21-Gene Recurrence Score Assay As a Predictor of Adjuvant Chemotherapy Administration for Early-Stage Breast Cancer: An Analysis of Use, Therapeutic Implications, and Disparity Profile

Jagar Jasem, Arya Amini, Rachel Rabinovitch, Virginia F. Borges, Anthony Elias, Christine M. Fisher, and Peter Kabos

All authors: University of Colorado, Aurora, CO

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Corresponding author: Peter Kabos, MD, University of Colorado, 12801 E 17th Ave, MS 8117, Aurora, CO 80045; e-mail: peter.kabos@ucdenver.edu.

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ABSTRACT

Purpose

The 21-gene Recurrence Score (RS) assay is used to predict disease recurrence and benefit of chemotherapy in estrogen receptor–positive, lymph node–negative early-stage breast cancer (EBC). Our study is the first analysis of trends and differences in the use of the RS assay and its impact on recommending chemotherapy in a population-based data set.

Methods

Patients with EBC diagnosed from 2004 to 2012 and included in the National Cancer Data Base were analyzed. Multivariate logistic regression analysis was used to estimate the covariates associated with use of the test and its impact on chemotherapy decisions.

Results

The RS assay was ordered for 54.0% of the 143,032 identified patients. Of all the variables, RS assay had the strongest association with recommendation for chemotherapy, with an adjusted odds ratio (AOR) of 83 for high assay scores. When indicated, test use was significantly associated with younger age, white race, academic centers, private insurance, and pT2/pN0(i+) grade 2 to 3 disease. Black patients (AOR, 1.31; 95% CI, 1.20 to 1.43) and those treated in community facilities (AOR, 1.49; 95% CI, 1.35 to 1.63) were more likely to be tested outside the National Comprehensive Cancer Network guidelines. Black patients (AOR, 1.51; 95% CI, 1.31 to 1.69) and those with high tumor grade (AOR, 30.76; 95% CI, 26.48 to 35.73) had significantly higher assay scores. Younger black patients (AOR, 1.33; 95% CI, 1.16 to 1.54) were more likely to receive chemotherapy despite low assay scores.

Conclusion

The RS assay significantly influences clinicians' recommendations for chemotherapy in patients with EBC. Black patients tended to have higher assay scores, which may reflect use patterns or less favorable tumor biology for estrogen receptor–positive disease. There are significant differences in use and clinical implications of the test on the basis of race, insurance, and type of facility.

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INTRODUCTION

Chemotherapy was traditionally recommended in the United States and Europe for patients with primary breast cancer with tumor size more than 1 cm regardless of axillary lymph node involvement.¹⁻⁴ However, most patients with estrogen receptor (ER) –positive, lymph node–negative disease did not benefit from the addition of chemotherapy, given less than 20% disease recurrence rates at 10 years for patients treated with local and/or hormonal therapy alone.⁵

The Recurrence Score (RS) test (Oncotype DX; Genomic Health, Redwood City, CA) is a reverse transcriptase polymerase chain reaction–based assay of five reference genes and 16 cancer-related genes associated with cell proliferation, invasion, and hormone response.⁶ It became commercially available in 2004 and uses a continuous scale (from 0 to 100) to predict 10-year cancer recurrence risk and benefit of adjuvant chemotherapy in patients with early-stage ER-positive, lymph node–negative disease.^{5,7} The RS assay can be subdivided into three risk categories:

low risk (score of less than 18), intermediate risk (score from 18 to 30), and high risk (score of 31 or higher). The cutoff points were chosen based on the results of National Surgical Adjuvant Breast and Bowel Project (NSABP) Protocol B20 (A Clinical Trial to Determine the Worth of Chemotherapy and Tamoxifen Over Tamoxifen Alone in the Management of Patients with Primary Invasive Breast Cancer, Negative Axillary Nodes and Estrogen-Receptor-Positive Tumors) trial.^{5,8} The test has been validated through numerous studies⁹⁻¹¹ and is shown to be highly cost-effective by restricting the use of chemotherapy to those patients with the greatest likelihood of benefit.¹²⁻¹⁶

Numerous studies have addressed the impact of the RS assay on clinicians' recommendations for adjuvant chemotherapy in early-stage breast cancer (EBC). Although many smaller, academic-based studies proved such an impact,¹⁵⁻¹⁸ the first nationwide study that involved Medicare beneficiaries in the United States recently showed no change in recommendations for chemotherapy after the adoption of the RS assay.¹⁹ The adoption of the assay was expected to eliminate differences in patient care by providing an evidence-based, objective tool for the clinical decision-making process. However, test results can paradoxically aggravate the differences if the test is differentially ordered or interpreted on the basis of factors such as race, socioeconomic status, and type of facility that delivers care.²⁰ Numerous gaps in knowledge still exist in addressing differences in the use and clinical implications of the test.²¹

Our study aims to provide an analysis of the current trends and differences in the use of the RS assay and its impact on recommendations for chemotherapy by using a large sample of patients with EBC diagnosed between 2004 and 2012.

METHODS

Data Source and Study Population

This study is a retrospective analysis of patients with breast cancer diagnosed between 2004 and 2012 who were included in the National Cancer Data Base (NCDB). Sponsored by the Commission on Cancer of the American College of Surgeons and the American Cancer Society, the NCDB is a nationwide cancer database that captures approximately 70% of all newly diagnosed cancers in the United States from approximately 1,500 hospitals accredited by the Commission on Cancer.²² The data were de-identified, and The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology used or the conclusions drawn from these data by the investigators.

All patients for whom the RS assay was ordered were initially included in the study to determine whether ordering the test was compatible with the original recommendations (Appendix Fig A1, online only). A test was considered to be ordered outside the current recommendations or overused if patients were pT0, pT3, pT4, pM1, ER-negative, pN+ before 2009 onward or human epidermal growth factor receptor 2 (HER2) positive. Ordering the test for node-positive disease from 2009 onward was considered appropriate because the test was used for this category of patients after the results of the Southwest Oncology Group SWOG-8814 (Phase III Comparison of Adjuvant Chemoendocrine Therapy with CAF and Concurrent or Delayed Tamoxifen to Tamoxifen Alone in Postmenopausal Patients with Involved Axillary Lymph Nodes and Positive Receptors [Intergroup]) trial were published.⁹ To check for the factors associated with ordering the test and the effect of ordering the test on the use of adjuvant chemotherapy, those for whom the test was ordered and

who had pT1, pT2, N0, ER-positive, and HER2-negative disease were later selected and compared with those for whom the test was not ordered but who did have corresponding disease status. The RS assay results were classified into low risk (less than 18), intermediate risk (18 to 30), and high risk (31 and above).⁵ Cancer centers were divided according to the National Cancer Institute classification into community cancer centers that assess more than 100 but fewer than 500 newly diagnosed cancer cases each year, comprehensive community centers that assess 500 or more newly diagnosed cancer cases each year, and academic centers that are similar to other two types of centers but also provide postgraduate medical education in at least four program areas, including internal medicine and general surgery.^{23,24}

Statistical Analysis

Multivariate binary logistic regression analysis was used to calculate the adjusted odds ratios (AORs), 95% CIs, and *P* values for the association of selected covariates (age, race, sex, type of facility, insurance status, and tumor grade) with the outcome variable of being tested outside the National Comprehensive Cancer Network (NCCN) recommendations. A similar analysis was performed to determine the differences between those who had the test and those who did not on the basis of selected covariates (age, race, sex, type of facility, insurance status, year of diagnosis, tumor grade, tumor size, and pN0(i+) disease), as well as the odds of receiving chemotherapy for each group. RS was added to the latter regression model as a categorical variable.

The covariates were selected on the basis of clinical significance (age, tumor grade, tumor size, and pN0(i+) disease) and relevance to potential areas of differential test utility or implications (sex, race, type of facility, year of diagnosis, and insurance status).

To check for differences in the trends of adjuvant chemotherapy use across different RS assay results for age and the presence of isolated tumor cells on lymph node pathology, the test score was plotted as a continuous variable against the mean predictive probability of using adjuvant chemotherapy for each of the aforementioned variables as obtained from multiple regression analysis (Figs 1 and 2). Both age and the presence of isolated tumor cells on lymph node pathology (pN0(i)) were used as categorical variables.

The Hosmer-Lemeshow test was used to check for the goodness of fit of the regression models. All analyses were performed by using SPSS 18 for Windows/MAC (PASW Statistics GradPack 18; SPSS, Chicago, IL). All tests were two-sided with a 0.05 level of significance.

RESULTS

Use of the RS Assay Test

Of 143,032 patients with ER-positive/HER2-negative early-stage breast cancer included in the study (Appendix Fig A1), the RS assay test was ordered for 77,308 patients (54.0%). Table 1 shows the differences between those for whom the test was ordered and those for whom the test was not ordered. Significantly lower adjusted odds of having the test when indicated were observed for older ages (AOR, 0.42; 95% CI, 0.40 to 0.44), black race (AOR, 0.79; 95% CI, 0.76 to 0.83) and other nonwhite races (AOR, 0.86; 95% CI, 0.81 to 0.92), and those who have governmental health insurance compared with those who have private health insurance (AOR, 0.74; 95% CI, 0.72 to 0.77). Higher odds of ordering the test were observed for academic centers (AOR, 1.25; 95% CI, 1.19 to 1.30), larger tumor size (AOR, 1.36; 95% CI, 1.32 to 1.41), high tumor grade, and pN0(i+) disease (AOR, 1.31; 95% CI, 1.23 to 1.40). Higher trends of ordering the test were observed in the later years of the study.

Fig 1. Age differences in the predictive probability of being given chemotherapy on the basis of the score for the Recurrence Score (RS) assay. Error bars represent 95% CIs.

Overuse of the RS Assay Test

Of those for whom the RS assay test was ordered, 6,337 (8.1%) had it ordered outside the original NCCN recommended guidelines (ie, they had an ER-negative/HER2-positive tumor; tumor size > 5 cm; ductal carcinoma in situ; node-positive disease before 2009; or metastatic disease). The odds of having the test ordered despite those characteristics were higher for younger age

(AOR, 1.33; 95% CI, 1.20 to 1.49), black race (AOR, 1.3; 95% CI, 1.20 to 1.43), community facilities (AOR, 1.49; 95% CI, 1.35 to 1.63), higher tumor grade (AOR, 3.12; 95% CI, 2.89 to 3.38), and male sex (AOR, 1.42; 95% CI, 1.11 to 1.81). Slightly higher odds were also observed for beneficiaries of governmental health insurance compared with those who have private health insurance (Table 2).

Fig 2. The predictive probability of being given chemotherapy based on the score for the Recurrence Score (RS) assay test and the presence of isolated tumor cells on pathology. Error bars represent 95% CIs.

Table 1. Adjusted ORs of Ordering the RS Assay Test for ER-Positive, HER2-Negative, pN0, and pT1-2 Disease Based on Selected Variables

Variable	Test Ordered				Crude OR	95% CI	P	AOR	95% CI	P
	Yes		No							
	No.	%	No.	%						
Age, years										
< 45	5,740	57.7	4,205	42.3	1			1		
45-64	33,777	55.5	27,040	44.5	0.91	0.87 to 0.95	< .001	0.95	0.91 to 1.00	.05
65+	15,887	31.5	34,479	68.5	0.33	0.32 to 0.35	< .001	0.42	0.40 to 0.44	< .001
Sex										
Male	423	41.8	588	58.2	1			1		
Female	54,981	45.8	65,136	54.2	1.17	1.030 to 1.33	.01	1.14	1.00 to 1.30	.05
Race										
White	48,505	45.9	57,113	54.1	1			1		
Black	4,157	43.0	5,512	57.0	0.88	0.85 to 0.92	< .001	0.79	0.76 to 0.83	< .001
Other	2,227	46.9	2,518	53.1	1.04	0.98 to 1.10	.17	0.86	0.81 to 0.92	< .001
Unknown	515	47.0	581	53.0	1.04	0.92 to 1.17	.48	0.96	0.85 to 1.09	.60
Year of diagnosis										
2010 or earlier	15,476	41.6	21,767	58.4	1			1		
2011	19,113	46.5	22,006	53.5	1.22	1.18 to 1.25	< .001	1.24	1.20 to 1.28	< .001
2012	20,815	48.7	21,951	51.3	1.33	1.29 to 1.37	< .001	1.38	1.34 to 1.42	< .001
Type of facility										
Community	5,469	41.2	7,810	58.8	1			1		
Comprehensive community	32,065	44.6	39,764	55.4	1.15	1.10 to 1.19	< .001	1.09	1.05 to 1.13	< .001
Academic	17,772	49.6	18,035	50.4	1.40	1.35 to 1.46	< .001	1.25	1.19 to 1.30	< .001
Insurance										
Private	35,976	54.9	29,577	45.1	1			1		
Governmental	18,037	34.4	34,460	65.6	0.43	0.42 to 0.44	< .001	0.74	0.72 to 0.77	< .001
Grade										
1	15,786	38.6	25,059	61.4	1			1		
2	28,550	49.8	28,733	50.2	1.57	1.53 to 1.61	< .001	1.55	1.51 to 1.59	< .001
3	8,488	49.8	8,552	50.2	1.57	1.52 to 1.63	< .001	1.39	1.34 to 1.45	< .001
Unknown	2,580	43.3	3,380	56.7	1.21	1.14 to 1.28	< .001	1.16	1.09 to 1.22	< .001
Tumor size										
pT1	43,150	44.1	54,785	55.9	1			1		
pT2	12,254	52.8	10,939	47.2	1.42	1.38 to 1.46	< .001	1.36	1.32 to 1.41	< .001
Isolated tumor cells in nodes										
pN0(i-)	53,057	45.4	63,822	54.6	1			1		
pN0(i+)	2,347	55.2	1,902	44.8	1.48	1.39 to 1.57	< .001	1.31	1.23 to 1.40	< .001

Abbreviations: AOR, adjusted odds ratio; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; OR, odds ratio; RS, recurrence score.

Use of Adjuvant Chemotherapy

Table 3 demonstrates the odds of receiving chemotherapy for patients for whom the RS test was ordered and for those for whom the RS test was not ordered. The group for which the RS test was not ordered served as a control for estimating the pattern of chemotherapy use independent from the test score. For this particular group, the odds of receiving chemotherapy were higher for younger ages, black race, community facilities, larger tumor size, higher tumor grade, and pN0(i+) disease. Similar patterns of chemotherapy receipt were observed for the group that was given the RS test. There was an additional difference between patients with private health insurance and those with governmental health insurance, with the latter group being less likely to receive chemotherapy. The RS assay test score had the highest adjusted odds of using chemotherapy, with AOR as high as 12.00 (95% CI, 11.38 to 12.65) for intermediate scores and 83.07 (95% CI, 74.25 to 92.94) for high scores. The use of the RS assay did not eliminate the overall racial differences noted for the group that did not have the test. Younger black patients were more likely to receive chemotherapy despite a low score (AOR, 1.33; 95% CI, 1.16 to 1.54; data not shown).

As evident from Figures 1 and 2, the use of chemotherapy increased with increased test scores, with significantly higher trends for younger ages and the presence of isolated tumor cells on lymph node pathology; those differences were eliminated at higher test scores.

Factors Associated With High RS Test Scores

High RS scores (31 and above) were independently noted for black patients (AOR, 1.51; 95% CI, 1.31 to 1.69), grade 2 to 3 tumors (grade 3: AOR, 30.76; 95% CI, 26.48 to 35.73), and larger tumor size (AOR, 1.43; 95% CI, 1.33 to 1.54; Table 4).

DISCUSSION

To the best of our knowledge, our study is the first analysis of the use of, therapeutic implications of, and disparity profile for the RS assay in patients with EBC registered in a national cancer data base. Our study revealed that the RS assay is an important predictor of the use of adjuvant chemotherapy in EBC, as evidenced by AORs as

Table 2. AORs of Ordering the RS Test Outside the Current Guidelines Based on Selected Characteristics

Table 2. AORs of Ordering the No Test Outside the Current Guidelines Based on Selected Characteristics							
Variable	Test Ordered Outside Recommendations				AOR	95% CI	P
	Yes (n = 6,337)		No (n = 70,971)*				
Age, years							
< 45	889	10.9	7,238	89.1	1		
45-64	3,444	7.5	42,670	92.5	0.70	0.65 to 0.76	< .001
65+	2,004	8.7	21,063	91.3	0.75	0.67 to 0.83	< .001
Sex							
Male	82	12.1	593	87.9	1		
Female	6,255	8.2	70,378	91.8	0.70	0.55 to 0.90	.005
Race							
White	5,351	7.9	62,033	92.1	1		
Black	668	10.9	5,449	89.1	1.31	1.20 to 1.43	< .001
Other	265	8.6	2,825	91.4	1.04	0.91 to 1.19	.49
Unknown	53	67.4	664	92.6	1.00	0.75 to 1.33	.97
Type of facility							
Community	817	10.4	7,038	89.6	1		
Comprehensive community	3,658	8.2	41,166	91.8	0.77	0.71 to 0.83	< .001
Academic	1,851	7.6	22,630	92.4	0.67	0.61 to 0.74	< .001
Other	11	7.4	137	92.6	0.71	0.38 to 1.33	.29
Insurance							
Private	3,829	7.8	45,289	92.2	1		
Governmental	2,319	8.9	23,818	91.1	1.10	1.03 to 1.19	.006
Grade							
1	1,121	5.3	19,907	94.7	1		
2	2,848	7.2	36,874	92.8	1.34	1.265 to 1.45	< .001
3	1,978	15.3	10,923	84.7	3.12	2.89 to 3.38	< .001
Unknown	390	10.7	3,267	89.3	2.09	1.84 to 2.36	< .001

Abbreviations: AOR, adjusted odds ratio; RS, recurrence score.

*Those with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, lymph node-positive disease from 2009 onward were considered to be appropriate for testing (n = 15,567) and were added to the pool of patients with ER-positive, HER2-negative, T1-2, and lymph node-negative disease (see Methods).

high as 12 for intermediate scores and 83 for high scores. This is comparable with the results of other smaller and mostly academic-based studies conducted in the United States, Germany, Japan, Australia, Spain, and Israel.^{15-18,25,26} Conversely, a recent study of a large sample of patients with early-stage ER-positive breast cancer included in the SEER Medicare database in the United States revealed no change in the use of chemotherapy in the overall study population after the adoption of the RS assay.¹⁹ However, the study included only patients older than age 65 years with Medicare insurance and did not account for the actual test results (low, intermediate, and high). It is noteworthy that in our study, patients with higher tumor grades had significantly higher test scores, with AORs as high as 30 for those with grade 3 tumors. Likewise, higher scores were found for patients with larger tumor size. These findings likely reflect the difference in tumor biology implicated in score for the RS assay. Similar findings were seen in at least two other smaller studies.^{27,28}

For the untested population, the odds of receiving chemotherapy were significantly higher for patients who were younger, had larger tumor size, and had higher tumor grades. Although still higher for patients with larger tumor size and higher tumor grades, receipt of chemotherapy did decrease after adopting the RS assay. An opposite trend was found for age: older patients were more likely to receive chemotherapy after testing was adopted, which shows that both patients and clinicians were giving weight to tumor biology. Similar findings for patients who were tested were observed in a retrospective observational cohort study that used the

electronic health record system of McKesson Specialty Health and The US Oncology Network for patients diagnosed between 2008 and 2009.² Patients with larger tumor size had higher odds of getting tested. Likewise, younger patients and those with higher tumor grades were more likely to be tested, both appropriately and inappropriately (ie, outside the original NCCN recommendations).

To the best of our knowledge, this is the first study that accounts for the effect of pN0(i+) in clinicians' decisions about ordering the RS assay and recommending chemotherapy. Patients with N0(i+) were independently more likely to be tested. Although patients with N0(i+) disease were still significantly more likely to be given adjuvant chemotherapy compared with patients who had N0(i-) disease, patients with N0(i+) disease were less likely to be given chemotherapy if they were tested with the RS assay compared with those who were not tested. The findings regarding tumor size, tumor grade, and node invasion further indicate that the RS assay is more likely than any other factor to drive decision making for adjuvant chemotherapy and that it reduced the overall use of chemotherapy in patients with early-stage ER-positive/HER2-negative breast cancer.

Numerous studies have shown racial disparities in the incidence, treatment, and outcomes in patients with breast cancer.^{20,29-32} Although black women are less likely to get breast cancer, they are more likely to die of the disease.^{29,33} Previous studies showed that black women are more likely to have ER-negative/progesterone-negative/HER2-negative (triple-negative) tumors, indicating less favorable tumor biology. Nevertheless,

Table 3. AORs of Chemotherapy Based on Selected Patient Characteristics of Those for Whom the RS Assay Was Ordered and Those for Whom the RS Assay Was Not Ordered

Variable	RS Assay Ordered (group A)			RS Assay Not Ordered (group B)		
	AOR	95% CI	P	AOR	95% CI	P
Score for RS assay						
Low	1			—		—
Intermediate	12.00	11.38 to 12.65	< .001	—		—
High	83.07	74.25 to 92.94	< .001	—		—
Age, years						
< 45	1			1		
45-64	0.45	0.40 to 0.51	< .001	0.31	0.29 to 0.34	< .001
65+	0.23	0.21 to 0.25	< .001	0.08	0.07 to 0.09	< .001
Sex						
Male	1			1		
Female	1.23	0.92 to 1.65	.15	0.79	0.63 to 0.98	.03
Race						
White	1			1		
Black	1.13	1.03 to 1.23	.007	1.29	1.21 to 1.38	< .001
Other	1.15	1.02 to 1.30	.01	0.90	0.71 to 1.14	.39
Unknown	0.73	0.56 to 1.97	.03	0.89	0.69 to 1.18	.42
Year of diagnosis						
2010 or earlier	1			1		
2011	0.66	0.54 to 0.80	< .001	0.95	0.90 to 1.00	.10
2012	0.53	0.44 to 0.65	< .001	0.84	0.79 to 0.88	< .001
Type of facility						
Community	1			1		
Comprehensive community	0.90	0.82 to 0.98	.01	0.96	0.90 to 1.03	.33
Academic	0.91	0.83 to 1.00	.05	0.87	0.80 to 0.94	.001
Other	1.33	0.77 to 2.27	.29	1.77	1.11 to 2.83	.01
Insurance						
Private	1			1		
Governmental	0.88	0.82 to 0.94	< .002	0.94	0.88 to 1.04	.28
Tumor size						
pT1	1			1		
pT2	1.80	1.70 to 1.90	< .001	6.22	5.91 to 6.53	< .001
Grade						
1	1			1		
2	1.63	1.54 to 1.74	< .001	2.45	2.31 to 2.60	< .001
3	3.06	2.83 to 3.31	< .001	9.12	8.50 to 9.78	< .001
Unknown	1.58	1.40 to 1.79	< .001	2.17	1.98 to 2.46	< .001
Isolated tumor cells in nodes						
pN0(i-)	1			1		1
pN0(i+)	1.49	1.33 to 1.67	< .001	2.28	2.05 to 2.46	< .001

Abbreviations: AOR, adjusted odds ratio; RS, recurrence score.

disparities in survival seem to persist for ER-positive patients despite similar demographic characteristics, cancer stages, and treatment modalities.^{30,32} Our study revealed that black patients with ER-positive disease are 1.5 times more likely to have higher scores after RS testing, even when the scores are adjusted for age, tumor size, and tumor grade, a finding compatible with our 2012 study²⁷ that entailed a retrospective analysis of tumor registry data from three Atlanta hospitals from 2005 through 2009. This may represent a difference in tumor behavior for black women with ER-positive breast cancer that at least partially contributes to their observed higher mortality. Studies that examined racial differences in receiving breast cancer therapy often have conflicting results.^{20,27,31} However, most of these studies targeted smaller populations and all stages of breast cancer rather than early-stage disease only. Our study²⁷ revealed that minority patients are significantly less likely to be tested despite meeting the criteria for testing, and that black women are significantly more likely to be

tested outside the recommended guidelines. The data suggest that testing guidelines do not seem to be applied equally to different racial groups in the United States. Our study also revealed that black patients are more likely to receive chemotherapy regardless of whether they were tested with the RS assay. This may indicate that the test did not change the overall impact of race on receiving chemotherapy. However, the differences among races in receiving chemotherapy were significant for low test scores and younger age, and they disappeared with older age and higher test scores, indicating that the former group receives chemotherapy despite their low scores on the RS assay.

Insurance status varies by the socioeconomic status of the insurance holders and is a measure of health care accessibility, affordability, and use.³⁴ Only 1% of our study population was uninsured; thus, the analysis exclusively compared those with private and governmental insurance. When adjusted for factors such as score on the RS assay, age, tumor grade, tumor size, and the

Table 4. Characteristics Associated With Higher RS Assay Results

Table 2. Characteristics Associated With Higher RS Assay Results							
Variable	RS Assay Results				AOR	95% CI	P
	Low/ Intermediate		High				
	No.	%	No.	%			
Age, years							
< 45	5,243	91.3	497	8.7	1		
45-64	31,369	92.9	2,408	7.1	0.93	0.83 to 1.03	.20
65+	14,629	92.1	1,258	7.5	0.97	0.86 to 1.09	.69
Race							
White	4,492	92.8	3,513	7.2	1		
Black	3,715	89.4	442	10.6	1.51	1.31 to 1.69	.001
Other	2,058	92.4	169	7.6	0.93	0.78 to 1.10	.42
Grade							
1	15,592	98.8	194	1.2	1		
2	27,195	95.3	1,355	4.7	3.87	3.32 to 4.50	< .001
3	6,019	70.9	2,469	29.1	30.76	26.48 to 35.73	< .001
Unknown	2,435	94.4	145	5.6	4.62	3.71 to 5.76	< .001
Tumor size							
pT1	40,409	93.6	2,741	6.4	1		
pT2	10,832	88.4	1,422	11.6	1.43	1.33 to 1.54	< .001

Abbreviations: AOR, adjusted odds ratio; RS, recurrence score.

Abbreviations: AOR, adjusted odds ratio; RS, recurrence score.

presence of isolated tumor cells in lymph nodes, the trend for use of chemotherapy was lower in the population with governmental insurance. Likewise, those with governmental insurance were less likely to be tested when testing was indicated.

An overwhelming majority of previous studies involved either academic^{16,18,35-37} or community facilities.³⁸⁻⁴⁰ A recent meta-analysis of 23 studies revealed that 74% were conducted in academic centers, and the rest were conducted in either community hospitals or mixed community and academic centers, but none compared RS assay trends across facilities.²¹ Our study revealed differences between community facilities and comprehensive community and academic facilities. Patients treated at community facilities were significantly more likely to be tested when testing was not indicated, less likely to be tested when testing was otherwise indicated, and more likely to receive adjuvant chemotherapy regardless of whether they were tested or not.

It should be noted that these differences in the use and clinical implications of the RS assay do not necessarily reflect biases in the clinicians' decision-making process but may instead reflect

differences in patient preferences and the estimated biologic aggressiveness of the disease.

Our study has certain limitations. Given that the RS assay is a relatively new test, it is susceptible to coding errors. Information about the test may be under-reported or erroneously reported. Despite the fact that NCDB covers about two thirds of all newly diagnosed cancers, it has been shown that NCDB coverage is lower for elderly patients, Hispanics, Alaskan natives, and American Indians.²² Moreover, race is self-reported by patients and is susceptible to reporting errors. This study did not include information on patients tested after 2012 because of a lag in the availability of NCDB data. Factors associated with the use and overuse of the test may be different after 2012 owing to a presumably wider availability, better accessibility, and higher adoption rates of the test by oncologists. Finally, the lower representation of uninsured patients may limit the generalizability of the study to that selected population of patients with breast cancer.

In conclusion, our study revealed that using the RS assay test affected clinicians' decisions regarding recommending adjuvant chemotherapy more than other variables studied, with overall lower use of chemotherapy for patients with lower scores as intended from the RS test. Furthermore, significant differences exist in the use of the test and receipt of chemotherapy on the basis of race, insurance status, and type of facility.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: Jagar Jasem, Arya Amini, Rachel Rabinovitch, Anthony Elias, Christine M. Fisher, Peter Kabos

Collection and assembly of data: Jagar Jasem, Arya Amini, Peter Kabos

Data analysis and interpretation: Jagar Jasem, Arya Amini, Virginia F. Borges, Christine Fisher, Peter Kabos

Manuscript writing: All authors

Final approval of manuscript: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

21-Gene Recurrence Score Assay As a Predictor of Adjuvant Chemotherapy Administration for Early-Stage Breast Cancer: An Analysis of Use, Therapeutic Implications, and Disparity Profile

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Appendix

Fig A1. CONSORT diagram. All patients with breast cancer diagnosed from 2004 to 2012 for whom the Recurrence Score (RS) assay was ordered were selected and were divided into three categories. A cohort of controls was later selected that met the original National Comprehensive Cancer Network recommendations for RS assay testing but they were not tested; they were compared with those who were tested who had corresponding disease characteristics. ER, estrogen receptor; HER2, human epidermal growth factor receptor 2.