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Practice Changing Potential of TAILORx: A Retrospective Review of the National Cancer Data Base from 2010 to 2015

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ABSTRACT

Background. Uncertainty regarding chemotherapy benefit among breast cancer patients with intermediate Oncotype Dx® recurrence scores (RS; 11–25) led to the TAILORx study. We evaluated chemotherapy use in patients with intermediate RS to determine practice change potential based on the TAILORx results.

Methods. National Cancer Data Base patients with hormone receptor-positive/human epidermal growth factor receptor 2 (HER2)-negative, N0 breast cancer were identified and were divided into three groups: Group A, $\leq$ 50 years of age (RS 11–15); Group B, $\leq$ 50 years of age (RS 16–25); and Group C, $>$ 50 years of age (RS 11–25). Demographic and clinical factors were compared using Chi square tests and Poisson regression models to determine predictors of chemotherapy receipt.

Results. Overall, 37,087 patients met the inclusion criteria, with 6.3% in Group A and 11.7% in Group C having received chemotherapy that may have been avoided based on TAILORx. The majority of Group B (64.7%) did not receive chemotherapy, whereas TAILORx showed potential benefit from treatment. Chemotherapy use decreased over time for all intermediate RS patients. T2 tumors, high grade, and treatment before 2012 increased the likelihood of chemotherapy receipt among both groups. Younger patients with the lower intermediate RS (Group A) were more likely to receive chemotherapy if they had treatment at community or comprehensive centers, whereas moderate grade was also a significant factor to receive chemotherapy in Group B. Significant factors in older patients (Group C) were Black race, estrogen receptor-positive/progesterone receptor-negative, and moderate/high grade.

Conclusions. The most potential impact of TAILORx findings on practice change is for patients $\leq$ 50 years of age with RS of 16–25 who did not receive chemotherapy but may benefit. These findings may serve as a baseline for future analysis of practice patterns related to TAILORx.

The use of multigene panel assays as genomic predictors of distant breast cancer recurrence and chemotherapy response have become a staple in modern treatment algorithms for early-stage breast cancer. The Oncotype Dx® 21-gene assay has been included in the National Comprehensive Cancer Network (NCCN) guidelines for early-stage hormone-sensitive, node-negative, invasive breast cancers since 2008 and is now listed as a category 1 recommendation.[1] The Oncotype Dx 21-gene Breast Cancer Recurrence Score® (RS) [Genomic Health, Redwood City, CA, USA] is based on an algorithm of quantitative expression of 16 cancer-related genes and 5 reference genes.[2] The RS results range from 0 to 100, originally reported as low ($<$ 18), intermediate (18–30), and high ($\geq$ 31). A high RS ($\geq$ 31) indicates an increased risk of

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recurrence and predicts chemotherapy benefit, whereas a low RS (< 18) is unlikely to benefit from chemotherapy.[2–6] Sparano et al. later revised these definitions to better emulate how the test was being used in clinical practice and to account for the absence of human epidermal growth factor receptor 2 (HER2) patients in prospective validation studies.[7,8] The revised RS scale was defined as low (≤ 10), intermediate (11–25), and high (≥ 26).

The clinical use of Oncotype Dx gene assay among patients with breast cancer has increased over time and is associated with a decreased use of adjuvant chemotherapy, as seen in multiple population studies that queried the National Cancer Data Base (NCDB) from 2009 to 2014.[9,10] Bhutiani et al. compared the rate of chemotherapy administration among 476,128 eligible women with invasive breast cancer in the NCDB from 2011 to 2014 and found the use of chemotherapy was significantly less among patients who used multigene signature panels (MSPs; 24.6%), compared with 37.2% among those without MSPs ($p < 0.001$).[9] They found that of the 136,805 patients who had Oncotype Dx testing, only 20% were identified as low risk (RS ≤ 10), whereas 70,307 (51.4%) were identified with intermediate RS of 11–25. At that time, the clinical implications of an intermediate RS were not as clear as in the other risk groups.

As a result, the use of chemotherapy in patients with intermediate RS ranges widely, and, in some cases, outcomes are based on subgroups within the intermediate RS groups. A Surveillance, Epidemiology, and End Results (SEER) database study demonstrated that practice patterns with regard to chemotherapy within the intermediate-risk group varied: 12.8% (RS 18–19), 35.0% (RS 20–23), and 84.0% (RS 24–30).[11]

This uncertainty regarding chemotherapy benefit for the intermediate RS group (11–25) led to a large prospective randomized controlled trial known as the Trial Assigning IndividuaLized Options for treatment (TAILORx),[5] where 6711 patients with hormone-positive, HER2-negative invasive breast cancer with an intermediate RS were randomized to chemotherapy + endocrine therapy versus endocrine therapy alone. All patients were free of axillary disease (N0) and did not have prior breast cancer treatments. Cut-off points used in TAILORx were low RS (≤ 10), intermediate RS (11–25), and high RS (≥ 26). Prior to this study, patients with an intermediate RS lacked definitive guidelines to direct the decision to include chemotherapy. Results of this landmark study published in the New England Journal of Medicine in 2018 clarified which subsets of women were more or less likely to benefit from chemotherapy, allowing many to safely avoid adjuvant chemotherapy treatment as a breast cancer treatment, as well as identifying those that are most likely to benefit. Endocrine treatment alone was noninferior to chemoendocrine treatment in women ≤ 50 years of age with RS of 11–15 and in women > 50 years of age with RS of 11–25. When adjusted for age, chemotherapy benefit was supported in women ≤ 50 years of age with RS of 16–25.[5]

The purpose of this study was to identify factors associated with receipt of chemotherapy in patients with intermediate RS, as well as nationwide patterns of care since the addition of Oncotype Dx to the NCDB in 2010. By assessing the practice patterns within the NCDB prior to the 2018 results of the TAILORX study, we sought to obtain a baseline for future analysis and to identify patient populations that have the most potential to benefit from practice change based on TAILORx conclusions.

METHODS

We retrospectively reviewed patient data from the NCDB between 2010 and 2015. The NCDB is a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society that records information regarding approximately 70% of newly diagnosed cancers in the US.[12] The data used in this study are derived from a de-identified NCDB-approved file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology employed, or the conclusions drawn from these data by the investigator. This study was approved by our Institutional Review Board.

Study Population

Patients 18–75 years of age diagnosed with hormone receptor-positive (estrogen receptor-positive [ER+] or progesterone receptor-positive [PR+]), HER2-negative, N0 invasive breast cancer between 2010 and 2015 were identified. In concordance with TAILORx criteria, patients with T1 or T2 tumors were included if the tumors were 5 mm–1.0 cm in size with intermediate, high grade or lymphovascular invasion, or if they were 1.1–5.0 cm in size. All patients must have received surgery with tumor-free margins and an axillary procedure for complete diagnosis, as well as complete Oncotype DX data (numeric reporting) available.

As in the TAILORx study, patients not treated with adjuvant endocrine therapy, and with T3-T4, node-positive, M1, in situ, and/or bilateral disease, were excluded. Patients previously treated for cancer with chemotherapy or prior radiation (RT), receiving palliative RT, or who started endocrine therapy later than 8 weeks from diagnosis were also excluded. For detailed eligibility criteria, please refer to the selection map in Fig. 1.

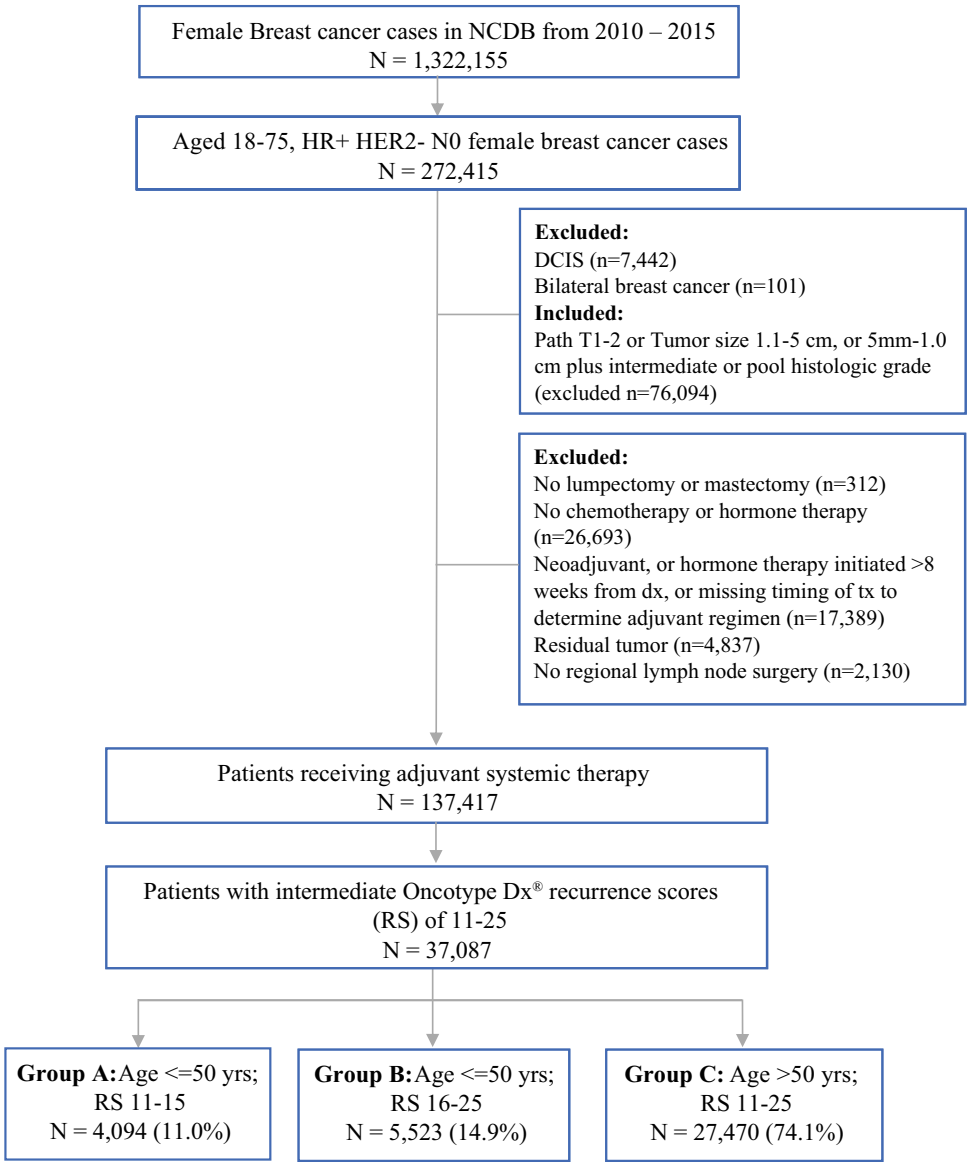

FIG. 1 Selection map of the NCDB cohort. *NCDB* National Cancer Data Base, *HR* hormone receptor, *HER2* human epidermal growth factor receptor 2, *DCIS* ductal carcinoma in situ

Patient groups were divided based on their age at the time of diagnosis and RS consistent with the TAILORx cohorts. Group A: $\leq$ 50 years of age, RS 11–15; Group B: $\leq$ 50 years of age, RS 16–25; Group C: $>$ 50 years of age, RS 11–25. We compared demographic, clinical, and pathologic factors to determine predictors of chemotherapy receipt in each group. Demographic analyses included the Charlson–Deyo score, which is a comorbidity index.[13]

Statistical Analysis

Within each cohort, baseline prognostic variables were summarized as *n* (%) for categorical variables and median [minimum–maximum] for continuous variables. We compared categorical variables, including patient demographics, and clinical and treatment characteristics, among the different treatment groups using Chi square tests or Fisher's exact tests when appropriate, and the Kruskal–Wallis test for continuous variables in univariable analyses. Poisson regression models with a robust error variance were used for multivariable analysis in each cohort, adjusting for all significant factors in the univariable analyses. Prevalence ratios (PRs) and 95% confidence intervals (CIs) were calculated to quantify the magnitude of the associations between factors and chemotherapy utilization. Due to the relatively small percentage of missing/unknown values, complete case analysis was performed. Temporal trends in annual chemotherapy use were analyzed using a log-linear piecewise regression model implemented with the Joinpoint Regression Program version 4.6.0.0 (National Cancer Institute, Bethesda, MD, USA).[14] All statistical analyses described above were

performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). Hypothesis testing was two-sided and was conducted at the 5% level of significance.

RESULTS

We identified 37,087 eligible patients with intermediate RS. Median age was 58 years (range 19–75), with the majority of patients > 50 years of age (27,470, 74.1%), White race (31,413, 84.7%), in the fourth quartile income status (highest quartile status; 15,496, 41.8%), and treated at comprehensive cancer centers (16,127, 43.5%) (Table 1a). The overall majority of patients had invasive ductal carcinoma (IDC; 27,588, 74.4%), were ER+/PR+ (34,334, 92.6%), had a tumor size < 2 cm (28,753, 77.5%), and were treated with breast-conservation surgery (25,648, 69.2%) (Table 1b).

In univariable analyses, we assessed the association of prognostic factors with the treatment decisions in an overall cohort as well as within each age group. A younger age was a significant indicator of the receipt of chemotherapy, both in the entire cohort and within each age group. Non-White patients and private insurance were also associated with chemotherapy in Group C. Patients in Group A treated in an academic facility were less likely to receive chemotherapy. Clinical factors were generally well-associated with chemotherapy use, as IDC tumors or poor prognostic factors such as larger tumor size or worse tumor grade were associated with a higher chance of chemotherapy. Using the significant factors selected from the univariable analyses, we built multivariable models to further assess the contributions of clinical factors on the receipt of chemotherapy among each age group (Tables 2, 3). We found that younger patients (age ≤ 50 years) with more favorable intermediate RS (Group A) were more likely to receive chemotherapy if their tumors were high grade (PR 2.63, 95% CI 1.66–4.15), T2 (PR 1.5, 95% CI 1.11–2.02), or if they were treated at community or comprehensive cancer centers (PR 1.88, 95% CI 1.14–3.10; and PR 1.57, 95% CI 1.14–2.16) (Table 2). Among young patients with less favorable intermediate RS (Group B), moderate grade (PR 1.28, 95% CI 1.15–1.43), high grade (PR 1.88, 95% CI 1.66–2.11), and a larger tumor size of T2, (PR 1.39, 95% CI 1.29–1.50) were more likely to receive chemotherapy, whereas those patients with government insurance (PR 0.86, 95% CI 0.76–0.97) were significantly less likely to receive chemotherapy. Neither race, receptor status, facility location, income, or comorbidities were significant factors affecting chemotherapy administration among the younger groups (A or B) (Table 2).

Demographics and clinical factors appeared to play a larger role among the older patients with intermediate RS (Group C). In this group, Black patients (PR 1.17, 95% CI 1.04–1.32), those with ER+/PR− tumors (PR 1.63, 95% CI 1.48–1.79), moderate grade (PR 1.48, 95% CI 1.34–1.63), high grade (PR 3.04, 95% CI 2.72–3.39), or T2 (PR 1.54, 95% CI 1.44–1.66) were more likely to receive chemotherapy, whereas those patients with government insurance (PR 0.62, 95% CI 0.58–0.67) or Charlson–Deyo scores ≥ 2 (PR 0.74, 95% CI 0.57–0.95) were less likely to receive chemotherapy (Table 3).

In addition, we analyzed the practice trend of chemotherapy use over time and found an overall significant decrease in receipt of chemotherapy in all patients with intermediate RS across all age groups (Fig. 2). From 2010 to 2015, the percentage of patients receiving chemotherapy decreased from 11.2 to 2.9% in Group A, with a decreasing annual percentage change (APC) of 23.3% (95% CI 15.9–30.1), 41.9% to 26.9% in Group B, with a decreasing APC of 7.5% (95% CI 1.7–13.0); and 16.1% to 8.3% in Group C, with a decreasing APC of 11.9% (95% CI 8.9–14.9). Thus, for Groups A and C, practice patterns more closely approached current recommendations based on TAILORx results over time, while for Group B, practice patterns diverged from optimal practice patterns based on TAILORx results.

The TAILORx study demonstrated that chemotherapy could safely be avoided in Groups A and C. We found that the majority of these patients were already avoiding chemotherapy prior to release of the TAILORx results; specifically, 93.7% in Group A and 88.3% in Group C did not receive chemotherapy (Table 4). As such, 6.3% of patients in Group A and 11.7% of patients in Group C (total $n = 3483$) received chemotherapy but may have avoided it based on the TAILORx findings. By contrast, the majority of women in Group B (64.7%, $n = 3573$) did not receive chemotherapy, whereas TAILORx has shown this group of patients may have benefited from this additional treatment. While the raw numbers appear to be similar, those in Groups A and C were becoming more compliant towards not receiving chemotherapy, as seen in the practice trends. Therefore, patients in Group B show the largest potential for optimizing practice change based on the TAILORx results, whereas practice patterns for Groups A and C are already predominantly in accordance with the TAILORx results and recommendations.

DISCUSSION

To the best of our knowledge, our study is the first analysis of the therapeutic implications of TAILORx in patients with breast cancer registered in the NCDB. The

TABLE 1 (a) Cohort demographics stratified by intermediate RS. (b) Clinical characteristics stratified by intermediate RS

	Total			Group A			Group B			Group C		
				≤ 50 years; RS 11–15			≤ 50 years; RS 16–25			> 50 years; RS 11–25		
	N = 37,087			*N* = 4094			*N* = 5523			*N* = 27,470		
	No chemo *N* = 31,654, 85.4% *N* (%)	Chemo *N* = 5433, 14.7% *N* (%)	*p*	No chemo *N* = 3835, 93.7% *N* (%)	Chemo *N* = 259, 6.3% *N* (%)	*p*	No chemo *N* = 3573, 64.7% *N* (%)	Chemo *N* = 1950, 35.3% *N* (%)	*p*	No chemo *N* = 24,246, 88.3% *N* (%)	Chemo *N* = 3224, 11.7% *N* (%)	*p*
(a)												
Age (median [min–max])	59 [19–75]	53 [22–75]	< **0.01**	46 [23–50]	44 [25–50]	< **0.01**	46 [19–50]	45 [22–50]	< **0.01**	62 [51–75]	59 [51–75]	< **0.01**
Race												
White	26,914 (85.0)	4499 (82.8)	< **0.01**	3091 (80.6)	206 (79.5)	0.83	2827 (79.1)	1545 (79.2)	0.70	20,996 (86.6)	2748 (85.2)	< **0.01**
Black	2107 (6.7)	421 (7.8)		240 (6.3)	20 (7.7)		284 (8)	142 (7.3)		1583 (6.5)	259 (8)	
Hispanic	1171 (3.7)	247 (4.6)		229 (6)	16 (6.2)		205 (5.7)	123 (6.3)		737 (3)	108 (3.4)	
Asian/other	1237 (3.9)	231 (4.3)		244 (6.4)	16 (6.2)		228 (6.4)	125 (6.4)		765 (3.2)	90 (2.8)	
Unknown	225 (0.7)	35 (0.6)		31 (0.8)	1 (0.4)		29 (0.8)	15 (0.8)		165 (0.7)	19 (0.6)	
Income[a]												
1st quartile	3645 (11.5)	607 (11.2)	< **0.01**	394 (10.3)	27 (10.4)	0.81	364 (10.2)	189 (9.7)	0.09	2887 (11.9)	391 (12.1)	0.16
2nd quartile	6141 (19.4)	1046 (19.3)		627 (16.4)	43 (16.6)		605 (16.9)	354 (18.2)		4909 (20.3)	649 (20.1)	
3rd quartile	8717 (27.5)	1353 (24.9)		1022 (26.7)	62 (23.9)		920 (25.8)	447 (22.9)		6775 (27.9)	844 (26.2)	
4th quartile	13,084 (41.3)	2412 (44.4)		1780 (46.4)	126 (48.7)		1674 (46.9)	954 (48.9)		9630 (39.7)	1332 (41.3)	
Unknown	67 (0.2)	15 (0.3)		12 (0.3)	1 (0.4)		10 (0.3)	6 (0.3)		45 (0.2)	8 (0.3)	
Insurance												
Private	20,192 (63.8)	4113 (75.7)	< **0.01**	3329 (86.8)	224 (86.5)	0.78	3004 (84.1)	1686 (86.5)	**0.03**	13,859 (57.2)	2203 (68.3)	< **0.01**
Uninsured	433 (1.4)	110 (2)		68 (1.8)	6 (2.3)		84 (2.4)	48 (2.5)		281 (1.2)	56 (1.7)	
Government	10,739 (33.9)	1159 (21.3)		411 (10.7)	26 (10)		438 (12.3)	192 (9.9)		9890 (40.8)	941 (29.2)	
Unknown	290 (0.9)	51 (0.9)		27 (0.7)	3 (1.2)		47 (1.3)	24 (1.2)		216 (0.9)	24 (0.7)	
Facility type												
Academic	11,054 (34.9)	1829 (33.7)	0.40	1464 (38.2)	59 (22.8)	**0.01**	1335 (37.4)	668 (34.3)	0.14	8255 (34.1)	1102 (34.2)	0.07
Community	2605 (8.2)	441 (8.1)		242 (6.3)	20 (7.7)		236 (6.6)	98 (5)		2127 (8.8)	323 (10)	
Comprehensive	13,933 (44)	2194 (40.4)		1427 (37.2)	93 (35.9)		1288 (36.1)	665 (34.1)		11,218 (46.3)	1436 (44.5)	
Integrated	3424 (10.8)	554 (10.2)		384 (10)	23 (8.9)		394 (11)	168 (8.6)		2646 (10.9)	363 (11.3)	
Unknown	638 (2)	415 (7.6)		318 (8.3)	64 (24.7)		320 (9)	351 (18)				
Facility location												
East	14,454 (45.7)	2341 (43.1)	0.40	1726 (45)	93 (35.9)	0.93	1603 (44.9)	790 (40.5)	0.93	11,125 (45.9)	1458 (45.2)	0.37
Central	11,646 (36.8)	1917 (35.3)		1248 (32.5)	71 (27.4)		1169 (32.7)	579 (29.7)		9229 (38.1)	1267 (39.3)	
West	4916 (15.5)	760 (14)		543 (14.2)	31 (12)		481 (13.5)	230 (11.8)		3892 (16.1)	499 (15.5)	
Unknown	638 (2)	415 (7.6)		318 (8.3)	64 (24.7)		320 (9)	351 (18)				

TABLE 1 continued

	Total			Group A			Group B			Group C		
				≤ 50 years; RS 11–15			≤ 50 years; RS 16–25			> 50 years; RS 11–25		
	N = 37,087			*N* = 4094			*N* = 5523			*N* = 27,470		
	No chemo *N* = 31,654, 85.4% *N* (%)	Chemo *N* = 5433, 14.7% *N* (%)	*p*	No chemo *N* = 3835, 93.7% *N* (%)	Chemo *N* = 259, 6.3% *N* (%)	*p*	No chemo *N* = 3573, 64.7% *N* (%)	Chemo *N* = 1950, 35.3% *N* (%)	*p*	No chemo *N* = 24,246, 88.3% *N* (%)	Chemo *N* = 3224, 11.7% *N* (%)	*p*
Residence location												
Metro	26,490 (83.7)	4568 (84.1)	0.41	3282 (85.6)	216 (83.4)	0.58	3043 (85.2)	1678 (86.1)	0.10	20,165 (83.2)	2674 (82.9)	0.71
Urban	3861 (12.2)	659 (12.1)		393 (10.3)	30 (11.6)		364 (10.2)	199 (10.2)		3104 (12.8)	430 (13.3)	
Rural	481 (1.5)	70 (1.3)		51 (1.3)	2 (0.8)		53 (1.5)	16 (0.8)		377 (1.6)	52 (1.6)	
Unknown	822 (2.6)	136 (2.5)		109 (2.8)	11 (4.3)		113 (3.2)	57 (2.9)		600 (2.5)	68 (2.1)	
(b)												
Charlson–Deyo score												
0	27,104 (85.6)	4767 (87.7)	< **0.01**	3547 (92.5)	236 (91.1)	0.53	3255 (91.1)	1784 (91.5)	0.86	20,302 (83.7)	2747 (85.2)	< **0.01**
1	3832 (12.1)	593 (10.9)		247 (6.4)	21 (8.1)		287 (8)	151 (7.7)		3298 (13.6)	421 (13.1)	
2+	718 (2.3)	73 (1.3)		41 (1.1)	2 (0.8)		31 (0.9)	15 (0.8)		646 (2.7)	56 (1.7)	
Tumor size												
pT1	24,995 (79)	3758 (69.2)	< **0.01**	3025 (78.9)	177 (68.3)	< **0.01**	2892 (80.9)	1377 (70.6)	< **0.01**	19,078 (78.7)	2204 (68.4)	< **0.01**
pT2	6659 (21)	1675 (30.8)		810 (21.1)	82 (31.7)		681 (19.1)	573 (29.4)		5168 (21.3)	1020 (31.6)	
Receptor status												
ER+PR+	29,418 (92.9)	4916 (90.5)	< **0.01**	3795 (99)	257 (99.2)	1.00	3467 (97)	1872 (96)	0.10	22,156 (91.4)	2787 (86.5)	< **0.01**
ER+PR−	2225 (7)	514 (9.5)		39 (1)	2 (0.8)		104 (2.9)	77 (4)		2082 (8.6)	435 (13.5)	
ER−PR+	11 (0)	3 (0.1)		1 (0)	0 (0.0)		2 (0.1)	1 (0.1)		8 (0)	2 (0.1)	
Grade												
Well diff	7287 (23)	752 (13.8)	< **0.01**	968 (25.2)	44 (17)	< **0.01**	763 (21.4)	270 (13.9)	< **0.01**	5556 (22.9)	438 (13.6)	< **0.01**
Mod diff	19,791 (62.5)	3132 (57.7)		2421 (63.1)	162 (62.6)		2223 (62.2)	1136 (58.3)		15,147 (62.5)	1834 (56.9)	
Poorly diff	3417 (10.8)	1327 (24.4)		301 (7.8)	46 (17.8)		442 (12.4)	475 (24.4)		2674 (11)	806 (25)	
Unknown	1159 (3.7)	222 (4.1)		145 (3.8)	7 (2.7)		145 (4.1)	69 (3.5)		869 (3.6)	146 (4.5)	
Histology												
IDC	23,350 (73.8)	4238 (78)	< **0.01**	2952 (77)	218 (84.2)	**0.03**	2817 (78.8)	1604 (82.3)	< **0.01**	17,581 (72.5)	2416 (74.9)	**0.01**
ILC	4564 (14.4)	636 (11.7)		426 (11.1)	18 (7)		354 (9.9)	155 (8)		3784 (15.6)	463 (14.4)	
Mix	3740 (11.8)	559 (10.3)		457 (11.9)	23 (8.9)		402 (11.3)	191 (9.8)		2881 (11.9)	345 (10.7)	
Surgery type												
BCS	22,159 (70)	3489 (64.2)	< **0.01**	2196 (57.3)	122 (47.1)	< **0.01**	2227 (62.3)	1115 (57.2)	< **0.01**	17,736 (73.2)	2252 (69.9)	< **0.01**
Mastectomy	9495 (30)	1944 (35.8)		1639 (42.7)	137 (52.9)		1346 (37.7)	835 (42.8)		6510 (26.9)	972 (30.2)	

TABLE 1 continued

Total			Group A			Group B			Group C		
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Radiation											
No 10,107 (31.9)	1938 (35.7)	**< 0.01**	1641 (42.8)	133 (51.4)	**< 0.01**	1346 (37.7)	835 (42.8)	**< 0.01**	7120 (29.4)	984 (30.5)	0.18
Yes 21,547 (68.1)	3495 (64.3)		2194 (57.2)	126 (48.7)		2227 (62.3)	1129 (57.9)		17,126 (70.6)	2240 (69.5)	

Significant values are given in bold ($p < 0.05$)

RS Oncotype Dx recurrence score, *chemo* chemotherapy, *min* minimum, *max* maximum, *ER* estrogen receptor, *PR* progesterone receptor, *diff* differentiated, *IDC* invasive ductal carcinoma, *ILC* invasive lobular carcinoma, *Mix* mixed ductal and lobular carcinoma, *BCS* breast-conserving surgery, *SLNB* sentinel lymph node biopsy, *ALND* axillary lymph node dissection, *LN* lymph node

[a]Income based on U.S. Census 2007–2012 quartile values: 1st quartile = less than 38 K, 2nd quartile = 38–48 K, 3rd quartile = 48–63 K, 4th quartile = greater than 63 K

introduction of RS into clinical decision making has revolutionized the treatment of hormone-positive breast cancer, and the upward trend in the use of Oncotype DX is expected after the introduction and inclusion of recommendations for genomic profiling in the American Joint Committee on Cancer 8th edition cancer staging in 2016.[15] Until recently, patients with intermediate RS were considered in a 'gray area' and practice patterns varied widely across the country. Prior to release of the TAILORx results, clinical decision making for chemotherapy recommendations have been based largely on age and rising RS, with younger patients (< 50 years of age) in the intermediate RS group receiving significantly more chemotherapy than patients > 50 years of age.[16] A recent study, using the NCDB, also found that younger patients are more likely to agree to chemotherapy when recommended compared with patients > 50 years of age, underscoring that both patients and clinicians are factoring in both age and tumor biology in their decision making.[10] A meta-analysis looking at the proportion of patients receiving chemotherapy based on RS by risk group found that between 26.5 and 65% of patients with intermediate RS received chemotherapy.[17] This is in contrast to our findings where the younger patients (≤ 50 years of age) were mostly not receiving chemotherapy (7428/9617, 77%) and only 23% of the younger group and 11.7% of the older group (> 50 years of age) did receive chemotherapy.

Our study found that in all patients, even those in Group A who were considered to have a more favorable intermediate RS score, chemotherapy recommendation was based on apparent tumor biology despite genomic profiling. Tumor size > 2 cm (T2) and high grade (poor differentiation) were consistent factors that increased the likelihood of receiving chemotherapy across all groups. This is not surprising since prior to genomic profiling, tumor grade was an independent prognostic factor[18–20] that was incorporated into algorithims[21] and guidelines[22] to determine the use of adjuvant chemotherapy. Tumor size and age have long been a measure that influences the receipt of chemotherapy and was historically the best predictor of the need for systemic treatment.[23–25] Recent studies support the theory that Oncotype DX results are significantly impacted by clinicopathologic factors such as histologic grade (high grade) and subtype (progesterone receptor status), where tumors that have favorable biology are less likely to have high-risk RS, and vice versa.[26,27]

Insurance status varies by socioeconomic status of insurance holders and is a measure of health care accessibility, affordability, and use.[28] When adjusted for factors such as score on the RS assay, age, tumor grade, and tumor size, the trend in use of chemotherapy was lower in the population with government insurance. Medicaid insurance has been implicated in the lower use of guideline-

TABLE 2 Multivariable analysis of factors affecting receipt of chemotherapy among patients ≤ 50 years of age

Group A				Group B			
≤ 50 years; RS 11–15				≤ 50 years; RS 16–25			
N = 4094				*N* = 5523			
	Prevalence ratio	Confidence interval	*p* value		Prevalence ratio	Confidence interval	*p* value
Facility type				*Insurance*			
Academic	Ref			Private	Ref		
Community	**1.88**	1.14–3.10	0.01				
Comprehensive	1.57	1.14–2.16	< **0.01**	Uninsured	1.03	0.82–1.29	0.81
Integrated	**1.4**	0.87–2.25	0.16	Government	0.86	0.76–0.97	**0.02**
Tumor size				*Tumor size*			
pT1	Ref			pT1	Ref		
pT2	1.5	1.11–2.02	< **0.01**	pT2	1.39	1.29–1.50	< **0.01**
Grade				*Grade*			
Well diff	Ref			Well diff	Ref		
Mod diff	1.32	0.92–1.9	0.13	Mod diff	1.28	1.15–1.43	< **0.01**
Poorly diff	2.63	1.66–4.15	< **0.01**	Poorly diff	1.88	1.66–2.11	< **0.01**
Histology				*Histology*			
IDC	Ref			IDC	Ref		
ILC	0.67	0.41–1.1	0.11	ILC	0.83	0.72–0.96	**0.01**
Mix	0.78	0.49–1.24	0.3	Mix	0.89	0.79–1.01	0.07
Surgery type				*Surgery type*			
BCS	Ref			BCS	Ref		
Mastectomy	1.83	0.6–5.57	0.28	Mastectomy	1.12	0.91–1.37	0.3
Radiation				*Radiation*			
No	Ref			No	Ref		
Yes	1.25	0.41–3.79	0.69	Yes	1.03	0.84–1.26	0.8
Year of diagnosis				*Year of diagnosis*			
2010	Ref			2010	Ref		
2011	0.9	0.61–1.34	0.6	2011	0.9	0.61–1.34	0.6
2012	0.62	0.41–0.95	**0.03**	2012	0.62	0.41–0.95	**0.03**
2013	0.56	0.36–0.87	< **0.01**	2013	0.56	0.36–0.87	< **0.01**
2014	0.32	0.19–0.54	< **0.01**	2014	0.32	0.19–0.54	< **0.01**
2015	0.17	0.09–0.33	< **0.01**	2015	0.17	0.09–0.33	< **0.01**

Significant values are given in bold ($p < 0.05$)

Factors found significant on univariate analysis were selected for analysis in the multivariate table

RS Oncotype Dx recurrence score, *diff* differentiated, *IDC* invasive ductal carcinoma, *ILC* invasive lobular carcinoma, *Mix* mixed ductal and lobular carcinoma, *BCS* breast-conserving surgery, *Ref* reference

TABLE 3 Multivariable analysis of factors affecting receipt of chemotherapy among patients > 50 years of age

Group C			
> 50 years; RS 11–25			
N = 27,470			
	Prevalence ratio	Confidence interval	*p* value
Race			
White	Ref		
Black	1.17	1.04–1.32	**0.01**
Hispanic	1.07	0.89–1.28	0.46
Asian/other	0.9	0.74–1.10	0.32
Insurance			
Private	Ref		
Uninsured	1.07	0.83–1.37	0.62
Government	0.62	0.58–0.67	< **0.01**
Charlson–Deyo score			
0	Ref		
1	1	0.90–1.10	0.94
2+	0.74	0.57–0.95	**0.02**
Tumor size			
pT1	Ref		
pT2	1.54	1.44–1.66	< **0.01**
Receptor status			
ER+PR+	Ref		
ER+PR−	1.63	1.48–1.79	< **0.01**
ER−PR+	1.82	0.60–5.47	0.29
Grade			
Well diff	Ref		
Mod diff	1.48	1.34–1.63	< **0.01**
Poorly diff	3.04	2.72–3.39	< **0.01**
Histology			
IDC	Ref		
ILC	0.93	0.84–1.03	0.17
Mix	0.89	0.80–0.99	**0.04**
Surgery type			
BCS	Ref		
Mastectomy	1.06	0.99–1.14	0.11
Year of diagnosis			
2010	Ref		
2011	0.91	0.81–1.01	0.08
2012	0.76	0.68–0.85	< **0.01**
2013	0.73	0.65–0.81	< **0.01**
2014	0.66	0.59–0.74	< **0.01**
2015	0.53	0.47–0.60	< **0.01**

Significant values are given in bold ($p < 0.05$)

Factors found significant on univariate analysis were selected for analysis in the multivariate table

RS Oncotype Dx recurrence score, *ER* estrogen receptor, *PR* progesterone receptor, *diff* differentiated, *IDC* invasive ductal carcinoma, *ILC* invasive lobular carcinoma, *Mix* mixed ductal and lobular carcinoma, *BCS* breast-conserving surgery, *Ref* reference

concordant chemotherapy compared with privately insured women in numerous studies,[29–32] and may be due to factors pertaining to Medicaid status, such as social support or transportation. In addition, our particular subset may have been influenced by selecting only those patients who had complete Oncotype DX information. While performance of genomic assays gives patients the opportunity of personalized prognostic and predictive information, these tests have a cost. Utilization is calculated to be approximately in one-third of patients who meet the criteria in developed countries, and studies have shown that utilization of this test is largely influenced by socioeconomic status and race.[33–35] An attempt at creating a surrogate to this genomic assay has been done using clinicopathologic factors alone, including age, tumor size, grade, progesterone receptor status, and histologic type. This nomogram is thought to predict Oncotype Dx RS and therefore be used in the absence of genomic testing, potentially bridging that gap for those patients who are unable to obtain testing due to socioeconomic barriers.[26]

Despite the trend seen in the decreasing recommendation and administration of chemotherapy for women < 50 years of age, we found that the group with the highest potential for impact based on the TAILORx results was the ≤ 50 years age group and RS between 16 and 25 who did not receive chemotherapy, but may benefit from receiving it. A recent study by Sparano et al. utilized tumor size and histologic grade to stratify these women (≤ 50 years of age with intermediate RS) into low and high clinical risk to better identify which of these patients may benefit from chemotherapy.[36] There is also potential for a further decrease in chemotherapy administration for those subjects in Groups A and C, and the overall decreasing trend of receiving chemotherapy makes it promising that this will be met. It will be interesting to track data for chemotherapy administration for the time period after the TAILORx results were released to see if practice patterns comply with the recommendations based on the TAILORx results, with the hope that the trend seen in decreasing chemotherapy among those < 50 years of age with RS of 16–25 is reversed. This practice implication will not only impact overall quality of life by avoiding or receiving systemic therapy but will also have a financial impact that may lead to an increase in testing that may be beneficial in the long term by decreasing chemotherapy utilization. A recent study looked at the impact on healthcare costs of the TAILORx study and found that pretrial mean initial costs were $2.816 billion, and, post-trial, Oncotype DX testing costs were projected to increase from $115 to $231 million and chemotherapy use to decrease from 25 to 17%, resulting in initial care costs of $2.766 billion, or a net savings of $49 million (1.8% decrease). Although there

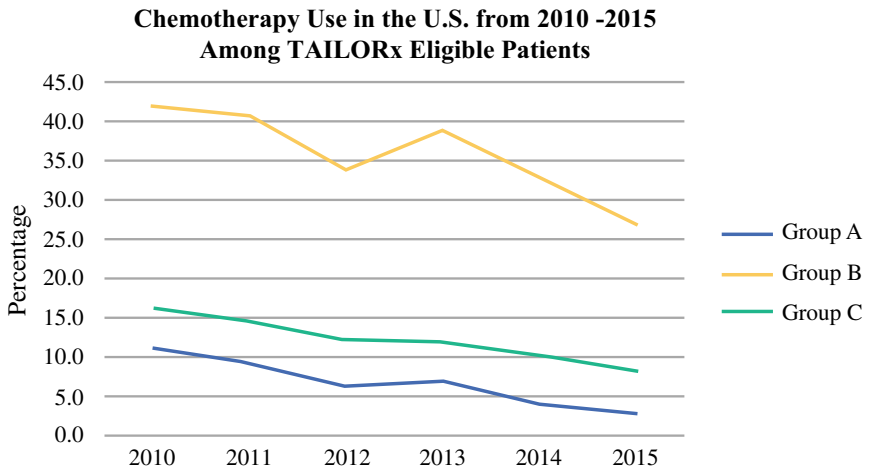

FIG. 2 Chemotherapy use in the US from 2010 to 2015 among TAILORx-eligible patients. *Chemo* chemotherapy, *RS* Oncotype Dx recurrence score

		No Chemo		Chemo	
	Year of Diagnosis	N	%	N	%
Group A ≤50 years RS 11-15	2010	451	88.8	57	11.2
	2011	532	90.8	54	9.2
	2012	673	93.6	46	6.4
	2013	686	93.2	50	6.8
	2014	685	96.1	28	3.9
	2015	808	97.1	24	2.9
Group B ≤50 years RS 16-25	2010	420	58.1	303	41.9
	2011	511	59.4	350	40.7
	2012	606	66.1	311	33.9
	2013	566	61.0	362	39.0
	2014	705	67.3	342	32.7
	2015	765	73.1	282	26.9
Group C >50 years RS 11-25	2010	2609	83.9	500	16.1
	2011	3339	85.3	577	14.7
	2012	3783	87.8	528	12.3
	2013	4273	88.1	578	11.9
	2014	4857	89.7	557	10.3
	2015	5385	91.8	484	8.3

TABLE 4 Receipt of chemotherapy stratified among intermediate RS groups

Total *N* = 37,087		No chemo	Chemo
Group A ≤ 50 years, RS 11–15	4094 (11.0%)	3835 (93.7%)	259 (6.3%)
Group B ≤ 50 years, RS 16–25	5523 (14.9%)	3573 (64.7%)	1950 (35.3%)
Group C > 50 years, RS 11–25	27,470 (74.1%)	24,246 (88.3%)	3224 (11.7%)

RS Oncotype Dx recurrence score, *chemo* chemotherapy

was one exception for patients < 50 years of age with RS of 16–25 if they elected to receive chemotherapy, initial care costs could increase by $105 million (4% increase).[37]

There are several strengths to this study, including a large, nationwide sample with sufficiently complete data on Oncotype DX for the years of analysis and refined

subgroup analysis. The study also has several limitations. First, observational studies are subject to confounding, and, second, the NCDB collects data from CoC-accredited hospitals, which may be limited to CoC-approved hospitals.

CONCLUSIONS

The use of chemotherapy in patients with intermediate RS has progressively decreased over time across all age groups. Based on our data, the most potential impact of the TAILORx recommendations on practice change is for the large group of patients 50 years of age with RS of 16–25 who did not receive chemotherapy but may benefit. Factors related to the omission of chemotherapy in this group should be further explored to optimize patient selection for chemotherapy in the future. These findings may serve as a baseline for future analysis of practice patterns related to TAILORx.

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