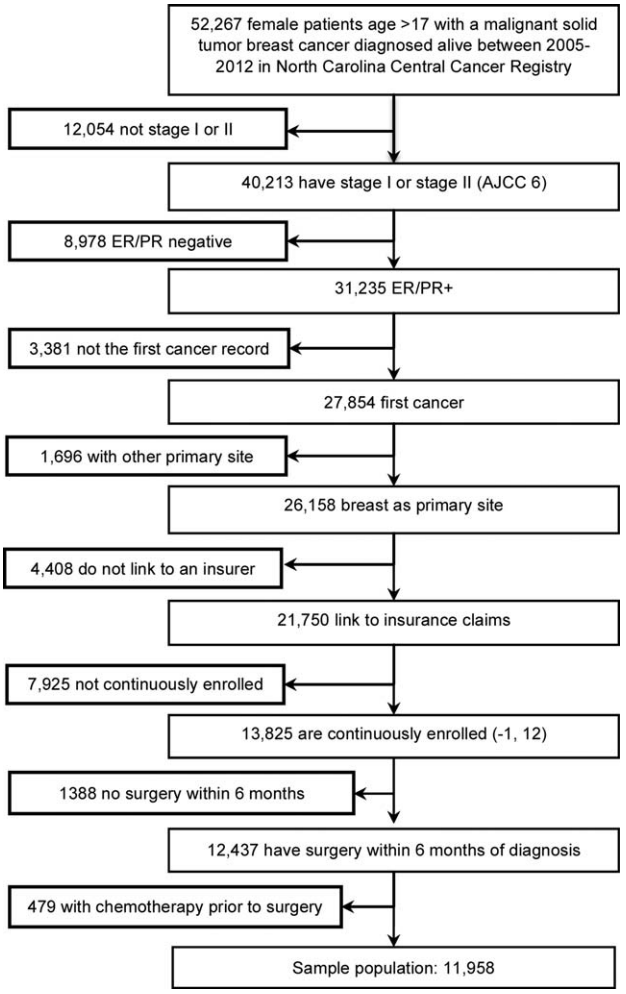

Figure 2. Composition of the sample population Consolidated Standards Of Reporting Trials (CONSORT) diagram of study with inclusion criteria: diagnosis year between 2005 and 2012, first cancer record, no report from death certificate and autopsy, age ≥18 years, stage I and II disease, hormone receptor-positive (+) disease, and continuous enrollment in an insurance plan. AJCC 6 indicates American Joint Committee on Cancer sixth edition; ER, estrogen receptor; PR, progesterone receptor.

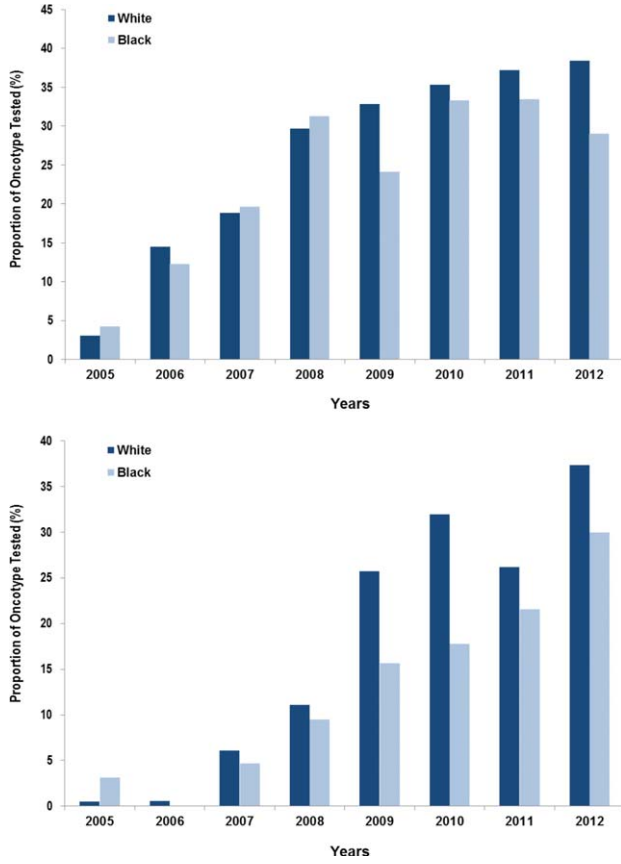

Figure 3. (*Top*) Percentage of patients with gene expression profile (GEP) testing by year and race for women with lymph node-negative disease. (*Bottom*) Percentage of patients with GEP testing by year and race for women with lymph node-positive disease.

of the lowest-volume providers had percentages similar to those of the highest-volume providers. This pattern differed from that among patients with N1 disease, in whom the adjusted likelihood of testing steadily decreased with lower patient volume.

After adjustment for provider specialty and volume, race and age remained significant predictors of testing. Among patients with N0 disease, black women were 16% less likely than non-Hispanic white women to receive testing after adjustment for other factors (95% CI, 0.77-0.93). Among patients with N1 disease, an adjusted difference of 26% was observed, but this did not reach statistical significance (95% CI, 0.55-1.01). Testing steadily decreased with age among patients with N0 disease, whereas among patients with N1 disease, only women aged ≥80 years were found to be significantly less likely to receive testing.

Other predictors of an increased likelihood of testing for patients with N0 disease included a tumor size of T1c or T2 compared with T1a-b, intermediate histologic grade, lack of medical comorbidity, and year of diagnosis, with testing increasing over time. Among patients with N1 disease, those with grade 3 tumors were less likely to receive testing compared with those with grade 1 tumors (aRR, 0.58; 95% CI, 0.42-0.79), and patients tested in any year before 2009 were less likely to be tested compared with those tested in the referent year of 2012. Commercial compared with public insurance was associated with higher testing rates among patients with N0 (aRR, 1.29; 95% CI, 1.13-1.46) but not N1 disease. Sensitivity analyses in which models were adjusted for neighborhood-level measures of household income and

TABLE 2. Adjusted Likelihood of GEP Testing (2005-2012) by Lymph Node Status

Variables	Levels	RR (95% CI)			
		Lymph Node Negative		Lymph Node Positive	
Race/ethnicity	White	1.00	-	1.00	-
	Black	0.84[a]	(0.77-0.93)	0.74	(0.55-1.01)
	Hispanic	0.94	(0.71-1.25)	0.86	(0.32-2.34)
	Other	0.92	(0.75-1.12)	1.22	(0.62-2.38)
Age at diagnosis, y	18-49	1.18[a]	(1.09-1.28)	0.85	(0.61-1.19)
	50-59	1.12[a]	(1.04-1.20)	1.03	(0.77-1.38)
	60-69	1.00	-	1.00	-
	70-79	0.59[a]	(0.54-0.65)	0.93	(0.71-1.21)
	≥80	0.14[a]	(0.11-0.18)	0.39[a]	(0.23-0.66)
Tumor classification	T1a-b	1.00	-	1.00	-
	T1c	2.09[a]	(1.93-2.26)	0.88	(0.68-1.15)
	T2	2.07[a]	(1.89-2.27)	0.62[a]	(0.46-0.83)
Tumor grade	1	1.00	-	1.00	-
	2	1.25[a]	(1.17-1.34)	0.95	(0.75-1.20)
	3	1.07	(0.98-1.17)	0.58[a]	(0.42-0.79)
Insurance type	Medicare only	1.00	-	1.00	-
	Any private	1.29[a]	(1.13-1.46)	0.75	(0.45-1.24)
NCI Comorbidity Index	0	1.00	-	1.00	-
	≥1	0.86[a]	(0.77-0.95)	0.91	(0.59-1.41)
	Unable to assess	0.98	(0.88-1.10)	0.84	(0.52-1.34)
Specialty of provider	Medical oncology	1.00	-	1.00	-
	General surgery	0.59[a]	(0.52-0.67)	0.37[a]	(0.23-0.58)
	Gyn oncology	0.82[b]	(0.67-1.00)	0.27[a]	(0.11-0.65)
	Surgical oncology	0.77	(0.46-1.31)	0.66	(0.21-2.09)
Surgery type	Lumpectomy	1.00	-	1.00	-
	Mastectomy	0.98	(0.92-1.04)	0.89	(0.73-1.08)
Volume of assigned provider	Top 10	1.00	-	1.00	-
(rank compared with other providers)	11th-30th	1.23[a]	(1.11-1.35)	0.93	(0.69-1.26)
	31st-50th	1.40[a]	(1.27-1.55)	0.73	(0.51-1.04)
	51st-100th	1.21[a]	(1.10-1.33)	0.78	(0.57-1.06)
	100th-200th	1.05	(0.95-1.17)	0.60[a]	(0.43-0.84)
	≤201st	1.08	(0.96-1.21)	0.63[b]	(0.43-0.92)
Y of diagnosis	2005	0.10[a]	(0.07-0.14)	0.03[a]	(0.01-0.12)
	2006	0.43[a]	(0.37-0.51)	0.02[a]	(0.00-0.11)
	2007	0.53[a]	(0.47-0.61)	0.17[a]	(0.10-0.29)
	2008	0.79[a]	(0.72-0.87)	0.33[a]	(0.22-0.49)
	2009	0.83[a]	(0.76-0.91)	0.78	(0.58-1.05)
	2010	0.93	(0.85-1.02)	0.92	(0.69-1.22)
	2011	0.98	(0.90-1.07)	0.80	(0.59-1.06)
	2012	1.00	-	1.00	-

Abbreviations: 95% CI, 95% confidence interval; GEP, gene expression profile; Gyn, gynecologic; NCI, National Cancer Institute; RR, risk ratio; y, years.
[a] $P = .01$.
[b] $P = .05$.

educational attainment slightly attenuated the effect of black race on the likelihood of testing (aRR, 0.88; 95% CI, 0.80-0.96 [data not presented]). To examine whether controlling for provider factors attenuated the relationship of race to the likelihood of testing, we performed sensitivity analyses in which provider variables were removed from the model. The effect of race on the likelihood of testing was similar to the primary model (aRR, 0.83; 95% CI. 0.76-0.92 [data not presented]).

DISCUSSION

Prior literature has suggested that racial disparities may be a significant barrier to the optimal use of GEPs, but to the best of our knowledge it remains unclear whether patient or health system characteristics are the most important drivers of this disparity. To the best of our knowledge, the current study is the first to examine the role of provider characteristics while considering patient characteristics as a predictor of testing.

We found that provider characteristics, including a moderate volume of patients with breast cancer and a medical oncology specialty, were associated with a higher likelihood of testing in patients with lymph node-negative disease, the largest group eligible for testing. There are multiple potential explanations for these findings. Although patients of both high-volume and low-volume providers were found to be less likely to receive testing, the reason for a lack of testing may vary, with

lower-volume providers feeling less comfortable with the test in general, and higher-volume providers being more skeptical regarding its applicability to all patients. With regard to specialty, medical oncologists may be more comfortable ordering and interpreting the test because the test informs treatment that they themselves will administer, or test ordering may be perceived as the medical oncologist's, rather than the surgical provider's, role within many practice settings. Alternatively, patients who seek testing may be channeled toward medical oncologists, whereas patients who are unwilling to consider chemotherapy or are lost to follow-up early in their treatment trajectory may see only surgical providers. In light of this finding, increased coordination of referrals to medical oncologists before or after surgery might be a system-level intervention to increase the uptake of GEP testing. Alternatively, one recent intervention using an algorithm for surgeon-triggered ordering, in consultation with medical oncologists, demonstrated success in reducing time to chemotherapy and high test uptake.[20]

We observed a racial disparity in GEP testing similar to that reported in earlier studies, with black women with lymph node-negative disease found to be 16% less likely than comparable non-Hispanic white women to receive GEP testing. This racial disparity was not attenuated by adjustment for provider characteristics, including volume of patients with breast cancer and specialty. Other explanations for this disparity in testing therefore must be considered. Despite the finding that all patients in the cohort had insurance coverage for GEP testing, generosity of coverage or the patient's ability to afford shared costs may differ by race and affect test uptake. Testing also may be accepted less often among black women even if offered due to unmeasured factors such as patient mistrust of the test; an aversion to genomic or genetic testing in general; or an unwillingness to defer testing decisions until results are available, particularly if care has already been delayed. Adequate evidence supports the concern that black patients are more vulnerable to treatment delays.[21,22] Poor quality of patient-provider communication, which is known to be problematic for black patients in many health care settings, also could play a role in a lower acceptance of the test.[23,24] Alternatively, black women might be less willing to consider chemotherapy regardless of the estimated benefit, and thus might not view information from the test as valuable. This concern is supported by several recent studies documenting racial disparities in adjuvant chemotherapy use,[25-27] although to the best of our knowledge the extent of this disparity and the issue of whether patient preference plays a role are unclear.[28,29] Although we adjusted for provider characteristics that might influence the adoption of GEP testing, including volume of patients with breast cancer and clinical specialty, there may be other provider features that were not measured and that explain some part of racial disparities in testing. We also must consider the possibility of within-provider variation. Providers may offer testing less often to similar black patients compared with white individuals due to biases regarding the patient's cancer risk, ability to interpret test results, or ability to tolerate chemotherapy.

We encountered several limitations that should be considered when interpreting the findings of the current study. We were able to observe the provider visits for which the patient was billed, but not the content of those visits, and made assumptions regarding whether a GEP test could have been offered appropriately by a specific provider during a specific visit. It is likely that in some cases, a provider other than the assigned provider made a recommendation for or against GEP testing, which cannot be directly observed in this data set. More important, we were unable to identify from claims and registry data whether a test was offered, only whether it was completed and reimbursed for, which limits the inferences we can draw regarding the reasons for lack of testing. We were not able to capture testing that was performed but not submitted for insurance reimbursement, or was paid for out of pocket. However, because all patients in the cohort had insurance and the test is relatively costly, it is unlikely that uncompensated testing was widespread. Given that uninsured patients have reduced access to costly GEP testing and are more likely to be members of vulnerable populations, the current analysis may underestimate the magnitude of racial disparity in the general population. Similarly, we were unable to include patients insured by Medicaid due to a lack of coverage for the test by that payor during the study period, and both patients and provider characteristics of the Medicaid population may differ from those in the current study sample. Last, the state cancer registry did not collect human epidermal growth factor receptor 2 (HER2) status as a mandatory data element during the study period, and a small percentage of the patients in the current study cohort with early-stage HR+ disease are assumed to have HER2-overexpressing tumors and thus to be inappropriate candidates for testing. However, the percentage of HR+/HER2-positive breast cancer is known to be similar between black and non-Hispanic white patients,[30] thereby reducing the concern that this factor would bias the analysis by either overestimating or underestimating racial disparities. The findings of the current study may not be generalizable to

uninsured patients, and may reflect patterns that differ by geographic region or within specialized health systems.

GEP testing is a novel risk stratification tool for women with early breast cancer that offers opportunities to personalize treatment decision making and more appropriately allocate chemotherapy while avoiding excess treatment morbidity. To achieve optimal outcomes in all patient groups, it must be a priority to offer such innovations equitably to all patients, including those in vulnerable populations. If we wish to optimize GEP use among vulnerable patients, more in-depth studies are needed examining factors throughout the breast cancer care delivery process that may explain the lower use of GEP tests among black women, including race-specific estimates of provider recommendations and patient preferences for testing and chemotherapy. A better understanding of provider-mediated decision making, such as barriers to or beliefs regarding the test and how patients are selected for testing, also is needed to design effective interventions. Institutional barriers to testing, which may limit providers' ability to use the test in certain care settings, also should be considered. Finally, racial differences in treatment decisions after testing also are important in understanding racial disparities, and are being explored in ongoing work.

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CONFLICT OF INTEREST DISCLOSURES

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AUTHOR CONTRIBUTIONS

Katherine E. Reeder-Hayes: Conceptualization, methodology, formal analysis, writing-original draft, writing-review and editing, visualization, supervision, project administration, and funding acquisition. **Stephanie B. Wheeler**: Conceptualization, methodology, formal analysis, writing-original draft, visualization, and supervision. **Christopher D. Baggett**: Conceptualization, methodology, software, formal analysis, data curation, writing-original draft, and visualization. **Xi Zhou**: Methodology, software, formal analysis, data curation, writing-original draft, and visualization. **Ke Meng**: Methodology, software, formal analysis, data curation, writing-original draft, and visualization. **Megan C. Roberts**: Conceptualization, methodology, formal analysis, writing-original draft, and visualization. **Lisa A. Carey**: Conceptualization, formal analysis, and writing-original draft. **Anne-Marie Meyer**: Conceptualization, methodology, software, formal analysis, data curation, writing-original draft, visualization, supervision, and project administration.

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