Original Article

Associations Between Use of the 21-Gene Recurrence Score Assay and Chemotherapy Regimen Selection in a Statewide Registry

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BACKGROUND: The 21-gene recurrence score (RS) assay predicts response to adjuvant chemotherapy in patients with early-stage, hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative invasive breast cancer, but to the authors' knowledge, the role of the assay in guiding the selection of chemotherapy regimen has not been established. The current study was conducted to examine patterns of use of the RS assay for selecting chemotherapy regimens across a statewide registry from 2006 through 2013. **METHODS:** Demographic, pathologic, and treatment data were abstracted from medical records for 16,666 women with breast cancer who were treated at 25 hospital systems across Michigan that were participating in the Michigan Breast Oncology Quality Initiative. Treatment patterns were examined based on the RS assay test result. **RESULTS:** Approximately 25% of patients with lymph node-negative disease who underwent testing with the RS assay and who were treated with chemotherapy received an anthracycline-based regimen, compared with 49% of patients with lymph node-negative disease who were treated with chemotherapy and who had not undergone testing with the RS assay. Of those patients with lymph node-positive disease who underwent testing with the RS assay and who received chemotherapy, 31% received an anthracycline-based regimen. In comparison, 71% of patients with lymph node-positive, chemotherapy-treated disease who did not undergo testing received an anthracycline. From 2006 through 2013, there was a statistically significant decrease in the use of anthracycline-containing regimens in both patients with lymph node-negative and lymph node-positive disease. **CONCLUSIONS:** Use of anthracycline-containing chemotherapy regimens in eligible patients appears to vary with use of the RS assay, despite the lack of evidence supporting use of the assay to guide regimen selection. Results of ongoing prospective trials should help to define the role of the RS assay in this setting. *Cancer* **2017;123:948-56.** © *2016 American Cancer Society.*

KEYWORDS: 21-gene recurrence score, anthracycline, breast cancer, chemotherapy, treatment regimen.

INTRODUCTION

The 21-gene recurrence score (RS) assay is a multiparameter gene expression profile test originally designed to identify patients with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-), lymph node-negative breast cancer who are unlikely to benefit from the addition of chemotherapy to endocrine therapy.[1] Data supporting the use of the RS assay in this patient population for the prediction of response to chemotherapy were published in 2006.[2] Patients with a low RS (0-17) did not appear to benefit from the addition of adjuvant chemotherapy to endocrine therapy, whereas those with a high RS (31-100) did benefit from both chemotherapy and endocrine therapy. To the best of our knowledge, the benefit of adding chemotherapy for those with an intermediate RS (18-30) remains uncertain.[3]

As a result of these initial reports, guidelines from multiple organizations, including the American Society of Clinical Oncology and the National Comprehensive Cancer Network (NCCN) now recommend the use of this assay for making decisions regarding whether to administer adjuvant chemotherapy to women with HR+, HER2-, lymph node-negative

breast cancer.[4,5] Multiple studies have demonstrated increased use of the assay over time, with a concomitant decline in the use of adjuvant chemotherapy.[6-8] In addition, a recent analysis of patients with invasive breast cancer with an RS between 0 and 10 who were treated with endocrine therapy alone demonstrated excellent long-term outcomes, with a rate of invasive disease-free survival at 5 years of 93.8% and a rate of freedom from disease recurrence at 5 years of 98.7%.[3]

As a result of the high level of evidence supporting the use of the RS assay in patients with lymph node-negative disease, subsequent studies have been conducted to determine whether the assay would be similarly useful for making decisions regarding the use of adjuvant chemotherapy in patients with breast cancer with lymph node involvement. Retrospective-prospective analyses evaluating the use of the RS assay for this population demonstrated that, although patients with lymph node involvement had a higher risk of disease recurrence compared with those without lymph node involvement, patients whose tumors had a low RS obtained minimal benefit, and those whose tumors had a high RS obtained substantial benefit from adjuvant chemotherapy.[9,10] A recently reported prospective trial of patients with 1 to 3 positive lymph nodes and an RS <12 who were treated with endocrine therapy alone demonstrated a 3-year disease-free survival rate of 97.9%.[11] Based on the retrospective-prospective data described above, the Centers for Medicare and Medicaid Services authorized coverage for testing tumors from patients with 1 to 3 involved lymph nodes, and since 2015 the NCCN guidelines have recommended the consideration of testing among patients with up to 3 involved lymph nodes.[12] In contrast, recently updated American Society of Clinical Oncology guidelines do not recommend testing for treatment decision making in this patient population.[5]

Since 2006, the Michigan Breast Oncology Quality Initiative (MiBOQI) has prospectively collected data regarding patient and pathologic characteristics, diagnostic tests performed, and treatments administered for women with newly diagnosed breast cancer at its 25 member hospital systems across the state of Michigan. Using data from this registry, we investigated changes in the pattern of use of the RS assay over time in patients with lymph node-negative and lymph node-positive disease and associations between RS assay results and chemotherapy administration in multiple patient cohorts. The primary objective of the current study was to examine the association between the RS assay result and the selection of anthracycline-containing versus non-anthracycline-containing regimens.

MATERIALS AND METHODS

Analyzed Cohort
Women with newly diagnosed breast cancer who were diagnosed between 2006 and 2013 and treated at 1 of the 25 hospitals participating in the MiBOQI were included in the current analysis. Because the purpose of the MiBOQI is to conduct quality initiatives, it has been granted an exemption by the University of Michigan Institutional Review Board. Demographic, pathologic, and treatment characteristics were abstracted from the medical records. Determination of socioeconomic status was estimated based on each patient's place of residence using data from the 2010 US Census. Patients with noninvasive breast cancer, those who were found to have distant metastases within 90 days of diagnosis, those treated with neoadjuvant chemotherapy, and those with bilateral breast cancer or a prior history of breast cancer were excluded.

Appropriateness Criteria for 21-Gene RS Assay Testing
Appropriateness for testing with the 21-gene RS assay was based on the NCCN breast cancer guidelines from 2010.[5] The NCCN concordant cohort was defined as patients with HR+, HER2- breast cancer measuring > 1 cm or measuring 6 to 10 mm in size with additional high-risk features, including either grade 2 or 3 tumors or evidence of angiolymphatic invasion, with either no evidence of lymph node metastases or only micrometastatic lymph node involvement. Tumors measuring ≤ 5 mm and those with tubular or mucinous histology were considered inappropriate for testing (nonconcordant).

21-Gene RS Assay Testing for the Lymph Node-Positive Cohort
Patients in the analyzed cohort who had HR+, HER2-negative breast cancer and macrometastatic involvement of at least 1 lymph node were included in the analysis of the lymph node-positive cohort. Participants in steps 1 or 2 of the Southwest Oncology Group (SWOG) S1007 clinical trial, in which enrolled patients' tumors were tested with the RS assay (step 1) and then randomized to adjuvant chemotherapy plus endocrine therapy versus endocrine therapy alone (step 2), were excluded from the analysis.

Statistical Analysis

All data were analyzed using the R statistical package (version 3.2.3; R Foundation, Vienna, Austria). All patient characteristics were summarized as percentages, and the statistical significance of variations in testing rates by patient characteristics was assessed using univariate and multivariate logistic regression. Statistical significance was defined as a P value $< .05$.

RESULTS

Use of RS Assay Results: Lymph-Node Negative Cohort

Over time, rates of chemotherapy administration to patients with both lymph node-negative and micrometastatic lymph node-positive disease in the NCCN concordant cohort decreased, from 39 of 116 patients (34%) and 6 of 6 patients (100%), respectively, in 2006 to 180 of 1013 patients (18%) and 25 of 74 patients (34%), respectively, in 2013 ($P<.001$ for both groups) (see Supporting Information Fig. 1). Chemotherapy use decreased over time in patients with lymph node-negative and micrometastatic lymph node-positive disease who underwent testing with the RS assay ($P<.001$ and $P = .001$, respectively), but not in those who were not tested (Figs. 1A and 1B). Although the percentage of patients treated with chemotherapy decreased overall, receipt of chemotherapy was found to be greater with increasing RS in the lymph node-negative cohort ($P<.001$) (Figs. 2A and 3A).

Of the 3911 patients in the lymph node-negative cohort who underwent testing with the RS assay from 2006 through 2013, 923 (24%) were treated with chemotherapy. Approximately 6% of patients with a low RS were treated with chemotherapy compared with 46% of those with an intermediate RS and 90% of those with a high RS ($P<.001$) (Fig. 2A). In those patients with a low RS, receipt of chemotherapy decreased from 2006 to 2013 ($P<.001$) (see Supporting Information Fig. 2). Among the 923 patients treated with chemotherapy, 232 (25%) received an anthracycline-based regimen (Fig. 2A) (see Supporting Information Fig. 3A). In comparison, of the 787 patients treated with chemotherapy in the lymph node-negative cohort who did not undergo testing, 49% received an anthracycline-based regimen. From 2006 to 2013, there was a statistically significant decrease in the use of anthracycline-containing regimens (Fig. 1A).

On univariate analysis, anthracycline use in those patients who were tested with the RS assay and received chemotherapy was associated with younger age, earlier year of diagnosis, higher tumor grade, and higher RS (Table 1) (see Supporting Information Fig. 3A). There
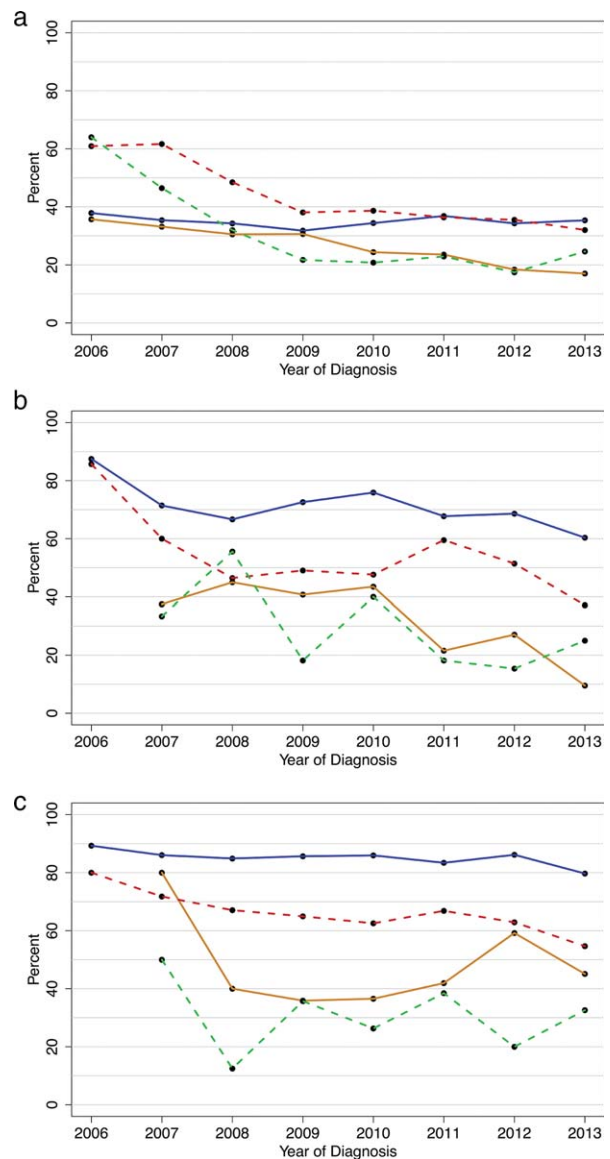
Figure 1. Percentage of patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative breast cancer who received treatment with any chemotherapy, over time, by 21-gene recurrence score assay testing (orange indicates tested; blue, not tested) and the percentage of patients treated with chemotherapy who received an anthracycline-based regimen, over time, by 21-gene recurrence score assay testing (dashed green line indicates tested; red dashed line, not tested) are shown for (A) patients with lymph node-negative disease, (B) patients with micrometastatic lymph node disease, and (C) patients with macrometastatic lymph node disease.

was a trend toward an association with lower socioeconomic status. No associations were identified with race, comorbidity, tumor size, or the presence of micrometastatic lymph node disease.
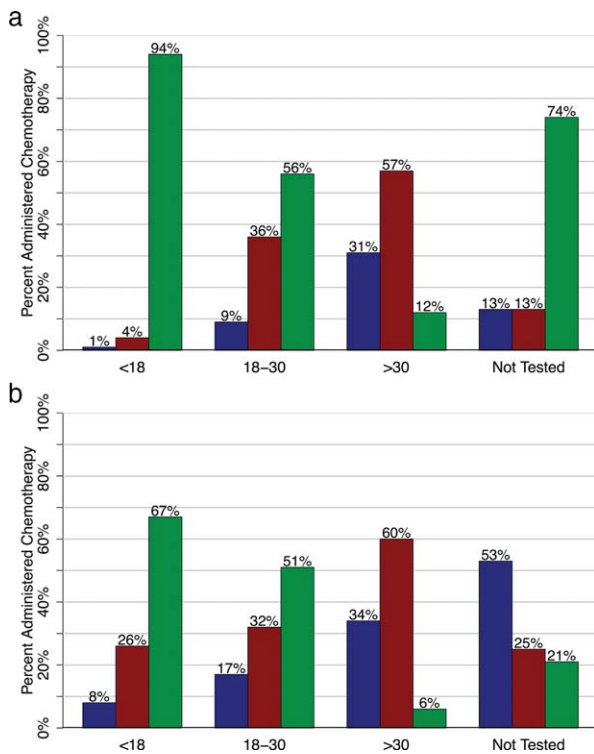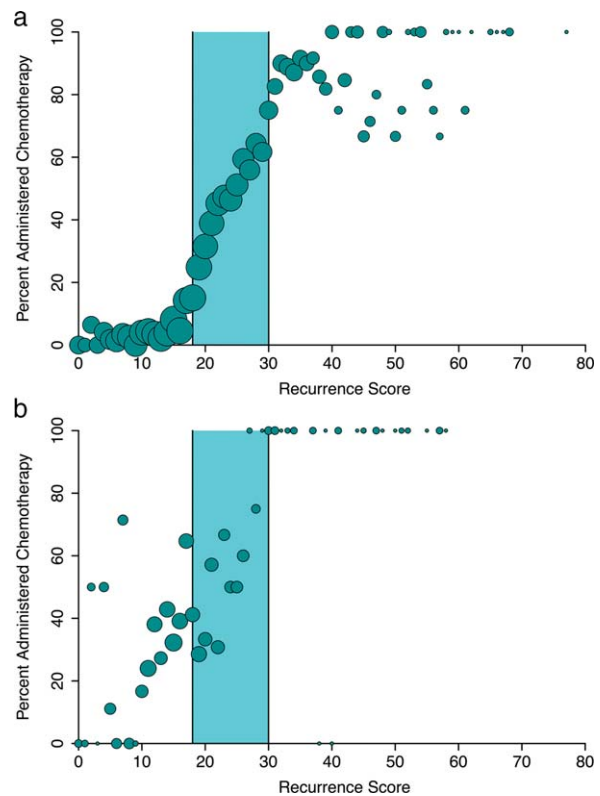
Figure 2. Percentage of patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative breast cancer who were treated with anthracycline-based (blue), non-anthracycline-based (red), and no chemotherapy (green) regimens by recurrence score (<18, 18-30, >30, and not tested) in (A) the lymph node-negative cohort and (B) patients with 1 to 3 positive lymph nodes.

Figure 3. Bubble plot demonstrating receipt of chemotherapy by recurrence score for patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative breast cancer. Each circle represents the average percentage of patients treated with chemotherapy for each recurrence score, and the size of each circle represents the number of patients with each recurrence score in (A) the lymph node-negative cohort and (B) the lymph node-positive cohort.

Similarly, of those patients who received chemotherapy and did not undergo testing with the RS assay, anthracycline use was associated with younger age and earlier year of diagnosis. In addition, anthracycline use was associated with larger tumor size, but not tumor grade. No associations were identified with race, comorbidity, or the presence of micrometastatic lymph node disease.

Use of RS Assay Results: Lymph Node-Positive Cohort

In patients with HR+, HER2- disease and macrometastatic lymph node involvement, testing with the RS assay was associated with decreased receipt of adjuvant chemotherapy compared with no testing (Fig. 1C) (see Supporting Information Fig. 4). Of the 392 patients who underwent testing with the RS assay, 165 (42%) were treated with chemotherapy, and 31% of those patients received an anthracycline-based chemotherapy regimen (see Supporting Information Figs. 3B and 4). Chemotherapy use was found to increase with increasing RS (Fig. 3B). In contrast, of the 1772 chemotherapy-treated patients with

HR+, HER2-, lymph node-positive disease who did not undergo testing, 71% received an anthracycline-based regimen. From 2006 to 2013, there was a statistically significant decrease in the use of anthracycline-containing regimens in patients with lymph node-positive disease (Fig. 1C).

Examination of the cohort with 1 to 3 involved lymph nodes indicated that treatment with chemotherapy increased with increasing RS, from 34% of those with a low RS, to 49% of those with an intermediate RS, to 94% of those with a high RS (Fig. 2B). In comparison, 79% of patients with HR+, HER2- disease and with 1 to 3 involved lymph nodes who did not undergo testing with the RS assay were treated with chemotherapy. The administration of anthracycline-based chemotherapy regimens in patients with 1 to 3 involved lymph nodes was found to increase with increasing RS. Anthracyclines were administered to 23%, 35%, and 36%, respectively, of patients

TABLE 1. Univariate Analyses of Associations Between Patient and Tumor Characteristics Among Patients With HR+, HER2-, Lymph Node-Negative Breast Cancer and Chemotherapy Regimen[a]

Characteristic	Lymph Node-Negative Cohort (pN0, pN1mi) No RS Assay			Lymph Node-Negative Cohort (pN0, pN1mi) RS Assay		
	Anthracycline Chemotherapy N=385	Non-Anthra Chemotherapy N=402	P	Anthracycline Chemotherapy N=232	Non-Anthra Chemotherapy N=691	P
Clinical						
Age at diagnosis, y						
<50	193 (50%)	140 (35%)	<.001	90 (39%)	231 (33%)	.037
50-69	172 (45%)	212 (53%)		133 (57%)	401 (58%)	
≥70	20 (5%)	50 (12%)		9 (4%)	59 (9%)	
Race						
Black	53 (14%)	58 (14%)	.929	29 (13%)	55 (8%)	.106
White	306 (79%)	319 (79%)		190 (82%)	600 (87%)	
Other	26 (7%)	25 (6%)		13 (6%)	36 (5%)	
Charlson Comorbidity Index						
0	343 (89%)	347 (86%)	.236	216 (93%)	623 (90%)	.471
1	25 (6%)	35 (9%)		13 (6%)	49 (7%)	
2	15 (4%)	13 (3%)		2 (1%)	9 (1%)	
≥3	2 (1%)	7 (2%)		1 (0%)	10 (1%)	
Socioeconomic status						
High	114 (30%)	111 (28%)	.939	71 (31%)	253 (37%)	.059
Medium	142 (37%)	143 (36%)		78 (34%)	233 (34%)	
Low	129 (34%)	134 (33%)		83 (36%)	190 (27%)	
Missing data	0 (0%)	14 (3%)		0 (0%)	15 (2%)	
Y of diagnosis						
2006-2007	120 (31%)	41 (10%)	<.001	41 (18%)	42 (6%)	<.001
2008-2011	162 (42%)	204 (51%)		97 (42%)	300 (43%)	
2012-2014	103 (27%)	157 (39%)		94 (41%)	349 (51%)	
Tumor						
Tumor size						
pT1	161 (42%)	215 (53%)	.005	153 (66%)	488 (71%)	.408
pT2	199 (52%)	165 (41%)		76 (33%)	195 (28%)	
pT3	25 (6%)	22 (5%)		3 (1%)	8 (1%)	
Other	0 (0%)	0 (0%)		0 (0%)	0 (0%)	
Lymph node involvement						
pN0	283 (74%)	315 (78%)	.111	218 (94%)	652 (94%)	.825
pN1mi	102 (26%)	87 (22%)		14 (6%)	39 (6%)	
Tumor grade						
1	41 (11%)	45 (11%)	.364	26 (11%)	83 (12%)	.003
2	165 (43%)	189 (47%)		101 (44%)	379 (55%)	
3	176 (46%)	163 (41%)		102 (44%)	222 (32%)	
Missing data	3 (1%)	5 (1%)		3 (1%)	7 (1%)	
RS						
0-17	NA	NA	NA	30 (13%)	98 (14%)	<.001
18-30	NA	NA		100 (43%)	408 (59%)	
31-100	NA	NA		102 (44%)	185 (27%)	

Abbreviations: + , positive; -, negative; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; NA, not applicable; Non-Anthra, nonanthracycline; RS, recurrence score.
[a] Patients were divided into those tested and not tested with the RS assay.

with a low, intermediate, and high RS (Fig. 2B). In contrast, 68% of chemotherapy-treated patients with HR+, HER2- disease and 1 to 3 involved lymph nodes who were not tested with the RS assay received an anthracycline-containing regimen.

Among those patients who were tested with the RS assay and received chemotherapy, there were no statistically significant associations noted between anthracycline use and age, race, comorbidity, socioeconomic status, year of diagnosis, tumor grade, tumor size, lymph node involvement, or RS (Table 2). In contrast, of those who received chemotherapy and who did not undergo testing with the RS assay, anthracycline use was associated with younger age, lower comorbidity, intermediate socioeconomic status, earlier year of diagnosis, larger tumor size, and increased lymph node involvement. There was a trend toward an association with white race. No associations were identified with tumor grade.

TABLE 2. Univariate Analyses of Associations Between Patient and Tumor Characteristics Among Patients With HR+, HER2-, Lymph Node-Positive Breast Cancer and Chemotherapy Regimen[a]

| Characteristic | HR+, HER2−, Lymph Node-Positive Cohort No RS Assay | | | HR+, HER2-, Lymph Node-Positive Cohort RS Assay | | |
	Anthracycline Chemotherapy N=1261	Non-Anthra Chemotherapy N=511	P	Anthracycline Chemotherapy N=51	Non-Anthra Chemotherapy N=114	P
Clinical						
Age at diagnosis, y						
<50	512 (41%)	128 (25%)	<.001	22 (43%)	33 (29%)	.097
50-69	674 (53%)	278 (54%)		26 (51%)	64 (56%)	
≥70	75 (6%)	105 (21%)		3 (6%)	17 (15%)	
Race						
Black	155 (12%)	79 (15%)	.065	4 (8%)	10 (9%)	.616
White	1020 (81%)	408 (80%)		45 (88%)	95 (83%)	
Other	86 (7%)	24 (5%)		2 (4%)	9 (8%)	
Charlson Comorbidity Index						
0	1134 (90%)	423 (83%)	<.001	48 (94%)	97 (85%)	.251
1	80 (6%)	49 (10%)		3 (6%)	9 (8%)	
2	35 (3%)	23 (5%)		0 (0%)	7 (6%)	
≥3	12 (1%)	16 (3%)		0 (0%)	1 (1%)	
Socioeconomic status						
High	400 (32%)	167 (33%)	.011	19 (37%)	39 (34%)	.427
Medium	436 (35%)	134 (26%)		19 (37%)	34 (30%)	
Low	425 (34%)	191 (37%)		13 (25%)	40 (35%)	
Missing data	0 (0%)	19 (4%)		0 (0%)	1 (1%)	
Y of diagnosis						
2006-2007	210 (17%)	60 (12%)	.001	2 (4%)	2 (2%)	.619
2008-2011	567 (45%)	212 (41%)		10 (20%)	27 (24%)	
2012-2014	484 (38%)	239 (47%)		39 (76%)	85 (75%)	
Tumor						
Tumor size						
pT1	479 (38%)	227 (44%)	.022	20 (39%)	64 (56%)	.124
pT2	614 (49%)	227 (44%)		30 (59%)	49 (43%)	
pT3	149 (12%)	45 (9%)		1 (2%)	1 (1%)	
Other	19 (2%)	12 (2%)		0 (0%)	0 (0%)	
Lymph node involvement						
pN1	757 (60%)	361 (70%)	<.001	46 (90%)	110 (96%)	.253
pN2	350 (28%)	100 (20%)		4 (8%)	3 (3%)	
pN3	154 (12%)	49 (10%)		1 (2%)	1 (1%)	
Tumor grade						
1	204 (16%)	81 (16%)	.919	11 (22%)	23 (20%)	.731
2	688 (55%)	280 (55%)		27 (53%)	66 (58%)	
3	338 (27%)	143 (28%)		13 (25%)	23 (20%)	
Missing data	31 (2%)	7 (1%)		0 (0%)	2 (2%)	
RS						
0-17	NA	NA	NA	19 (37%)	57 (50%)	.296
18-30	NA	NA		19 (37%)	36 (32%)	
31-100	NA	NA		13 (25%)	21 (18%)	

Abbreviations: + , positive; -, negative; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; NA, not applicable; Non-Anthra, nonanthracycline; RS, recurrence score.
[a] Patients were divided into those tested and not tested with the RS assay.

Rate of Testing Over Time

Of the 16,666 patients in the MiBOQI included in the current analysis, 7124 (42.7%) met the NCCN criteria for testing of patients with lymph node-negative or micrometastatic lymph node-positive disease, referred to as the lymph node-negative cohort. Overall, 3911 patients in the lymph node-negative cohort (54.9%) underwent test-

ing, and this rate increased from 43.8% in 2006 to 62.2% in 2013 ($P<.001$). Corresponding increases over time were from 46% to 63% in patients without involved lymph nodes (n = 6623; $P<.001$) and from 0% to 49% in patients with microscopic lymph node metastases (n = 501; $P<.001$). The percentage of patients in the lymph node-negative cohort between 2006 and 2013 who

underwent testing at each participating site ranged from 35.4% to 73.3% (see Supporting Information Fig. 5). Of the 3911 tumors that were tested, 2383 (60.9%) had an RS in the low range, 1187 (30.4%) had an RS in the intermediate range, and 341 (8.7%) had an RS in the high range.

Of the remaining 9542 patients who did not meet the NCCN criteria for testing, 2671 (28%) had HR+, HER2- breast cancer with macrometastatic involvement of at least 1 lymph node. Rates of testing in this patient cohort increased from 0% in 2006 to 26% in 2013 (P<.001). At the 25 participating sites, the percentage of patients tested between 2006 and 2013 ranged from 4% to 30% (see Supporting Information Fig. 5). Of the 392 tumors that were tested, 239 (61%) had an RS in the low range, 116 (29.6%) had an RS in the intermediate range, and 37 (9.4%) had an RS in the high range.

Factors Associated With Testing With the 21-Gene RS Assay

In the lymph node-negative cohort, variables found to be associated with receipt of testing on univariate analysis included younger age, white race, smaller tumor size, lack of lymph node involvement, lower tumor grade, lower comorbidity, and more recent time period (see Supporting Information Table 1). No association with area-level socioeconomic status was identified. Similar findings were noted on multivariate analysis.

In the cohort of patients with HR+, HER2-, lymph node-positive disease, variables associated with receipt of testing on univariate analysis included increased age, smaller tumor size, fewer number of lymph nodes involved, lower tumor grade, and more recent time period (see Supporting Information Table 1). There were no associations noted with race, socioeconomic status, or comorbidity. In multivariate analyses, the same associations were identified except tumor grade was found to be of only borderline significance.

DISCUSSION

In hospital systems across Michigan, use of the 21-gene RS assay for determining prognosis and likely benefit from chemotherapy among patients with HR+, HER2-, lymph node-negative breast cancer has been increasing since the introduction of the assay a decade ago. This increasing use has been associated with a concomitant decline in the administration of adjuvant chemotherapy, especially in those patients with RS in the low and low-to-intermediate range. The rate of chemotherapy administration in patients with a low RS is very low across the state

(average of 6% from 2006-2013), and has been decreasing over time. The rate of omission of chemotherapy in patients with a high RS is higher, at approximately 10%. Both of these findings are similar to those previously reported in other cohorts, and demonstrate excellent concordance with published guidelines for patients with lymph node-negative disease.[13] The results of the current study confirm previously reported findings regarding the increasing use of the RS assay over time and concomitant declining use of chemotherapy. One large study evaluating the association in the first years (2006-2008) after the introduction of the RS assay demonstrated that testing was associated with a lower odds of the receipt of chemotherapy, with an odds ratio of 0.70 (95% confidence interval, 0.62-0.80).[6] A second study analyzed the association in a Medicare population between 2005 and 2009 and similarly demonstrated the decreased use of chemotherapy over time in this older population who underwent testing with the RS assay.[7] The current study results also extend these findings by including a more recent time period, and demonstrate that the reduction in chemotherapy use has persisted over the nearly 10 years since introduction of the RS assay into routine clinical practice.

It is important to note that we found that use of the RS assay was associated with a shift in the use of chemotherapy regimens from anthracycline-based regimens to non-anthracycline-based regimens in both the lymph node-negative and lymph node-positive cohorts. This trend was observed despite a lack of clinical data to support using the RS assay results to select specific adjuvant chemotherapy regimens. However, we were unable to determine how much of the decreased use of anthracycline-containing regimens is due to use of the RS assay and how much is due to the publication of findings from other clinical trials. During the same time period, the US Oncology Research Group published the results of a clinical trial of docetaxel and cyclophosphamide versus doxorubicin and cyclophosphamide, demonstrating superior disease-free and overall survival with the non-anthracycline-containing regimen.[14,15] It is interesting to note that the anthracycline-containing comparator arm in that trial did not include a taxane. Subsequent analysis of national patient cohorts demonstrated a decline in the use of anthracyclines among patients with breast cancer since 2005.[16]

In contrast, recently reported data have demonstrated that for patients with lymph node involvement, anthracycline-containing regimens are more effective than non-anthracycline-containing regimens, although exploratory subset analyses have suggested less benefit in

patients with HR+, HER2- disease.[17] The findings of the current study suggest that physicians may be using the results of the RS assay to select patients for non-anthracycline-containing regimens. Alternatively, the observation that use of the RS assay is associated with a preference for non-anthracycline-based chemotherapy regimens could reflect, in part, patient selection. In the lymph node-negative cohort, unfavorable tumor characteristics and younger age were found to be associated with use of an anthracycline regardless of testing with the RS assay. However, in the lymph node-positive cohort, similar findings were identified only in those patients who did not undergo testing with the RS assay.

There has been a substantial increase in the testing of patients with HR+, HER2-, lymph node-positive breast cancer over time, which has occurred despite a lack of prospective randomized data to support the clinical usefulness of the RS assay for this purpose. A prospective, randomized validation study to determine whether chemotherapy can be safely omitted in patients with HR+, HER2- disease with lymph node involvement has completed accrual (SWOG S1007; ClinicalTrials.gov identifier NCT01272037), but the results are not yet available. In our statewide cohort, we found that those patients with 1 to 3 involved lymph nodes who underwent testing with the RS assay were significantly less likely to receive chemotherapy compared with those who did not undergo testing. This likely reflects a bias of ordering physicians for the selection of patients that they would prefer to avoid treating with chemotherapy because those patients who were tested were older and had more favorable tumor characteristics. These findings are consistent with a previously published physician survey that reported that physicians were more likely to consider using the RS assay for patients with 1 to 3 involved lymph nodes with smaller tumors, and that testing would lead to reduced recommendations for treatment with chemotherapy.[18]

Finally, in our registry, fewer black patients with lymph node-negative breast cancer underwent testing with the RS assay compared with white patients, whereas there were no detectable racial differences in test ordering noted for those individuals with lymph node-positive breast cancer. This is in contrast to a recent publication from the Carolina Breast Cancer Study, in which rates of testing of patients with lymph node-negative disease were similar between white and black patients, but black patients with lymph node-positive disease were found to be 46% less likely to undergo testing.[19] The basis for these differing findings between the 2 states is unclear, but

could represent differences in provider practice patterns or insurance coverage.

Strengths of the current study include data derived from a large, prospective registry specifically designed to evaluate patterns of breast cancer care at multiple institutions across a single state, in which comprehensive demographic, clinical, and treatment data are collected. There was considerable heterogeneity in terms of both practice setting and patient characteristics. However, due to limitations in the registry, we were unable to determine the reasons why patients did not receive guideline-concordant testing or chemotherapy treatment, why specific chemotherapy regimens were selected, or the impact of treatment selection on patient outcome. This information is essential for the performance of root cause analyses to develop site-level interventions to improve concordance with guidelines related to use of the RS assay result for treatment decision making.

Overall, use of the 21-gene RS assay for the management of patients with both lymph node-negative and lymph node-positive breast cancer has increased in the MiBOQI since 2006, and this increase has been accompanied by a concomitant decrease in treatment with chemotherapy. In particular, the results of the RS assay appear to influence selection of the chemotherapy regimen by physicians, despite the lack of evidence supporting this use of the assay. The results of ongoing clinical trials (ClincalTrials.gov identifiers NCT00310180 and NCT01272037) should help to further define the clinical usefulness of the 21-gene RS assay in both the lymph node-negative and lymph node-positive settings for treatment decision making.

FUNDING SUPPORT

CONFLICT OF INTEREST DISCLOSURES

Samuel M. Silver has received personal fees from Amgen, 3M, and Blue Care Network.

AUTHOR CONTRIBUTIONS

Conceptualization: **N. Lynn Henry, Tara M. Breslin,** and **Jennifer J. Griggs**. Formal analysis: **Thomas Braun** and **Khan Munir**. Investigation: **N. Lynn Henry** and **Thomas Braun**. Data curation: **Thomas Braun** and **Khan Munir**. Writing–original draft: **N. Lynn Henry**. Writing–review and editing: **N. Lynn Henry, Thomas Braun, Haythem Y. Ali, Samuel M. Silver, David H.**

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REFERENCES

1. Paik S, Shak S, Tang G, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. *N Engl J Med*. 2004;351:2817-2826.
2. Paik S, Tang G, Shak S, et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. *J Clin Oncol*. 2006;24:3726-3734.
3. Sparano JA, Gray RJ, Makower DF, et al. Prospective validation of a 21-gene expression assay in breast cancer. *N Engl J Med*. 2015;373:2005-2014.
4. Carlson RW, Allred DC, Anderson BO, et al; National Comprehensive Cancer Network. Invasive breast cancer. *J Natl Compr Canc Netw*. 2011;9:136-222.
5. Harris LN, Ismaila N, McShane LM, et al; American Society of Clinical Oncology. Use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol*. 2016;34:1134-1150.
6. Hassett MJ, Silver SM, Hughes ME, et al. Adoption of gene expression profile testing and association with use of chemotherapy among women with breast cancer. *J Clin Oncol*. 2012;30:2218-2226.
7. Dinan MA, Mi X, Reed SD, Lyman GH, Curtis LH. Association between use of the 21-gene recurrence score assay and receipt of chemotherapy among Medicare beneficiaries with early-stage breast cancer, 2005-2009. *JAMA Oncol*. 2015;1:1098-1109.
8. Dinan MA, Mi X, Reed SD, Hirsch BR, Lyman GH, Curtis LH. Initial trends in the use of the 21-gene recurrence score assay for patients with breast cancer in the Medicare population, 2005-2009. *JAMA Oncol*. 2015;1:158-166.
9. Albain KS, Barlow WE, Shak S, et al; Breast Cancer Intergroup of North America. Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: a retrospective analysis of a randomised trial. *Lancet Oncol*. 2010;11:55-65.
10. Dowsett M, Cuzick J, Wale C, et al. Prediction of risk of distant recurrence using the 21-gene recurrence score in node-negative and node-positive postmenopausal patients with breast cancer treated with anastrozole or tamoxifen: a TransATAC study. *J Clin Oncol*. 2010;28:1829-1834.
11. Gluz O, Nitz UA, Christgen M, et al. West German Study Group Phase III PlanB Trial: first prospective outcome data for the 21-gene recurrence score assay and concordance of prognostic markers by central and local pathology assessment. *J Clin Oncol*. 2016;34:2341-2349.
12. Gradishar WJ, Anderson BO, Balassanian R, et al. Breast cancer version 2.2015. *J Natl Compr Canc Netw*. 2015;13:448-475.
13. Chen C, Dhanda R, Tseng WY, Forsyth M, Patt DA. Evaluating use characteristics for the oncotype dx 21-gene recurrence score and concordance with chemotherapy use in early-stage breast cancer. *J Oncol Pract*. 2013;9:182-187.
14. Jones S, Holmes FA, O'Shaughnessy J, et al. Docetaxel with cyclophosphamide is associated with an overall survival benefit compared with doxorubicin and cyclophosphamide: 7-year follow-up of US Oncology Research Trial 9735. *J Clin Oncol*. 2009;27:1177-1183.
15. Jones SE, Savin MA, Holmes FA, et al. Phase III trial comparing doxorubicin plus cyclophosphamide with docetaxel plus cyclophosphamide as adjuvant therapy for operable breast cancer. *J Clin Oncol*. 2006;24:5381-5387.
16. Giordano SH, Lin YL, Kuo YF, Hortobagyi GN, Goodwin JS. Decline in the use of anthracyclines for breast cancer. *J Clin Oncol*. 2012;30:2232-2239.
17. Blum JL, Flynn PJ, Yothers G, et al. Interim joint analysis of the ABC (anthracyclines in early breast cancer) phase III trials (USOR 06-090, NSABP B-46I/USOR 07132, NSABP B-49) comparing docetaxel + cyclophosphamide v anthracycline/taxane-based chemotherapy regimens in women with high-risk, HER2-negative breast cancer [abstract]. *J Clin Oncol*. 2016;34(suppl):1000.
18. Oratz R, Kim B, Chao C, et al. Physician survey of the effect of the 21-gene recurrence score assay results on treatment recommendations for patients with lymph node-positive, estrogen receptor-positive breast cancer. *J Oncol Pract*. 2011;7:94-99.
19. Roberts MC, Weinberger M, Dusetzina SB, et al. Racial variation in the uptake of Oncotype DX testing for early-stage breast cancer. *J Clin Oncol*. 2016;34:130-138.