Associations between use of the 21-gene Recurrence Score Assay and Chemotherapy Regimen Selecti

Registry

Running Title: Recurrence score and regimen selection

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Abstract

PURPOSE: The 21-gene recurrence score (RS) assay predicts response to adjuvant chemotherapy in early stage, hormone receptor-positive (HR+), HER2-negative (HER2-) invasive breast cancer, but the role of the assay in guiding selection of chemotherapy regimen has not been established. We conducted this study to examine patterns of use of the RS assay for selecting chemotherapy regimens across a statewide registry from 2006-2013.

METHODS: Demographic, pathologic, and treatment data were abstracted from medical records for 16,666 women with breast cancer treated at 25 hospital systems across Michigan who were participating in the Michigan Breast Oncology Quality Initiative. We examined treatment patterns based on the RS assay test result.

RESULTS: 25% of node-negative patients who underwent testing with the RS assay and who were treated with chemotherapy received an anthracycline-based regimen, compared to 49% of node-negative, chemotherapy-treated patients who had not undergone testing with the RS assay. Of the node-positive patients who underwent testing with the RS assay and who received chemotherapy, 31% received an anthracycline-based regimen. In comparison, 71% of node-positive, chemotherapy-treated patients who did not undergo testing received an anthracycline. From 2006-2013, there was a statistically significant decrease in the use of anthracycline-containing regimens in both node-negative and node-positive patients.

CONCLUSIONS: Use of anthracycline-containing chemotherapy regimens in eligible patients varies with use of the RS assay despite the lack of evidence supporting the use of the assay to guide regimen selection. Results of ongoing prospective trials should help define the role of the RS assay in this setting.

Condensed abstract: Use of the 21-gene RS assay was associated with a reduction in treatment with chemotherapy since 2006 in those with node-negative and node-positive ER-positive, HER2-negative breast cancer. Use of the RS assay was also associated with a reduction in receipt of anthracycline-containing chemotherapy regimens regardless of nodal status.

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

Introduction

The 21-gene recurrence score (RS) assay is a multi-parameter gene expression profile test originally designed to identify patients with hormone receptor-positive (HR+), HER2-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 prediction of response to chemotherapy were published in 2006.[2] Patients with low RS (0-17) did not benefit from the addition of adjuvant chemotherapy to endocrine therapy, whereas those with high RS (31-100) benefitted from both chemotherapy and endocrine therapy. The benefit of adding chemotherapy for those with 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 (ASCO) and the National Comprehensive Cancer Network (NCCN) now recommend the use of this assay for making decisions regarding whether or not 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 a RS between 0 and 10 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 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 if the assay would be similarly useful for making decisions regarding use of adjuvant chemotherapy in breast cancer patients with lymph node involvement. Retrospective-prospective analyses evaluating the

use of the RS assay for this population demonstrated that, although patients with nodal involvement had a higher risk of disease recurrence compared to those without, patients whose tumors had a low RS obtained minimal benefit, and those whose tumors had high RS obtained substantial benefit from adjuvant chemotherapy.[9, 10] A recently reported prospective trial of patients with 1-3 positive nodes and RS<12 who were treated with endocrine therapy alone demonstrated a 3-year disease free survival 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 1-3 involved lymph nodes, and since 2015 the NCCN guidelines have recommended consideration of testing of patients with up to 3 involved lymph nodes.[12] In contrast, recently updated ASCO guidelines do not recommend use 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 lymph node-negative and -positive patients and associations between RS assay result and chemotherapy administration in multiple patient cohorts. Our primary objective was to examine the association between RS assay result and selection of anthracycline-containing versus non-anthracycline-containing regimens based on RS assay result.

Methods

Analyzed cohort

Women with newly diagnosed breast cancer diagnosed between 2006 and 2013 and treated at one of the 25 hospitals participating in MiBOQI were included in this analysis. Because the purpose of MiBOQI is to conduct quality initiatives, MiBOQI has been granted an exemption by the University of Michigan Institutional Review Board. Demographic, pathologic, and treatment characteristics were abstracted from the medical record. Determination of socioeconomic status was estimated based on each patient's place of residence using data from the 2010 United States census. Patients with non-invasive 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 more than 1 cm or measuring 6-10 mm in size with additional high risk features, including either grade 2 or 3 or evidence of angiolymphatic invasion, with either no evidence of nodal metastases or only micrometastatic lymph node involvement. Tumors 5 mm or less and those with tubular or mucinous histology were considered inappropriate for testing (non-concordant).

21-gene RS assay testing for lymph node-positive cohort

Patients in the analyzed cohort who had HR+, HER2-negative breast cancer and macrometastatic involvement of at least one lymph node were included in the analysis of the lymph node-positive cohort. Participants in Steps 1 or 2 of the 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 Methods

All data were analyzed using the statistical package R, version 3.2.3. All patient characteristics were summarized as proportions, and statistical significance of variation in testing rates by patient characteristics was assessed using univariate and multivariate logistic regression. Statistical significance was defined as a *p*-value less than 0.05.

Results

Use of RS assay results: Node-negative

Over time, rates of chemotherapy administration to patients with both node-negative and micrometastatic 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 (18%) and 25 of 74 (34%), respectively, in 2013 ($p<0.001$ for both groups, Supplemental Figure 1). Chemotherapy use decreased over time in patients with node negative and micrometastatic node-positive disease who underwent testing with the RS assay ($p<0.001$ and $p=0.001$, respectively), but not in those who were not tested (Figures 1A and 1B). Although the proportion of patients treated with chemotherapy decreased overall, receipt of chemotherapy was greater with increasing RS in the node-negative cohort ($p<0.001$, Figures 2A and 3A).

Of the 3911 patients in the node-negative cohort who underwent testing with the RS assay from 2006-2013, 923 (24%) were treated with chemotherapy. Six percent 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 ($p<0.001$, Figure 2A). In those with a low RS, receipt of chemotherapy decreased from 2006 to 2013 ($p<0.001$, Supplemental Figure 2). Among the 923 patients, 232 (25%) received an anthracycline-based regimen (Figure 2A and Supplemental Figure 3A). In comparison, of the 787 chemotherapy-treated patients in the node-negative cohort who did not undergo testing, 49% received an anthracycline-based regimen. From 2006-2013, there was a statistically significant decrease in the use of anthracycline-containing regimens (Figure 1A).

On univariate analysis, anthracycline use in those who were tested with the RS assay and received chemotherapy was associated with younger age, earlier year of diagnosis, higher tumor grade, and higher recurrence score (Table 1 and Supplemental Figure 3A). There was a trend towards an association with lower socioeconomic status. No associations were identified with race, comorbidity, tumor size, or presence of micrometastatic nodal disease.

Similarly, of those 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 presence of micrometastatic nodal disease.

Use of RS assay results: Node-positive

In patients with HR+, HER2- disease and macrometastatic lymph node involvement, testing with the RS assay was associated with decreased treatment with adjuvant chemotherapy compared to no testing (Figure 1C and Supplemental Figure 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 (Supplemental Figures 3B and 4). Chemotherapy use increased with increasing RS (Figure 3B). In contrast, of the 1772 chemotherapy-treated patients with HR+, HER2-, node-positive disease who did not undergo testing, 71% received an anthracycline-based regimen. From 2006-2013, there was a statistically significant decrease in the use of anthracycline-containing regimens in node-positive patients (Figure 1C).

Examination of the cohort with 1-3 involved lymph nodes revealed that treatment with chemotherapy increased with increasing recurrence score, from 34% of those with a low RS, to 49% of those with an intermediate RS, to 96% of those with a high RS (Figure 2B). In comparison, 79% of patients with HR+, HER2- disease and with 1-3 involved lymph nodes who did not undergo testing with the RS assay were treated with chemotherapy. Administration of anthracycline-based chemotherapy regimens in patients with 1-3 involved lymph nodes increased with increasing RS. Anthracyclines were administered to 23%, 35%, and 36% of patients with a low, intermediate, and high RS, respectively (Figure 2B). In contrast, 68% of chemotherapy-treated patients with HR+, HER2- disease and 1-3 involved lymph nodes who were not tested with the RS assay received an anthracycline-containing regimen.

Of those who were tested with the RS assay and received chemotherapy, there were no statistically significant associations between anthracycline use and age, race, comorbidity, socioeconomic status, year of diagnosis, tumor grade, tumor size, nodal involvement, or recurrence score. In contrast, of those who were 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 nodal involvement. There was a trend towards an association with white race. No associations were identified with tumor grade.

Rate of testing over time

Of the 16,666 MiBOQI registry patients included in our analysis, 7124 (42.7%) met the NCCN criteria for testing of patients with node-negative or micrometastatic node-positive disease, referred to as the node-negative cohort. Overall, 3911 (54.9%) of patients in the node-negative cohort underwent testing, and this rate increased from 43.8% in 2006 to 62.2% in 2013 (Figure 4; p<0.001). Corresponding increases over time were from 46% to 63% in patients without involved lymph nodes (n=6623; p<0.001) and from 0% to 49% in patients with microscopic nodal metastases (n=501; p<0.001). The percentage of patients in the node-negative cohort between 2006 and 2013 who underwent testing at each participating site ranged from 35.4% to 73.3% (Supplemental Figure 5). Of the 3911 tumors that were tested, 2383 (60.9%) of RS were in the low range, 1187 (30.4%) in the intermediate range, and 341 (8.7%) 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 one lymph node. Rates of testing in this patient cohort increased from 0% in 2006 to 26% in 2013 (p<0.001, Figure 4). At the 25 participating sites, the percentage of patients tested in 2006-2013 ranged from 4% to 30% (Supplemental Figure 5). Of the 392 tumors that were tested, 239 (61.0%) of RS were in the low range, 116 (29.6%) in the intermediate range, and 37 (9.4%) in the high range.

Factors associated with testing with the 21-gene RS assay

In the node-negative cohort, on univariate analysis, variables associated with receipt of testing included younger age, white race, smaller tumor size, lack of lymph node involvement, lower tumor grade, lower comorbidity, and more recent time period

(Supplemental 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 (Supplemental 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 only borderline significant.

Discussion

In hospital systems across Michigan, use of the 21-gene RS assay for determining prognosis and likely benefit from chemotherapy for patients with HR+, HER2-, 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 adjuvant chemotherapy administration, especially in those patients with recurrence scores in the low and low-intermediate range. The rates of chemotherapy administration in patients with low RS is very low across the state (average of 6% from 2006-2013), and has been decreasing over time. The rates of omission of chemotherapy in patients with high RS is higher, 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 node-negative disease.[13] Our findings confirm previously reported findings regarding 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) following introduction of the RS assay demonstrated that testing was associated with a lower odds of receipt of chemotherapy, with an odds ratio of 0.70 (95% CI 0.62-

0.80).[6] A second study analyzed the association in a Medicare population between 2005-2009 and similarly demonstrated decreased use of chemotherapy over time in this older population who underwent testing with the RS assay.[7] Our results also extend these findings by including a more recent time period, and demonstrate that the reduction in chemotherapy has persisted over almost 10 years since introduction of the RS assay into routine clinical practice.

Importantly, 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 node-negative and node-positive cohorts. This trend was observed despite a lack of clinical data to support using the RS assay results for choosing specific adjuvant chemotherapy regimens. However, we are 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 publication of findings from other clinical trials. During the same time period, the US Oncology Research group published the results of the docetaxel and cyclophosphamide (TC) versus doxorubicin and cyclophosphamide (AC) clinical trial, demonstrating superior disease-free and overall survival with the non-anthracycline-containing regimen.[14, 15] Of note, 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 for breast cancer since 2005.[16]

In contrast, recently reported data demonstrate that for patients with nodal involvement, anthracycline-containing regimens are more effective than non-anthracycline-containing regimens, although exploratory subset analyses suggested less benefit in patients with HR+, HER2- disease.[17] Our findings suggest that physicians may be using results of the RS assay to select patients for non-anthracycline-containing regimens. Alternatively, the observation that use of RS assay is associated with a preference for non-anthracycline-based chemotherapy regimens could reflect, in part, patient selection. In the node-negative cohort, unfavorable tumor

characteristics and younger age were 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 the patients who did not undergo testing with the RS assay.

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

Finally, in our registry, fewer black patients with node-negative breast cancer underwent testing with the RS assay compared to white patients, whereas there were no detectable racial differences in test ordering for those with 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 node-negative disease were similar between white and black patients, but black patients with node-positive disease were 46% less likely to undergo testing.[19] The basis for these differing findings between the two states is unclear but could represent differences in provider practice patterns or insurance coverage.

Strengths of our 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 is considerable heterogeneity in terms of both practice setting and patient characteristics. However, due to limitations in the registry, we are unable to determine 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 in order to develop site level interventions to improve concordance with guidelines related to RS assay result utilization for treatment decision-making.

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

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Figure Legends

Figure 1. Percentage of patients with HR+, HER2- breast cancer who received treatment with any chemotherapy, over time, by 21-gene assay testing (tested: orange; not tested: blue). In addition, percentage of chemotherapy-treated patients who received an anthracycline-based regimen, over time, by 21-gene assay testing (tested: green dashed; not tested: red dashed). Rates are given for node-negative disease (part A), micrometastatic nodal disease (part B), and macrometastatic nodal disease (part C).

Figure 2. Percentage of patients with HR+, HER2- breast cancer treated with anthracycline-based (blue), non-anthracycline based (red), and no chemotherapy (green) regimens, by recurrence score (<18, 18-30, >30, not tested). (A) Node-negative cohort. (B) Patients with 1-3 positive lymph nodes.

Figure 3. Bubble plot demonstrating receipt of chemotherapy by recurrence score for patients with HR+, HER2- breast cancer. Each circle represents average percentage of patients treated with chemotherapy for each RS, and size of each circle represents the number of patients with each RS. (A) Node-negative cohort. (B) Node-positive cohort.

Table 1. Univariate analyses of associations between patient and tumor characteristics of patients with HR+, HER2-, lymph node-negative breast cancer and chemotherapy regimen (anthracycline (A) versus non-anthracycline (Non-A)). Patients are divided into those tested and not tested with the RS assay.

	Node-negative Cohort (pN0, pN1mi) No RS Assay			Node-negative Cohort (pN0, pN1mi) RS Assay		
Characteristic	A Chemo N=385	Non-A Chemo N=402	p-value	A Chemo N=232	Non-A Chemo N=691	p-value
Clinical						
Age at diagnosis, years						
<50	193 (50%)	140 (35%)	<0.001	90 (39%)	231 (33%)	0.037
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%)	0.929	29 (13%)	55 (8%)	0.106
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%)	0.236	216 (93%)	623 (90%)	0.471
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%)	

Table 1 (Continued)

Socioeconomic status						
High	114 (30%)	111 (28%)	0.939	71 (31%)	253 (37%)	0.059
Medium	142 (37%)	143 (36%)		78 (34%)	233 (34%)	
Low	129 (34%)	134 (33%)		83 (36%)	190 (27%)	
Missing	0 (0%)	14 (3%)		0 (0%)	15 (2%)	
Year of Diagnosis						
2006-2007	120 (31%)	41 (10%)	<0.001	41 (18%)	42 (6%)	<0.001
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%)	0.005	153 (66%)	488 (71%)	0.408
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%)	
Nodal Involvement						
pN0	283 (74%)	315 (78%)	0.111	218 (94%)	652 (94%)	0.825
pN1mi	102 (26%)	87 (22%)		14 (6%)	39 (6%)	
Tumor Grade						
1	41 (11%)	45 (11%)	0.364	26 (11%)	83 (12%)	0.003
2	165 (43%)	189 (47%)		101 (44%)	379 (55%)	
3	176 (46%)	163 (41%)		102 (44%)	222 (32%)	
Missing	3 (1%)	5 (1%)		3 (1%)	7 (1%)	

Table 1 (Continued)

RS						
0-17	n/a	n/a	n/a	30 (13%)	98 (14%)	<0.001
18-30	n/a	n/a		100 (43%)	408 (59%)	
31-100	n/a	n/a		102 (44%)	185 (27%)	

Table 2. Univariate analyses of associations between patient and tumor characteristics of patients with HR+, HER2-, lymph node-positive breast cancer and chemotherapy regimen (anthracycline (A) versus non-anthracycline (Non-A)). Patients are divided into those tested and not tested with the RS assay.

	HR+, HER2- Lymph Node + Cohort No RS Assay			HR+, HER2- Lymph Node + Cohort RS Assay		
Characteristic	A Chemo N=1261	Non-A Chemo N=511	p-value	A Chemo N=51	Non-A Chemo N=114	p-value
Clinical						
Age at diagnosis, years						
<50	512 (41%)	128 (25%)	<0.001	22 (43%)	33 (29%)	0.097
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%)	0.065	4 (8%)	10 (9%)	0.616
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%)	<0.001	48 (94%)	97 (85%)	0.251
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%)	

Table 2 (continued)

Socioeconomic status						
High	400 (32%)	167 (33%)	0.011	19 (37%)	39 (34%)	0.427
Medium	436 (35%)	134 (26%)		19 (37%)	34 (30%)	
Low	425 (34%)	191 (37%)		13 (25%)	40 (35%)	
Missing	0 (0%)	19 (4%)		0 (0%)	1 (1%)	
Year of Diagnosis						
2006-2007	210 (17%)	60 (12%)	0.001	2 (4%)	2 (2%)	0.619
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%)	0.022	20 (39%)	64 (56%)	0.124
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%)	
Nodal Involvement						
pN1	757 (60%)	361 (70%)	<0.001	46 (90%)	110 (96%)	0.253
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%)	0.919	11 (22%)	23 (20%)	0.731
2	688 (55%)	280 (55%)		27 (53%)	66 (58%)	
3	338 (27%)	143 (28%)		13 (25%)	23 (20%)	

Table 2 (continued)

Missing	31 (2%)	7 (1%)		0 (0%)	2 (2%)	
RS						
0-17	n/a	n/a	n/a	19 (37%)	57 (50%)	0.296
18-30	n/a	n/a		19 (37%)	36 (32%)	
31-100	n/a	n/a		13 (25%)	21 (18%)	

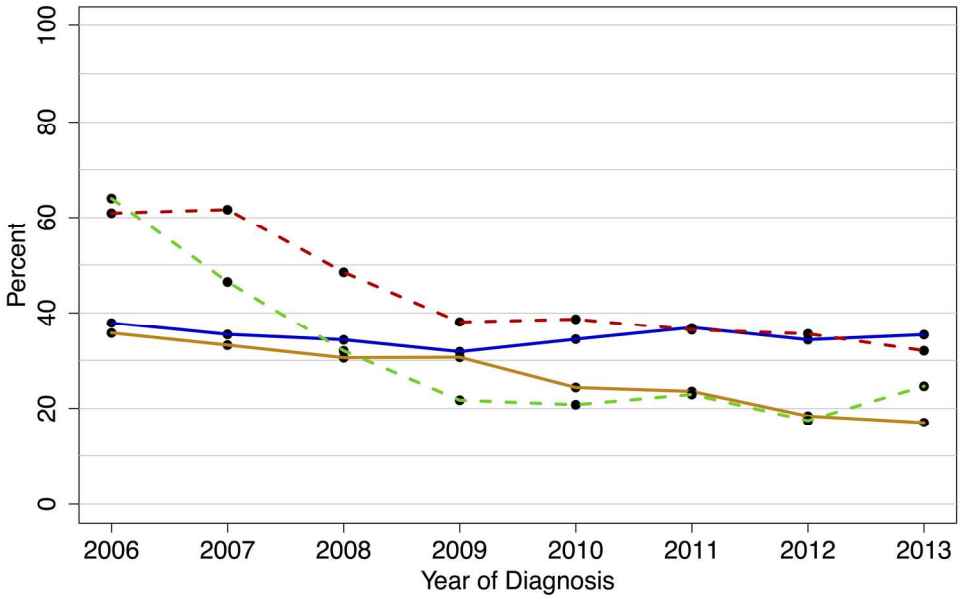

Figure 1. Percentage of patients with HR+, HER2- breast cancer who received treatment with any chemotherapy, over time, by 21-gene assay testing (tested: orange; not tested: blue). In addition, percentage of chemotherapy-treated patients who received an anthracycline-based regimen, over time, by 21-gene assay testing (tested: green dashed; not tested: red dashed). Rates are given for node-negative disease (part A), micrometastatic nodal disease (part B), and macrometastatic nodal disease (part C).
Figure 1A
177x124mm (300 x 300 DPI)

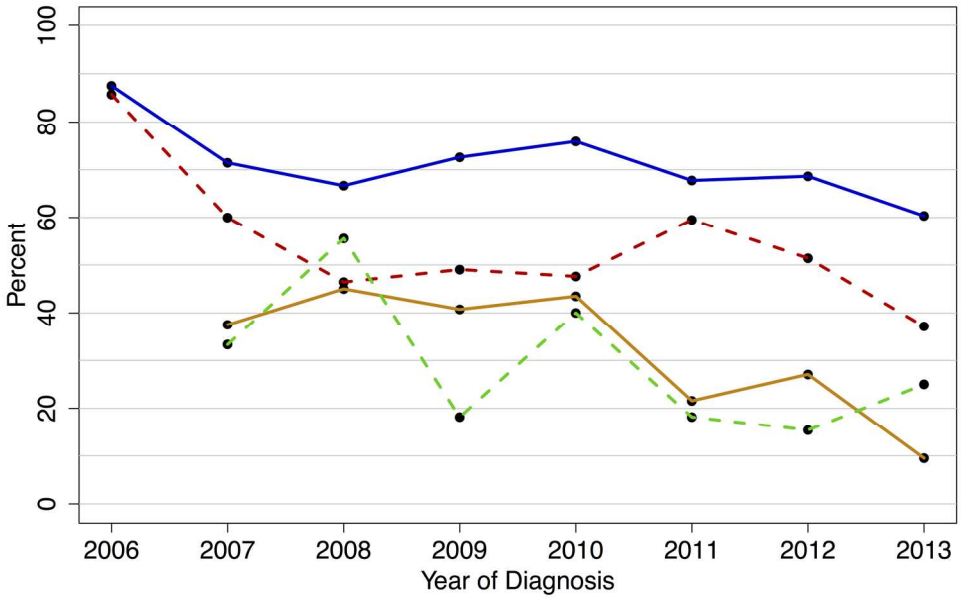

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Figure 1B
177x124mm (300 x 300 DPI)

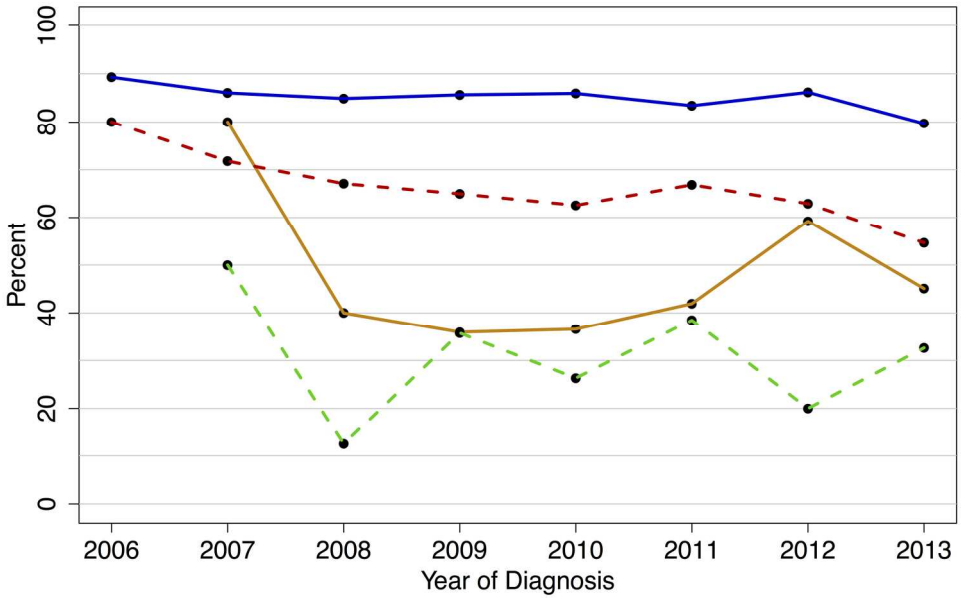

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Figure 1C
177x124mm (300 x 300 DPI)

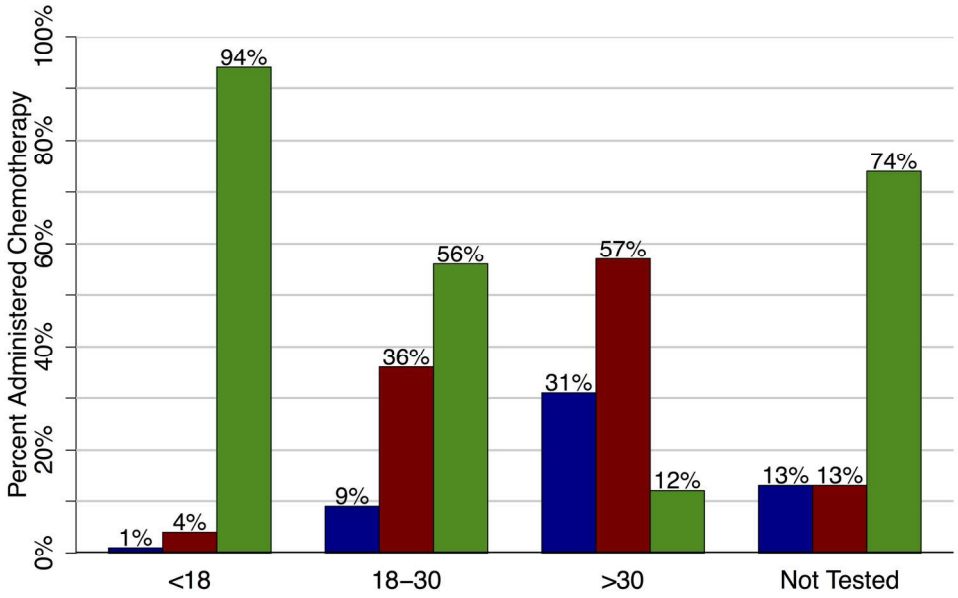

Figure 2. Percentage of patients with HR+, HER2- breast cancer treated with anthracycline-based (blue), non-anthracycline based (red), and no chemotherapy (green) regimens, by recurrence score (<18, 18-30, >30, not tested). (A) Node-negative cohort. (B) Patients with 1-3 positive lymph nodes.
Figure 2A
177x124mm (300 x 300 DPI)

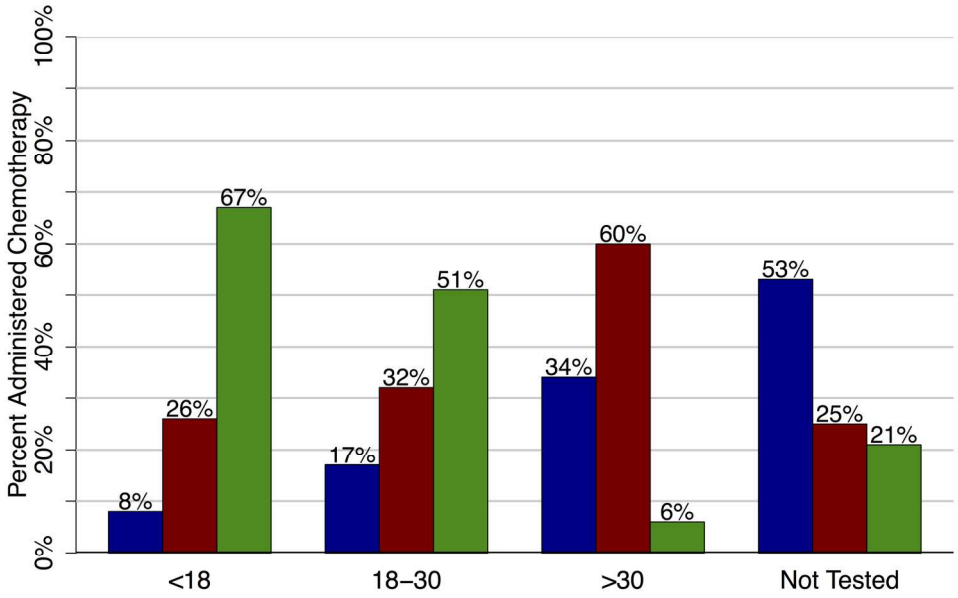

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Figure 2B
177x124mm (300 x 300 DPI)

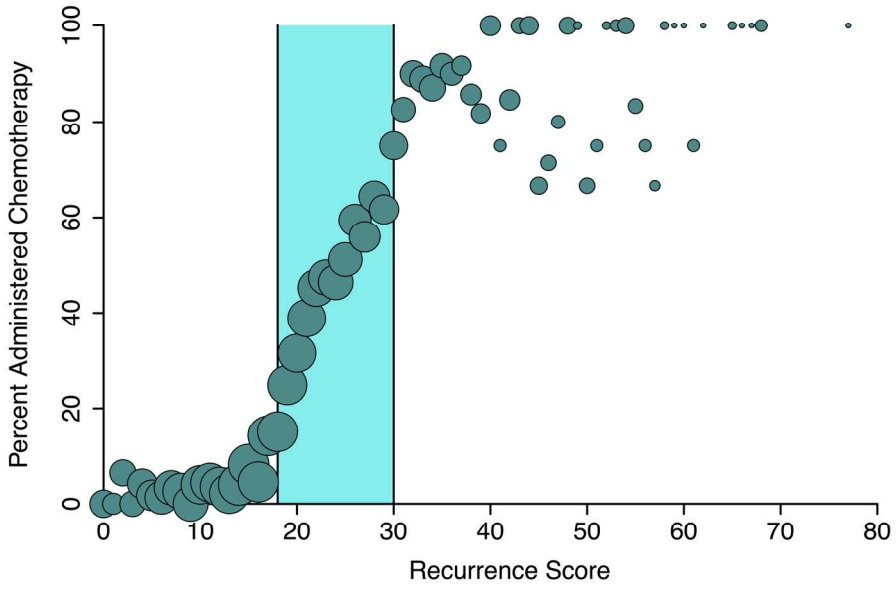

Figure 3. Bubble plot demonstrating receipt of chemotherapy by recurrence score for patients with HR+, HER2- breast cancer. Each circle represents average percentage of patients treated with chemotherapy for each RS, and size of each circle represents the number of patients with each RS. (A) Node-negative cohort. (B) Node-positive cohort.
Figure 3A
177x124mm (300 x 300 DPI)

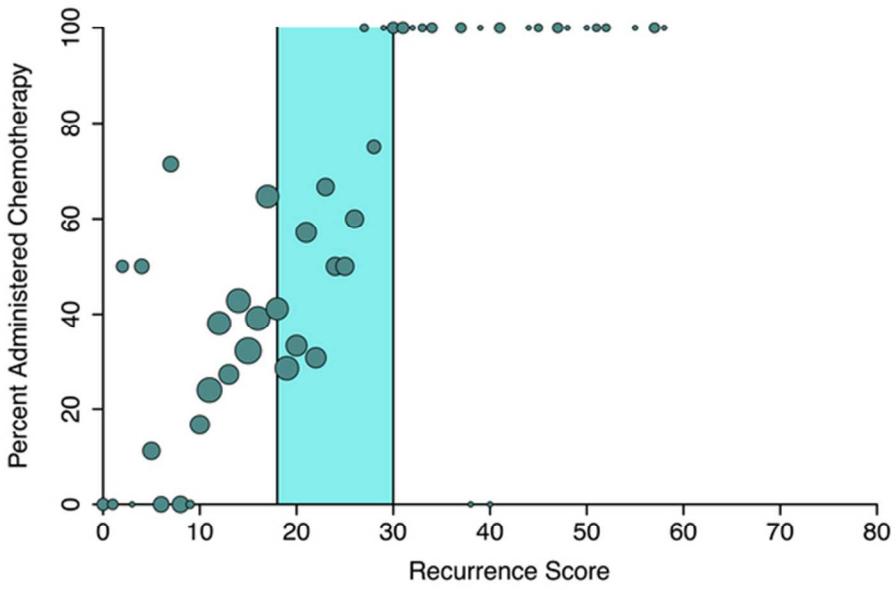

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Figure 3B
28x19mm (600 x 600 DPI)

Supplemental Data

Associations between use of the 21-gene Recurrence Score Assay and Chemotherapy Regimen Selection in a Statewide Registry

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Supplemental Table

Supplemental Figures

Supplemental Figure 1. Percentage of patients with HR+, HER2- breast cancer who were treated with chemotherapy, over time. Rates are given for node-negative disease (circles), micrometastatic nodal disease (triangles), macrometastatic nodal disease (diamonds), and all cohorts combined (solid line, squares).

Supplemental Figure 2. Percentage of patients with HR+, HER2-, lymph node-negative breast cancer with low recurrence scores who were treated with chemotherapy, over time.

Supplemental Figure 3A. Bubble plot demonstrating receipt of anthracycline-containing chemotherapy (chemo) regimens by recurrence score for chemotherapy-treated patients with HR+, HER2- breast cancer. Each circle represents average percentage of patients treated with an anthracycline-based regimen for each RS, and size of each circle represents the number of patients with each RS. (A) Node-negative cohort. (B) Node-positive cohort.

Supplemental Figure 4. Percentage of node-positive patients with HR+, HER2- breast cancer treated with anthracycline-based (blue), non-anthracycline based (red), and no chemotherapy (green) regimens, by recurrence score (<17, 18-30, >30, not tested).

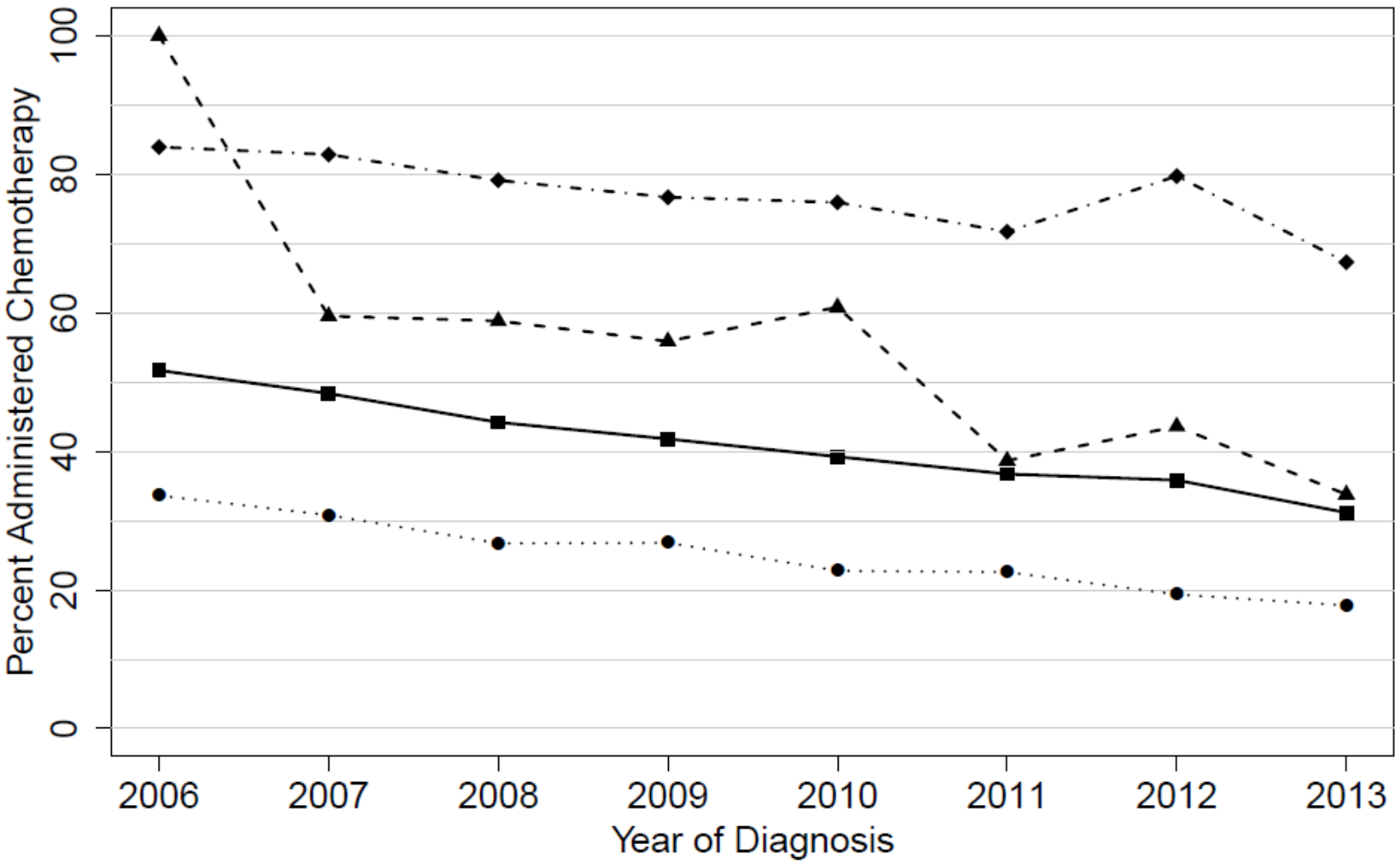
Supplemental Figure 5. Percentage of patients with HR+, HER2- breast cancer tested with the 21-gene RS assay by participating site (designated by letters on the x axis). Rates are given for patients in the NCCN concordant cohort (blue) and in the node-positive cohort (red).

Supplemental Table 1. Univariate and multivariate analyses of associations between patient and tumor characteristics of patients with HR+, HER2- breast cancer and testing with the recurrence score (RS) assay. Patients are divided into the NCCN concordant cohort and the lymph node-positive cohort.

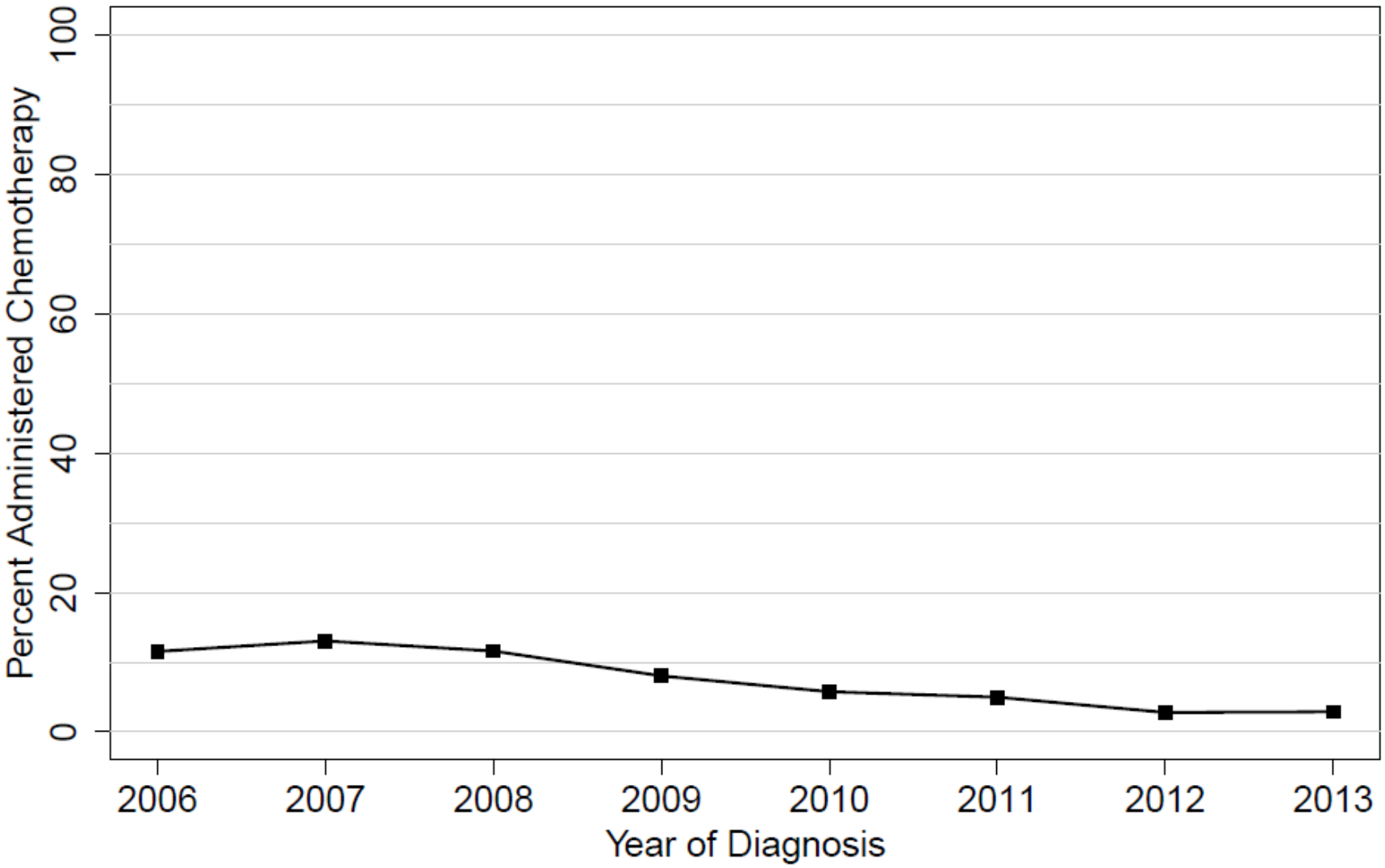
	NCCN Concordant Cohort (pN0, pN1mi)				HR+, HER2- Lymph Node + Cohort			
Characteristic	RS assay N=3911	No RS assay N=3213	Univariate p-value	Multivariate p-value	RS assay N=392	No RS assay N=2279	Univariate p-value	Multivariate p-value
Clinical								
Age at diagnosis, years			<0.0001	<0.0001			0.0008	<0.0001
<50	1024 (26%)	540 (17%)			87 (22%)	721 (32%)		
50-69	2294 (59%)	1258 (39%)			212 (54%)	1096 (48%)		
70+	593 (15%)	1415 (44%)			93 (24%)	462 (20%)		
Race			0.022	0.002			0.220	0.218
Black	352(9%)	349 (11%)			40 (10%)	304 (13%)		
White	3301 (84%)	2640 (82%)			326 (83%)	1838 (81%)		
Other	258 (7%)	224 (7%)			26 (7%)	137 (6%)		
Charlson Comorbidity Index			<0.0001	<0.0001			0.381	0.014
0	3439 (88%)	2504 (78%)			326 (83%)	1899 (83%)		
1	287 (7%)	424 (13%)			41 (10%)	218 (10%)		
2	126 (3%)	174 (5%)			19 (5%)	95 (4%)		
3+	59 (2%)	111 (3%)			6 (2%)	67 (3%)		
Socioeconomic status			0.077	0.303			0.244	0.546
High	1307 (33%)	1001 (31%)			129 (32%)	709 (31%)		
Medium	1335 (34%)	1099 (34%)			135 (34%)	741 (33%)		
Low	1198 (31%)	1050 (33%)			119 (30%)	798 (35%)		
Missing	71 (2%)	63 (2%)			9 (2%)	31 (1%)		

Year of Diagnosis			<0.0001	<0.0001			<0.0001	<0.0001
2006-2007	233 (6%)	513 (16%)			5 (1%)	333 (15%)		
2008-2011	1401 (36%)	1398 (44%)			107 (27%)	968 (42%)		
2012-2014	2277 (58%)	1302 (41%)			280 (71%)	978 (43%)		
Tumor								
Tumor Size			<0.0001	<0.0001			<0.0001	0.0003
pT1	2949 (75%)	2317 (72%)			228 (58%)	923 (41%)		
pT2	931 (24%)	810 (25%)			153 (39%)	1063 (47%)		
pT3	31 (1%)	86 (3%)			9 (2%)	239 (10%)		
Other	0	0			2 (1%)	54 (2%)		
Nodal Involvement			<0.0001	<0.0001			<0.0001	<0.0001
pN0	3711 (95%)	2912 (91%)			0	0		
pN1mi	200 (5%)	301 (9%)			0	0		
pN1	0	0			369 (94%)	1499 (66%)		
pN2	0	0			18 (5%)	534 (23%)		
pN3	0	0			3 (1%)	244 (11%)		
Missing	0	0			2 (1%)	2 (0%)		
Tumor Grade			0.0001	0.012			<0.0001	0.055
1	934 (24%)	673 (21%)			113 (29%)	397 (17%)		
2	2303 (59%)	1874 (58%)			218 (56%)	1247 (55%)		
3	625 (16%)	619 (19%)			55 (14%)	589 (26%)		
Missing	49 (1%)	47 (1%)			6 (2%)	46 (2%)		
Receipt of Chemotherapy			0.172	<0.0001			<0.0001	<0.0001
No	2835 (72%)	2239 (70%)			210 (54%)	402 (18%)		
Yes	923 (24%)	787 (24%)			165 (42%)	1772 (78%)		
Missing	153 (4%)	187 (6%)			17 (4%)	105 (5%)		

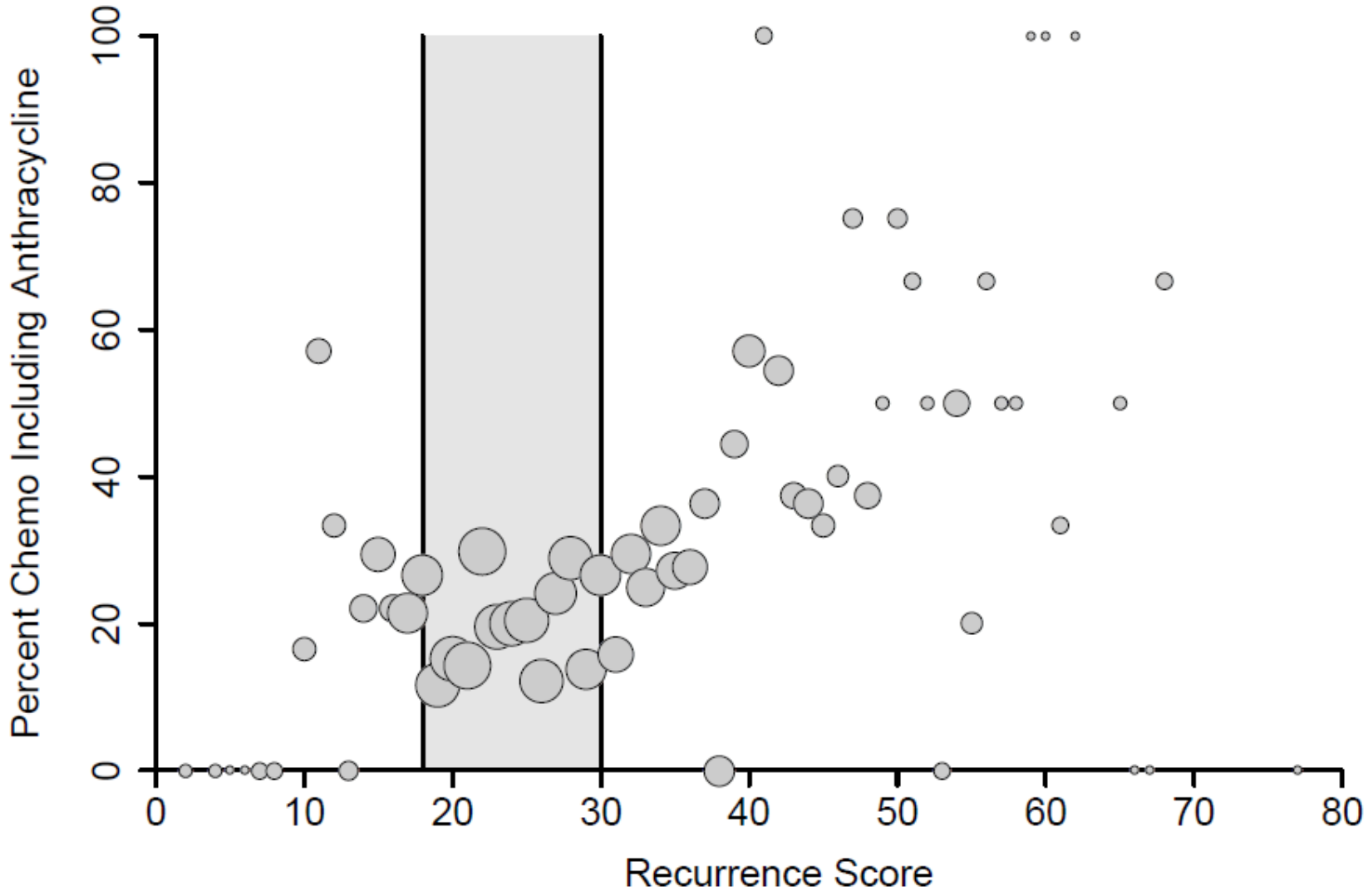
Supplemental Figure 1. Percentage of patients with HR+, HER2- breast cancer who were treated with chemotherapy, over time. Rates are given for node-negative disease (circles), micrometastatic nodal disease (triangles), macrometastatic nodal disease (diamonds), and all cohorts combined (solid line, squares).



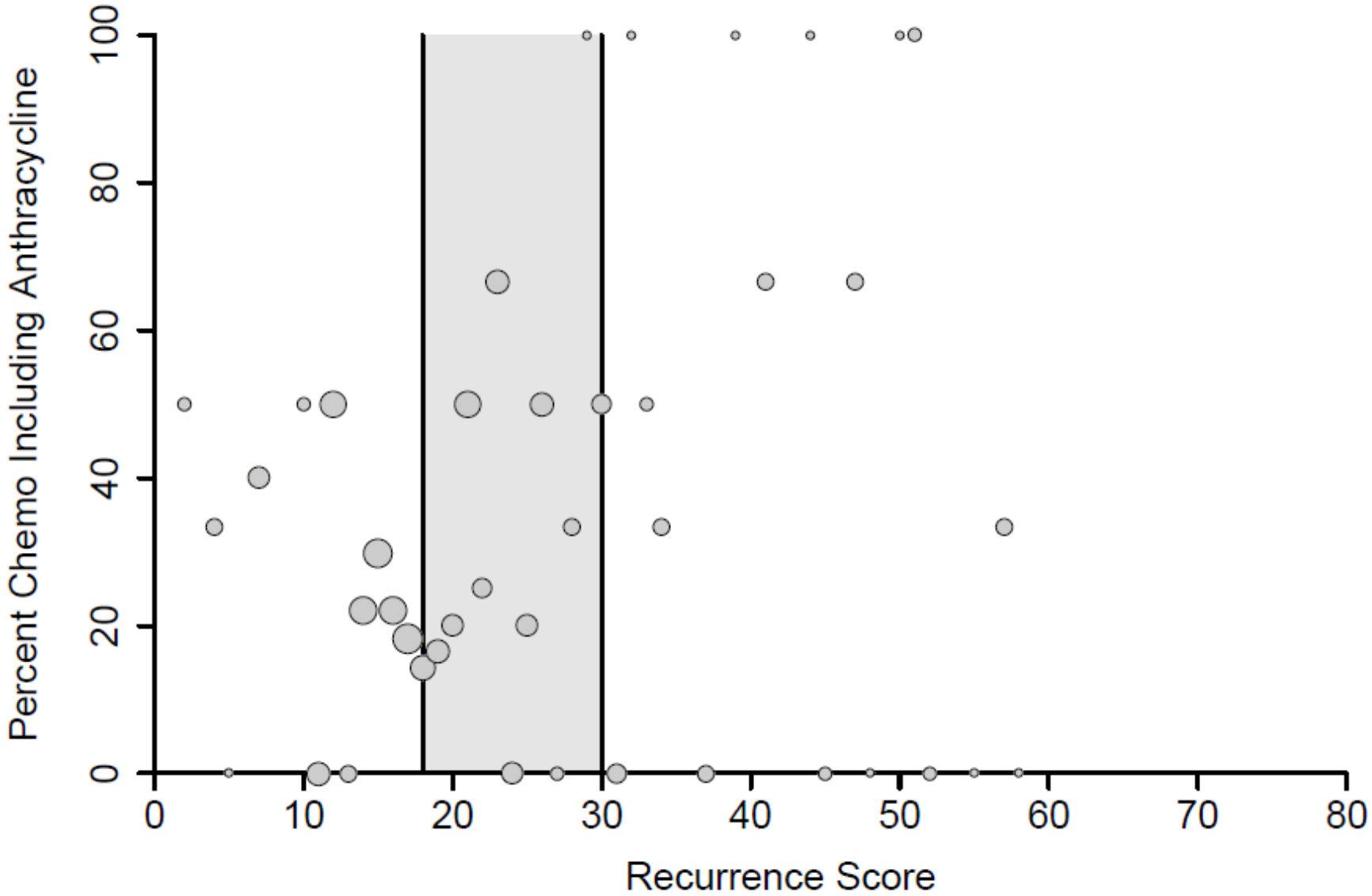
Supplemental Figure 2. Percentage of patients with HR+, HER2-, lymph node-negative breast cancer with low recurrence scores who were treated with chemotherapy, over time.



Supplemental Figure 3A. Bubble plot demonstrating receipt of anthracycline-containing chemotherapy (chemo) regimens by recurrence score for chemotherapy-treated patients with HR+, HER2- breast cancer. Each circle represents average percentage of patients treated with an anthracycline-based regimen for each RS, and size of each circle represents the number of patients with each RS. (A) Node-negative cohort.



Supplemental Figure 3B. Bubble plot demonstrating receipt of anthracycline-containing chemotherapy (chemo) regimens by recurrence score for chemotherapy-treated patients with HR+, HER2- breast cancer. Each circle represents average percentage of patients treated with an anthracycline-based regimen for each RS, and size of each circle represents the number of patients with each RS. (B) Node-positive cohort



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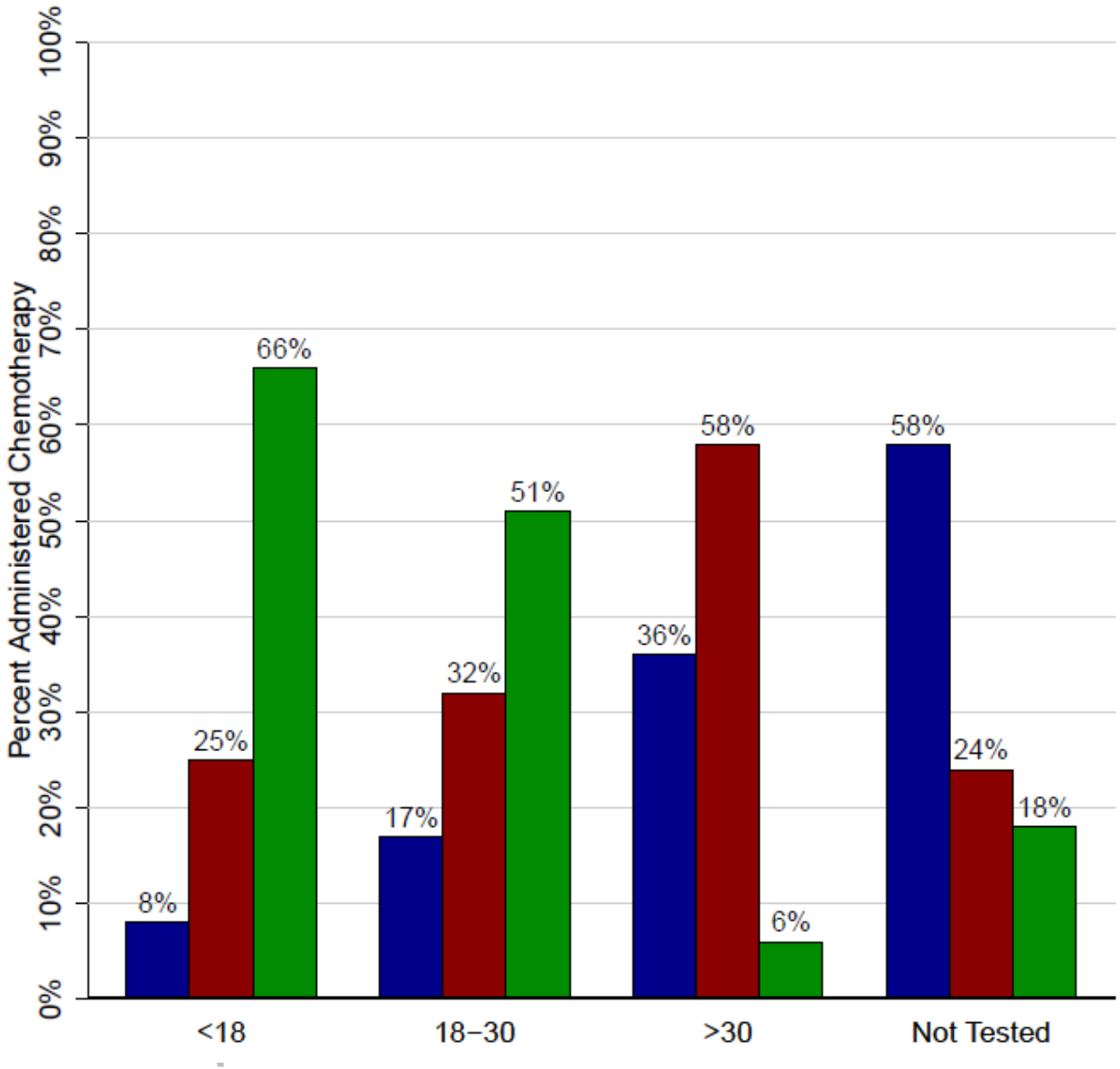

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