Adoption of Gene Expression Profile Testing and Association With Use of Chemotherapy Among Women With Breast Cancer

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See accompanying editorial on page 2173; listen to the podcast by Dr Pritchard at www.jco.org/podcasts

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ABSTRACT

Purpose

Gene expression profile (GEP) testing is a relatively new technology that offers the potential of personalized medicine to patients, yet little is known about its adoption into routine practice. One of the first commercially available GEP tests, a 21-gene profile, was developed to estimate the benefit of adjuvant chemotherapy for hormone receptor–positive breast cancer (HR-positive BC).

Patients and Methods

By using a prospective registry data set outlining the routine care provided to women diagnosed from 2006 to 2008 with HR-positive BC at 17 comprehensive and community-based cancer centers, we assessed GEP test adoption and the association between testing and chemotherapy use.

Results

Of 7,375 women, 20.4% had GEP testing and 50.2% received chemotherapy. Over time, testing increased (14.7% in 2006 to 27.5% in 2008; $P < .01$) and use of chemotherapy decreased (53.9% in 2006 to 47.0% in 2008; $P < .01$). Characteristics independently associated with lower odds of testing included African American versus white race (odds ratio [OR], 0.70; 95% CI, 0.54 to 0.92) and high school or less versus more than high school education (OR, 0.63; 95% CI, 0.52 to 0.76). Overall, testing was associated with lower odds of chemotherapy use (OR, 0.70; 95% CI, 0.62 to 0.80). Stratified analyses demonstrated that for small, node-negative cancers, testing was associated with higher odds of chemotherapy use (OR, 11.13; 95% CI, 5.39 to 22.99), whereas for node-positive and large node-negative cancers, testing was associated with lower odds of chemotherapy use (OR, 0.11; 95% CI, 0.07 to 0.17).

Conclusion

There has been a progressive increase in use of this GEP test and an associated shift in the characteristics of and overall reduction in the proportion of women with HR-positive BC receiving adjuvant chemotherapy.

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INTRODUCTION

Broadly defined, personalized medicine is the use of a person's genes, proteins, and environment to prevent, diagnose, and treat disease.¹ Since the human genome was first sequenced,² there has been much speculation and great hope that genetic information will transform the way we treat patients by facilitating personalized health care. Efforts to develop tests that use genetic/genomic data to guide treatment decisions have grown significantly in the past few years. Although several of these tests have been introduced into routine care, the impact of personal-

ized medicine on general medical practice has not been well quantified.

Breast cancer is the most frequently diagnosed nondermatologic malignancy among women in the United States. Although chemotherapy reduces the risk of recurrence and improves survival for non-metastatic breast cancer,³ most women never experience a recurrence and therefore derive no benefit from chemotherapy. To identify women who are unlikely to benefit from and can be spared the toxicity and risks associated with chemotherapy, investigators developed a tumor-specific gene expression profile (GEP) test for hormone receptor–positive

(HR-positive) breast cancer.⁴ To validate the ability of this test to predict benefit from chemotherapy, it was applied to the tumor samples of women who participated in two randomized controlled trials comparing adjuvant chemotherapy with no adjuvant therapy. Among women whose tumors were classified as low to intermediate risk by the test, chemotherapy resulted in no significant benefit, whereas among women with tumors characterized as high risk by the test, chemotherapy was associated with a significant improvement in 10-year recurrence-free status (from 60% to 88% for node-negative breast cancer⁵ and from 43% to 55% for node-positive breast cancer⁶).

Since the test became commercially available in 2004, its use has been recommended or endorsed by several clinical practice guidelines.^{7,8} Despite assertions that it has been ordered frequently and has improved clinical decision making,⁹⁻¹¹ in reality little is known about its adoption or impact on clinical practice. Since it is one of the first in what is likely to be a new wave of diagnostic tests designed to facilitate the delivery of personalized health care, understanding its use and association with treatment is critical. In a multi-institutional cohort of women with newly diagnosed breast cancer, we sought to characterize how quickly this GEP test was adopted into routine practice, whether there were sociodemographic or other disparities in its use, and whether there was an association between GEP testing and receipt of chemotherapy.

PATIENTS AND METHODS

Data Source

Since 1997, the National Comprehensive Cancer Network (NCCN) Breast Cancer Outcomes Database Project has prospectively collected patient and tumor characteristics, treatments, and outcomes for women with newly diagnosed breast cancer.^{12,13} The database, essentially a comprehensive registry of all patients with breast cancer who receive their primary cancer care at participating institutions, includes information from a patient survey conducted at first presentation and regularly scheduled, standardized medical record reviews conducted by trained, dedicated clinical research associates.¹⁴⁻¹⁶ Eleven National Cancer Institute–designated comprehensive cancer centers and six community-based cancer centers participating in the Michigan Breast Oncology Quality Initiative¹⁷—a regional collaborative improvement consortium led by the University of Michigan and supported by Blue Cross/Blue Shield of Michigan—contributed to this analysis (for a list of institutions, see Appendix Table A1, online only). All centers adhered to the data collection procedures and definitions developed by the NCCN Breast Cancer Outcomes Database. Institutional review boards (IRBs) from participating centers approved all data collection, transmission, and storage protocols. At centers where the IRB required signed informed consent for data collection, only patients who provided consent were included in the database; elsewhere, the IRB granted a waiver of signed informed consent.

Patient Selection and Variables of Interest

Women diagnosed with HR-positive stage I to III unilateral breast cancer who presented for initial treatment between January 1, 2006, and December 31, 2008, were included in this analysis. The cohort was restricted to patients presenting during or after 2006, because that is when the database began to collect GEP test results. Patients had to have an estrogen or progesterone receptor–positive cancer, evidence of nodal evaluation, at least 180 days of follow-up, and no previous cancers. We did not restrict the sample to the relatively small subset of patients with HR-positive breast cancer for whom the NCCN recommends GEP testing, because we were interested in characterizing test adoption, broadly speaking, across all stages of nonmetastatic, HR-positive disease, and we hypothesized that there would be testing for cancers with a range of clinical risk characteristics. Comorbidity scores were derived by using methods described by Charlson et al¹⁸ and Katz et al¹⁹ and grouped into

values ≤ 1 versus ≥ 2 . Two histologic types were defined: ductal/lobular and any of a series of more favorable subtypes (tubular, colloid, medullary, adenocystic, and papillary). Tumors were considered low grade if histologic and nuclear grade were low; all other were considered intermediate to high grade.

Two breast cancer GEP tests were available during the study period—a 70-gene profile (MammaPrint; Agendia, Irvine, CA) and a 21-gene profile (OncotypeDx; Genomic Health, Redwood City, CA). Few women had the former test ($n = 6$), so all analyses focused on the latter test. The 21-gene profile yields a numeric score ranging between 0 and 100. Standard, prespecified cut points defined during test development were used to classify tumors as low risk (< 18), intermediate risk (18 to 30), or high risk (≥ 31).⁴ The GEP test results included in this analysis were obtained as part of routine care. Patients were classified as having received adjuvant chemotherapy if they initiated cytotoxic, antineoplastic medications within 180 days after diagnosis and before any evidence of cancer recurrence.

Data Analyses

Temporal trends in GEP testing and chemotherapy use were derived for the whole cohort and for strata defined by nodal status (negative *v* positive) and type of cancer center (comprehensive *v* community-based). Bivariable relationships between the major covariates and both GEP testing and chemotherapy use were assessed. A multivariable logistic regression model was constructed to identify independent predictors of GEP testing. GEP testing could have an impact on chemotherapy use in two different ways: (1) for those who normally would not receive chemotherapy, testing could increase use by identifying women who might benefit from it; (2) for those who normally would receive chemotherapy, testing could decrease use by identifying women who are unlikely to benefit. We therefore assumed that the association between GEP testing and chemotherapy use was not monotonic, and we modeled this relationship separately for three clinically relevant strata defined by NCCN clinical practice guidelines.

By using traditional prognostic factors (tumor size, nodal involvement, histology, grade, angiolymphatic invasion, and human epidermal growth factor receptor 2 [HER2] status), the NCCN guidelines define three groups for which it makes distinct GEP testing and chemotherapy recommendations: (1) low-clinical-risk cancers that carry a good prognosis, such as node-negative tumors measuring ≤ 1 cm, for which the guidelines recommend “no chemotherapy”; (2) intermediate-clinical-risk cancers that have a moderate prognosis, such as node-negative, HER2-negative tumors measuring more than 1 cm, for which the guidelines recommend “consider GEP testing and chemotherapy”; and (3) high-clinical-risk cancers with a poor prognosis, such as node-positive cancers, for which the guidelines “recommend chemotherapy.”

After classifying patients into these three clinical-risk groups, we developed a separate multivariable logistic regression model for each group to determine whether testing was an independent predictor of chemotherapy after controlling for age, race, education, insurance, employment, comorbidity, cancer center type, diagnosis year, grade, HER2 status, tumor size, and number of involved nodes.

χ^2 and Mantel-Haenszel tests were used to evaluate bivariable associations and trends, respectively. The Wald and Clopper-Pearson exact tests were used to obtain CIs for the proportions of patients who received testing/chemotherapy. A $P \leq .2$ threshold was used to select variables for inclusion in the multivariable models; stepwise selection was used to determine the most parsimonious result with a $P \leq .05$ for the likelihood ratio test; and model results were reported by using odds ratios (ORs) with 95% CIs. All P values were two sided. Statistical analyses were conducted by using SAS 9.2 (SAS Institute, Cary, NC).

RESULTS

We identified 7,375 women diagnosed from 2006 to 2008 with stage I to III HR-positive breast cancer. Overall, 20.4% (95% CI, 19.5% to 21.3%) had GEP testing (Table 1). The frequency of testing varied across institutions (10.7% to 35.7%; $P < .01$). Women who were 50 to

Table 1. Patient, Cancer, and Treatment Characteristics

Characteristic	Total Patients		GEP Testing		Chemotherapy Use	
	No.	%	Proportion	<i>P</i>	Proportion	<i>P</i>
Total	7,375	100	20.4		50.2	
Age at diagnosis, years						
< 50	2,392	32.4	20.1		72.2	
50-59	2,181	29.6	24.7	< .001	54.5	< .001
60-69	1,634	22.2	23.0		39.5	
70+	1,168	15.8	9.4		12.4	
Race/ethnicity						
White non-Hispanic	5,930	80.4	21.3		48.4	
African American non-Hispanic	623	8.4	13.6	< .001	54.4	< .001
Other/unknown*	822	11.1	19.1		60.3	
Education						
Above high school	3,572	48.4	22.4		55.8	
High school degree or less	1,396	18.9	14.5	< .01	45.8	< .001
Other/unknown†	2,407	32.6	20.9		44.5	
Health insurance						
Managed care	4,244	57.6	22.0		58.8	
Indemnity	640	8.7	28.0	< .001	54.7	< .001
Medicare	1,805	24.5	14.7		22.7	
Other/unknown‡	686	9.3	18.4		65.3	
Employment						
Employed or student	3,172	43.0	23.0		60.1	
Homemaker/unemployed/retired	2,921	39.6	17.8	< .001	40.3	< .001
Other/unknown§	1,282	17.4	19.8		48.3	
Comorbidity score						
0-1	6,869	93.1	20.8	.001	51.6	< .001
≥ 2	506	6.9	14.8		30.8	
Year of diagnosis						
2006	2,172	29.5	14.7		53.9	
2007	2,828	38.4	18.8	< .001	50.1	< .001
2008	2,375	32.2	27.5		47.0	
Type of cancer center						
Comprehensive	5,970	81.0	21.0	.006	51.9	< .001
Community-based	1,405	19.0	17.7		43.1	
Stage						
I	3,715	50.4	30.5		23.2	
II	2,707	36.7	13.4	< .001	73.8	< .001
III	953	12.9	1.2		88.7	
Size of primary tumor, cm¶						
≤ 1	2,045	27.7	18.0		18.0	
1.1-2	2,753	37.3	31.0	< .001	49.0	< .001
≥ 2.1	2,496	33.8	11.3		78.2	
Unknown	81	1.1	3.7		43.2	
No. of nodes involved						
0	4,650	63.0	29.8		33.7	
1-3	1,786	24.2	5.8	< .001	80.7	< .001
4+	763	10.4	1.3		89.5	
Unknown	176	2.4	3.4		8.5	
Hormone receptors						
ER positive/PR positive	6,111	82.9	21.5		48.3	
ER positive/PR negative	1,129	15.3	15.8	< .001	57.8	< .001
ER negative/PR positive	117	1.6	6.8		76.9	
ER positive or PR positive/the other unknown	18	0.2	11.1		55.6	
HER2 status						
Not overexpressed	6,334	85.9	22.6		46.4	
Overexpressed	942	12.8	6.9	< .001	79.2	< .001
Unknown	99	1.3	6.1		16.2	

(continued on following page)

Table 1. Patient, Cancer, and Treatment Characteristics (continued)

Characteristic	Total Patients		GEP Testing		Chemotherapy Use	
	No.	%	Proportion	P	Proportion	P
Histologic or nuclear grade						
Low	1,563	21.2	22.8		25.1	
Intermediate or high	5,609	76.0	20.0	< .001	57.7	< .001
Unknown	203	2.8	12.3		37.4	
Lymphovascular invasion						
Absent	5,508	74.7	23.3		42.1	
Present	1,651	22.4	11.4	< .001	77.5	< .001
Unknown	216	2.9	16.2		49.1	
Histologic type						
Ductal and/or lobular	7,035	95.4	20.5	.25	51.7	< .001
Other	340	4.6	17.9		20.0	
Definitive breast cancer surgery						
Breast conserving	4,400	59.7	24.0		39.7	
Mastectomy	2,882	39.1	15.5	< .001	66.6	< .001
None	93	1.3	4.3		38.7	
Radiation therapy						
Yes	5,106	69.2	20.2	.42	51.3	< .001
No	2,269	30.8	21.0		47.7	
GEP test result						
Not tested	5,870	79.6	—		54.7	
Low risk (< 18)	758	10.3	—		12.0	
Intermediate risk (18-30)	547	7.4	—	N/A	46.4	< .001
High risk (≥ 31)	149	2.0	—		87.9	
Tested, unknown result	51	0.7	—		39.2	

Abbreviations: ER, estrogen receptor; GEP, gene expression profile; HER2, human epidermal growth factor receptor 2; N/A, not applicable; PR, progesterone receptor.

*Other race/ethnicity includes Hispanic, African American Hispanic, Asian, American Indian-Aleut, Eskimo, and unclassified. There were 69 patients with unknown race/ethnicity.

†Other/unknown includes 41 patients with unclassified education status and 2,366 with unknown values. A sensitivity analysis excluding patients with unknown education status yielded the same significant findings.

‡Other/unknown includes 556 patients with unclassified health insurance status and 130 with unknown values. A sensitivity analysis excluding patients with unknown health insurance status yielded the same significant findings.

§Other/unknown includes 366 patients with unclassified employment status and 916 with unknown values. A sensitivity analysis excluding patients with unknown employment status yielded the same significant findings.

||Size categories are based on pathologic data unless pathologic data were unavailable or patients received neoadjuvant chemotherapy, in which case clinical data were used.

||Other histology includes tubular, colloid, medullary, adenocystic, and papillary.

59 years old were more likely to have testing (24.7%; 95% CI, 22.9% to 26.7%) than women who were younger than age 50 years (20.1%; 95% CI, 18.5% to 21.8%) or age ≥ 70 years (9.4%; 95% CI, 7.8% to 11.2%). Compared with women who had intermediate size 1.1- to 2-cm tumors, testing was 42% less likely among those who had ≤ 1-cm tumors and 64% less likely among those who had ≥ 2-cm tumors (GEP testing rates of 31.0%, 18.0%, and 11.3%, respectively; $P < .01$). African American women were 36% less likely to have GEP testing than white non-Hispanic women. Chemotherapy was administered to 50.2% (95% CI, 49.1% to 51.4%) of the cohort (Table 1). Chemotherapy use increased as age decreased and tumor size increased. Chemotherapy use was lower among women who had GEP testing versus those who did not (33.0% [95% CI, 30.6% to 35.4%] v 54.7% [95% CI, 53.4% to 55.9%]; $P < .01$). Only 1% of the cohort participated in TAILORx [Trial Assigning Individualized Options for Treatment (Rx)],²⁰ the randomized trial that used GEP testing to guide chemotherapy use; it is unlikely that this substantively influenced the relationship between GEP testing and chemotherapy use.

On multivariable logistic regression analysis (Table 2), patient factors associated with lower odds of GEP testing included African American versus white non-Hispanic race (OR, 0.70; 95% CI, 0.54 to 0.92) and education to high school or less versus beyond high school

(OR, 0.63; 95% CI, 0.52 to 0.76). Cancer characteristics associated with lower odds of GEP testing included HER2 overexpression, lymphovascular invasion, progesterone receptor negativity, and nodal involvement; all suggest a higher risk of recurrence and historically have been associated with an increased likelihood of receiving chemotherapy. GEP testing was less common among community-based versus comprehensive cancer centers (OR, 0.59; 95% CI, 0.48 to 0.72). The rate of GEP testing increased 87%, from 14.7% (95% CI, 13.3% to 16.3%) in 2006 to 27.5% (95% CI, 25.8% to 29.4%) in 2008, and the rate of chemotherapy use decreased 13%, from 53.9% (95% CI, 51.8% to 56.0%) in 2006 to 47.0% (95% CI, 44.9% to 49.0%) in 2008 (Fig 1A). Similar trends were noted even after stratifying by nodal status and center type (Figs 1B and 1C).

Next, we examined the relationship between GEP testing and chemotherapy use for the three clinical risk groups (Table 3). Not surprisingly, testing was most common in the intermediate-clinical-risk group in which guidelines recommend that providers consider testing; chemotherapy use was most common in the high-clinical-risk group in which guidelines recommend chemotherapy (Table 1). The relationship between testing and chemotherapy use was not straightforward. Among patients with low-clinical-risk cancers, those who

Table 2. Predictors of Gene Expression Profile Testing, Multivariable Logistic Regression Analysis

Variable	OR	95% CI	P
Age at diagnosis, years			< .001
< 50	0.88	0.75 to 1.03	
50-59	Ref		
60-69	0.79	0.65 to 0.95	
70+	0.26	0.19 to 0.35	
Race/ethnicity			.018
White non-Hispanic	Ref		
African American non-Hispanic	0.70	0.54 to 0.92	
Other/unknown*	0.86	0.70 to 1.06	
Education			.014
Above high school	Ref		
High school degree or less	0.63	0.52 to 0.76	
Other/unknown†	1.06	0.90 to 1.24	
Health insurance			< .001
Managed care	0.64	0.51 to 0.81	
Indemnity	Ref		
Medicare	0.66	0.49 to 0.89	
Other/unknown‡	0.59	0.43 to 0.80	
Year of diagnosis			< .001
2006	Ref		
2007	1.59	1.34 to 1.88	
2008	2.68	2.27 to 3.18	
Type of cancer center			< .001
Comprehensive	Ref		
Community-based	0.59	0.48 to 0.72	
Size of primary tumor, cm§			< .001
≤ 1	0.32	0.28 to 0.38	
1.1-2	Ref		
≥ 2.1	0.43	0.36 to 0.51	
Unknown	0.14	0.04 to 0.47	
No. of nodes involved			< .001
0	Ref		
1-3	0.11	0.09 to 0.14	
4+	0.03	0.02 to 0.06	
Unknown	0.19	0.08 to 0.43	
Hormone receptor status			< .001
ER positive/PR positive	Ref		
ER positive/PR negative	0.80	0.66 to 0.97	
ER negative/PR positive	0.25	0.12 to 0.54	
ER positive or PR positive/the other unknown	0.55	0.10 to 2.96	
HER2 status			< .001
Not overexpressed	Ref		
Overexpressed	0.20	0.16 to 0.27	
Unknown	0.24	0.10 to 0.56	
Histologic or nuclear grade			.043
Low	Ref		
Intermediate or high	1.15	0.98 to 1.34	
Unknown/missing	0.70	0.43 to 1.14	
Lymphovascular invasion			.019
Absent	Ref		
Present	0.81	0.66 to 0.95	
Unknown/missing	1.46	0.95 to 2.26	
Histologic type			.010
Ductal and/or lobular	Ref		
Other ¶	0.66	0.48 to 0.90	

NOTE. A sensitivity analysis excluding all patients with any missing values yielded similar results, except that race/ethnicity, type of cancer center, histologic/nuclear grade, and lymphovascular invasion were no longer significant predictors.

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; OR, odds ratio; PR, progesterone receptor; Ref, reference group.

*Other race/ethnicity includes Hispanic, African American Hispanic, Asian, American Indian-Aleut, Eskimo, and unclassified. There were 69 patients with unknown race/ethnicity.

†Other/unknown includes 41 patients with unclassified education status and 2,366 with unknown values.

‡Other/unknown includes 556 patients with unclassified health insurance status and 130 with unknown values.

§Size categories based on pathologic data, unless pathologic data were unavailable or patients received neoadjuvant chemotherapy, in which case clinical data were used.

¶Other histology includes tubular, colloid, medullary, adenocystic, and papillary.

Fig 1. (A) Temporal trends in gene expression profile (GEP) testing and chemotherapy use for all patients, (B) stratified by nodal (N) status, and (C) by cancer center type. Patients with hormone receptor-positive stage I to III breast cancer were diagnosed from 2006 to 2008. Mantel-Haenszel χ^2 $P < .001$ for all trends except chemotherapy use at community-based cancer centers ($P = .74$). There were fewer patients from community-based cancer centers in 2006 than in subsequent years because these centers started contributing patients to the data set part way into 2006. Community, community-based cancer center; Comprehensive, comprehensive cancer center.

had GEP testing were more likely to receive chemotherapy. Conversely, among patients with high-clinical-risk cancers, those who had GEP testing were less likely to receive chemotherapy. After controlling for patient characteristics, cancer features, and cancer center type through multivariable modeling, these associations became even more prominent.

Among patients who had GEP testing, multivariable analysis confirmed that, compared with GEP intermediate-risk cancers, GEP high-risk cancers were more likely to receive chemotherapy (OR, 12.0; 95% CI, 6.7 to 21.3), and GEP low-risk cancers were less likely to receive chemotherapy (OR, 0.1; 95% CI, 0.1 to 0.2). Although patients with GEP high-risk cancers usually received chemotherapy and those with GEP low-risk cancers usually did not, there were exceptions: 12% of GEP low-risk cancers received chemotherapy and 12% of GEP high-risk cancers did not. Thus, GEP testing was only one of several factors, including stage, grade, HER2 status, and age, associated with receipt of chemotherapy.

Unlike the validation studies for the 21-gene profile⁴⁻⁶ in which GEP testing was universal, in this analysis, use of the test was selective. Although most GEP tests were performed on patients for whom the NCCN guidelines recommend testing, 20% of tests (303 of 1,505) were performed on patients who fell outside this group because they had low- or high-clinical-risk cancers. GEP high-risk results were less common in our cohort than in the validation studies (10% v 25% to 32%; Fig 2A). This may have occurred in part because patients who had cancers that often yield GEP high-risk results, such as HER2-positive cancers, were less likely to have testing and frequently just received chemotherapy. Regardless, GEP high-risk results were still more common among patients with high- versus low-clinical-risk cancers (Fig 2B).

DISCUSSION

We found that use of GEP testing for breast cancer care was widespread and increased over time. Overall, chemotherapy use decreased as GEP testing increased. Compared with nearly all previous studies exploring temporal trends in adjuvant chemotherapy,²¹⁻²⁵ the downward trend in chemotherapy use described in this more contemporary analysis is unique and suggests a notable change in patterns of care. To the best of our knowledge, few if any large-scale studies have described adoption of genetic/genomic technology for a common medical condition or suggested that its use may be associated with a change in routine practice. In light of the available evidence that adjuvant chemotherapy benefits only a fraction of patients with HR-positive breast cancer and that GEP testing helps predict the degree of chemotherapy benefit, the shift in practice suggested by this study is simultaneously reassuring and remarkable.

Although much of the impetus for the development of this GEP test was to identify women unlikely to benefit from chemotherapy who could forego its inherent risks, we found testing was not uniformly associated with less chemotherapy use. The relationship between testing and chemotherapy use varied depending on clinical risk factors. Among those at high clinical risk of recurrence, testing was associated with lower odds of chemotherapy use, whereas among those at low clinical risk of recurrence, testing was associated with greater odds of chemotherapy use. Interestingly, for those at intermediate clinical risk of recurrence (the group for which the NCCN guidelines actually recommend testing), there was only a modest association between GEP testing and chemotherapy use. In summary, testing was associated not only with a change in the rate of chemotherapy use but also with a change in the type of patients and the type of cancers receiving chemotherapy.

Table 3. GEP Testing and Chemotherapy Use Stratified by Clinical Risk Category

Variable	Clinical Risk Based on Clinical Characteristics (and guideline-recommended therapy)*											
	Low (recommend no chemotherapy)†				Intermediate (consider testing and chemotherapy)‡				High (recommend chemotherapy)§			
	No.	%	OR	95% CI	No.	%	OR	95% CI	No.	%	OR	95% CI
No. of patients	1,111				3,254				2,941			
Proportion who had GEP testing		13.8		11.8 to 15.9		36.8		35.2 to 38.5		5.1		4.3 to 6.0
Proportion who received chemotherapy												
All patients		4.9		3.7 to 6.3		37.1		35.4 to 38.8		82.3		80.9 to 83.6
Stratified by test use¶												
If tested		17.0		11.4 to 23.9		33.5		30.9 to 36.3		45.3		37.2 to 53.7
If not tested		2.9		2.0 to 4.2		39.1		37.0 to 41.3		84.3		82.9 to 85.6
Odds of receiving chemotherapy: tested versus not tested												
Unadjusted			6.80	3.9 to 12.0			0.78	0.68 to 0.91			0.15	0.11 to 0.22
Adjusted			11.13	5.39 to 22.99			0.59	0.49 to 0.71			0.11	0.07 to 0.17

NOTE. Sixty-nine patients (0.9% of the total cohort) could not be classified into a clinical risk group because of missing clinical characteristics (eg, grade or human epidermal growth factor receptor 2 [HER2] status).
Abbreviation: GEP, gene expression profile.
*Consensus and evidence-based recommendations made by the National Comprehensive Cancer Network breast cancer clinical practice guidelines are based on stage and other clinical characteristics.
†No chemotherapy recommended for invasive ductal/lobular cancers if stage T1aN0 or stage T1bN0 without unfavorable features (high nuclear or histologic grade, angiolymphatic invasion, or HER2 overexpression) or for tubular/colloid cancers in which the tumor is < 3 cm and nodes are not involved.
‡Consider testing and chemotherapy for invasive ductal/lobular cancers if stage T1bN0 with unfavorable features or if the tumor is > 1 cm, nodes are not involved, and HER2 is not overexpressed.
§Recommend chemotherapy for tubular/lobular cancers in which the tumor is ≥ 3 cm and for invasive ductal/lobular cancers in which the tumor is > 1 cm, nodes are not involved, and HER2 is positive, or any node-positive cancers.
¶P values for χ^2 test analyzing chemotherapy use among patients who did v did not have GEP testing were < .001 for the no chemotherapy, consider testing and chemotherapy, and recommend chemotherapy groups.
||Multivariable logistic regression model predicting odds of receiving chemotherapy within each stratum, controlling for test use, age, race, education, insurance, employment status, comorbidity, year of diagnosis, type of cancer center, grade, HER2 status, tumor size, and number of involved nodes (recommend chemotherapy group only). Factors consistently associated with lesser odds of receiving chemotherapy across all three strata included age ≥ 50 v < 50 years; education to high school or less v beyond high school; having Medicare v indemnity insurance; having ≥ two comorbid conditions v ≤ one; having a ≤ 1-cm v > 1-cm tumor; and having a low- v high-grade cancer. Of note, there was no significant interaction between GEP testing and year of diagnosis in the model predicting chemotherapy use.

Although the vast majority of GEP tests were performed for intermediate-clinical-risk cancers (the group for which the NCCN recommends testing), 20% were performed in patients for whom the NCCN does not recommend testing. This suggests that providers were sometimes willing to use the test in situations in which consensus and evidence were sparse or lacking (eg, small, low-grade cancers and HER2-positive cancers). Since guidelines and experts provide different recommendations regarding when the test should be used, it is not possible to conclude from these data how much of the observed GEP testing was appropriate versus inappropriate.

Many hope that GEP testing will improve quality of life, optimize outcomes, and reduce cost. There is little reason to expect that it will lead to worse outcomes. However, since this GEP test is only a few years old and the natural history of breast cancer is long, it is too early to assess its true impact on survival in the routine care setting. An ongoing prospective clinical trial²⁶ that randomly determines whether chemotherapy decision making should be based on GEP risk or clinical risk may help address this question. Other clinical trials continue to explore the benefits of chemotherapy for patients with GEP low- or intermediate-risk cancers.^{20,27}

We were not able to assess the association between GEP testing and cost, because charges are not captured in the database used for this analysis. GEP testing is not inexpensive (approximately \$4,175 per test). Early attempts to assess the cost-effectiveness of GEP testing through modeling²⁸⁻³² found that GEP testing was either cost-saving or associated with an acceptable incremental cost-effectiveness ratio,

but these models made assumptions that were inconsistent with the real-world practices we observed (eg, they assumed chemotherapy use for intermediate- to high-risk cancers was universal, whereas we found it was much more selective). A more recent model revealed more equivocal results.³³

The sample for this analysis was relatively large and diverse, but the results may not generalize to all care settings or patient populations. Since our analysis included a large number of institutions representing different geographic areas and practice settings, it is unlikely that any one institution, region, or practice setting biased the results substantially. We endeavored to control for potential confounding when describing predictors of GEP testing, and we used stratified multivariable models that included important covariates (eg, age and tumor size) when characterizing the relationship between GEP testing and chemotherapy. However, unmeasured factors associated with testing and chemotherapy could exist (eg, provider characteristics), so the potential for residual bias cannot be excluded.

Targeting medical therapies to specific patients has been a part of health care for many years. Historically, the rules that guided targeted treatment decisions were relatively straightforward (eg, use of HR status to guide adjuvant breast cancer therapy or use of age and race to guide antihypertensive therapy³⁴). The advent of more sophisticated genetic tests for patients and cancers offers the potential to fine-tune therapeutic decision making to a greater degree.³⁵⁻⁴¹ However, it also introduces new and potentially more complex treatment paradigms

Fig 2. (A) Distribution of gene expression profile (GEP) test results for this study and previously published results and (B) for this study stratified by clinically based risk. Cutoffs for low- (< 18), intermediate- (18-30), and high- (≥ 31) risk GEP test results were previously defined as part of the test development process.⁴⁻⁶ Treatment recommendation groups are based on clinical characteristics, as derived from National Comprehensive Cancer Network (NCCN) clinical practice guidelines. Results from this study include 95% CIs. Three of 1,454 patients with a known GEP result could not be assigned to a clinical risk stratum because of missing pathology data. NSABP, National Surgical Adjuvant Breast and Bowel Project; SWOG, Southwest Oncology Group.

that could translate into increased disparities. Sociodemographic disparities in the use of this GEP test were identified: African American women and those with no more than a high school education were less likely to have GEP testing.

Our findings suggest that GEP testing may be associated with a change in the type of patients who receive chemotherapy and with the

omission of chemotherapy for those unlikely to benefit. The integration of GEP testing into the routine care of patients with breast cancer may represent the early phase of a shift toward a new treatment paradigm in which health care decisions are more personalized. A majority of the more than 207,000 women diagnosed with breast cancer each year in the United States⁴² have nonmetastatic HR-positive disease, so the population for whom these findings could have an impact is substantial. Inconsistency between guidelines for testing and patterns of use argue that there is a lack of consensus regarding the appropriate indications for testing. More work is needed to understand when GEP testing should be used and how GEP results should be combined with clinical characteristics to influence decision making. As health care becomes more complicated, we must remain attentive to the possibility that disparities in the receipt of high-quality care and costs could increase.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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