

Practice-Changing Use of the 21-Gene Test for the Management of Patients With Early-Stage Breast Cancer in Latin America

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PURPOSE We present a physician survey of the impact of 21-gene Breast Recurrence Score test results on treatment decisions in clinical practice in Latin America.

METHODS This prospective survey enrolled consecutive patients at 14 sites in Argentina, Colombia, Mexico, and Peru who had routine 21-gene testing. Physician surveys captured patient and tumor characteristics and treatment decisions before and after 21-gene test results. The survey spanned the period before and after Trial Assigning Individualized Options for Treatment (TAILORx) results reported (June 2018). Overall net percent change in adjuvant chemotherapy recommendations was estimated, and asymptotic 95% CIs with continuity correction were calculated. The proportion with a change between pretest treatment recommendation and actual treatment received was calculated overall and by Recurrence Score groups per TAILORx.

RESULTS Between March 2015 and December 2019, the survey was completed for 647 patients; 20% were node-positive. The mean patient age was 54 years (24-85 years); 55% were postmenopausal; 17%, 63%, and 20% had grade 1, 2, and 3 tumors, respectively; and 30% had tumors > 2 cm. Recurrence Score (RS) results were as follows: 20% RS 0-10, 56% RS 11-25, and 24% RS 26-100. Overall, chemotherapy recommendations fell by a relative proportion of 39% (95% CI, 33.4 to 44.3) after 21-gene testing (33% decrease in node-negative and 55% decrease in node-positive). Among node-negative patients, the relative decrease in chemotherapy recommendations was 28% (95% CI, 18.9 to 39.5) before TAILORx and 36% (95% CI, 28.4 to 43.7) after.

CONCLUSION To our knowledge, this large survey of 21-gene test practice patterns was the first conducted in Latin America and showed the relevance of 21-gene testing in low- and medium-resource countries to minimize chemotherapy overuse and underuse in breast cancer. The results showed substantial reductions in chemotherapy use overall—especially after TAILORx reported—indicating the practice-changing potential of that study.

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INTRODUCTION

Breast cancer is the most common cancer and a leading cause of cancer death among women worldwide, including Latin America.¹⁻³ Although the incidence rate of breast cancer is lower in Latin America than in North America and Western Europe,¹ the mortality rate for breast cancer in Latin America is relatively higher and has been rising since the 1990s even as the rates have remained stable in high-income regions.⁴ Approximately 41% of breast cancer diagnoses in Latin America are made at advanced stages of disease (stage III and/or IV),⁵ in contrast to the 8%-23% of advanced diagnoses made in European countries⁶ and the 6% of metastatic diagnoses made in the United States.⁷ The considerable clinical burden of breast cancer in Latin America underscores the urgent need for strategies to improve outcomes for these patients.

Efforts to improve breast cancer care across Latin America depend on an understanding of practice patterns in breast cancer management. The factors that affect how physicians manage their patients with breast cancer are myriad and include type of insurance (public or private), patient socioeconomic status, country-specific medical policy, and level of access to treatments.^{2,8,9} In one study in Argentina that explored factors affecting prescribing practices in breast cancer, clinicopathologic factors such as age, nodal status, estrogen receptor (ER) and progesterone receptor (PR) status, human epidermal growth factor receptor 2 (HER2) status, and expression of the Ki67 proliferation marker influenced physicians' decisions to prescribe hormonal therapy with or without chemotherapy. Use of multigene assays to assess tumor biology was not

ASSOCIATED CONTENT

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

The study examined the effect of 21-gene test results on treatment decisions for 647 women with breast cancer treated at 14 sites in Argentina, Colombia, Mexico, and Peru.

Knowledge Generated

The mean age was 54 years; 55% of women were postmenopausal. High-risk clinicopathologic features included 20% node-positive, 20% grade 3 tumors, and 30% > 2 cm in size. Before 21-gene testing, on the basis of clinicopathologic features, 325 of 647 women (50%) were recommended chemotherapy. Samples were sent for 21-gene testing; 20% had Recurrence Score (RS) 0-10, 56% had RS 11-25, and 24% had RS 26-100. With RS results available, 199 patients were recommended chemotherapy, representing a 39% relative reduction (19% absolute reduction) in chemotherapy recommendations.

Relevance

Our findings showed the relevance of 21-gene testing in low- and medium-resource countries to minimize chemotherapy overuse and underuse in breast cancer.

named as an influential factor, however, primarily because of limited availability related to cost.⁸

The 21-gene Oncotype DX Breast Recurrence Score test (Genomic Health Inc, a wholly owned subsidiary of Exact Sciences Corp, Redwood City, CA) is a multigene assay validated as a prognosticator of 10-year risk of recurrence and a predictor of adjuvant chemotherapy benefit in patients with ER+, HER2-, node-negative, or node-positive early breast cancer who receive 5 years of hormonal therapy.¹⁰⁻¹⁷ Importantly, the primary analyses of the landmark Trial Assigning Individualized Options for Treatment (TAILORx) trial in node-negative breast cancer, reported in June 2018, showed that the cohort with Recurrence Score (RS) 0-25 derived little to no benefit from adjuvant chemotherapy. An exploratory analysis found, however, that patients ≤ 50 years with RS 11-25 may derive some benefit.^{16,18} The clinical utility of the Breast Recurrence Score test, or the capacity of the test to change clinical practice and improve outcomes of patients with node-negative or node-positive breast cancer in a cost-effective manner, has been demonstrated in numerous studies conducted worldwide.¹⁹⁻³⁸ One such study conducted in Mexico (N = 96; node-negative and node-positive breast cancer) showed that knowledge of RS results led to a 28% reduction in recommendations for chemotherapy at one center.²⁴ Another study (N = 551; node-negative and node-positive breast cancer) showed that physicians in Peru made treatment recommendations in line with RS results such that the rate of chemotherapy recommendations increased with RS groups of higher risk (13% with RS 0-17, 77% with RS 18-30, and 98% with RS 31-100).³⁹

The promising but limited data on the clinical utility of the Breast Recurrence Score test in Latin America highlight the need for further research on the potential health and economic impact of the test in this region. In this study, we presented the results of a physician survey to assess the

clinical utility of the Breast Recurrence Score test in routine practice across 14 centers in five countries in Latin America.

METHODS

This was a multicenter, prospective, observational physician survey. The primary objective of this physician survey was to provide a descriptive, qualitative assessment of patients with breast cancer who receive Oncotype DX Breast Recurrence Score testing as part of their routine care. Specific descriptive analyses aimed to characterize (1) the patterns of use of the Oncotype DX Breast Recurrence Score test in routine care across demographic and clinicopathologic variables (age, tumor size, tumor grade, and nodal status), (2) the distribution of RS results across all patients and subgroups stratified by clinicopathologic variables, (3) the effect of RS results on treatment planning as measured by the change in treatment recommendations before and after RS results are available (all patients and by nodal status), (4) the effect of RS results on physicians' level of confidence in their treatment recommendations as measured by the change in physicians' stated level of confidence before and after RS results are available, and (5) the association between the RS result and treatment decision as a function of clinicopathologic variables.

Participating physicians had to be medical oncologists or breast surgeons practicing in Latin America who make adjuvant treatment recommendations for patients with breast cancer, provide consent to participate, and complete questionnaires both before and after the Breast Recurrence Score test for each patient. The physician survey was completed for consecutive patients who met the following eligibility criteria: (1) male or female at least 18 years of age diagnosed with ER+, HER2-, node-negative, or node-positive breast cancer; (2) data available on age, tumor size, tumor grade, tumor histology, nodal status, ER and PR status by immunohistochemistry (IHC), and HER2 status by

TABLE 1. Patient Baseline Clinical and Pathologic Characteristics

Characteristic	Overall (N = 647)	NO (n = 516)	N1mi (n = 25)	N1 (n = 86)	N2 (n = 20)
Age, years					
Mean (SD)	54 (12)				
Median (IQR)	54 (45-63)				
≤ 50, No. (%)	279	219 (42)	12 (48)	38 (44)	10 (50)
> 50, No. (%)	368	297 (58)	13 (52)	48 (56)	10 (50)
Menopausal status, No. (%)					
Premenopausal	244 (38)	186 (36)	12 (48)	36 (42)	10 (50)
Perimenopausal	45 (7)	40 (8)	2 (8)	3 (3)	0 (0)
Postmenopausal	357 (55)	289 (56)	11 (44)	47 (55)	10 (50)
Tumor grade, No. (%)					
1	109	72 (14)	1 (4)	26 (30)	10 (50)
2	411	336 (65)	20 (80)	48 (56)	7 (35)
3	127	108 (21)	4 (16)	12 (14)	3 (15)
Tumor size, cm					
Mean (SD)	1.9 (1.0)				
Median (IQR)	1.7 (1.2-2.3)				
≤ 1, No. (%)	125 (19)	100 (19)	11 (44)	14 (16)	0 (0)
> 1 to 2, No. (%)	325 (50)	264 (51)	8 (32)	43 (50.0)	10 (50)
> 2 to 4, No. (%)	181 (28)	139 (27)	5 (20)	27 (31)	10 (50)
> 4, No. (%)	16 (2)	13 (3)	1 (4)	2 (2)	0 (0)
Ki67%					
Mean (SD)	23 (18)				
Median (range)	20 (0-90)				
0%-10%, No. (%)	191 (30)	127 (25)	8 (32)	46 (53)	10 (50)
11%-20%, No. (%)	209 (32)	174 (34)	9 (36)	24 (28)	2 (10)
21%-30%, No. (%)	116 (18)	101 (20)	3 (12)	7 (8)	5 (25)
> 30%, No. (%)	127 (20)	110 (21)	5 (20)	9 (10)	3 (15)
Missing	4 (< 1)	4 (< 1)	0 (0)	0 (0)	0 (0)

Abbreviations: IQR, interquartile range; NO, node-negative; N1, 1-3 positive nodes; N1mi, micrometastases; N2, 4-9 positive nodes; SD, standard deviation.

IHC and/or fluorescence in situ hybridization; (3) Breast Recurrence Score test ordered as part of routine care (either self-funded by patients or covered as part of a state-funded research grant); and (4) written and signed informed consent provided. Patients who received hormonal therapy or chemotherapy before Breast Recurrence Score testing were ineligible. If available, other clinicopathologic characteristics collected included menopausal status, tumor histology, lymphovascular invasion, and Ki67 by IHC.

Clinical and treatment decision data (chemotherapy, hormonal therapy, or chemotherapy plus hormonal therapy) were collected before and after the Breast Recurrence Score test was ordered in the course of routine care. Treatment recommendations made before testing were based on physician-patient discussions that included available clinicopathologic information and patient preferences. Treatment recommendations made after testing

also included RS results. Attending physician's confidence in treatment recommendation before Breast Recurrence Score testing and 2-3 months after test results received were recorded.

All analyses were descriptive in nature unless otherwise indicated. Descriptive statistics included, as appropriate, frequency counts and percentages in contingency tables; means, standard deviations (SDs), medians, quartiles, and ranges; Pearson and Spearman correlation coefficients; and concordance percentages and other measures of association. McNemar's test was conducted on paired preassay and postassay recommendation for chemotherapy. Trend in chemotherapy recommendation by increasing results in five-unit categories was assessed using the Cochran-Armitage trend test at both preassay and postassay recommendations. Statistics included point estimates and asymptotic 95% CIs with continuity correction

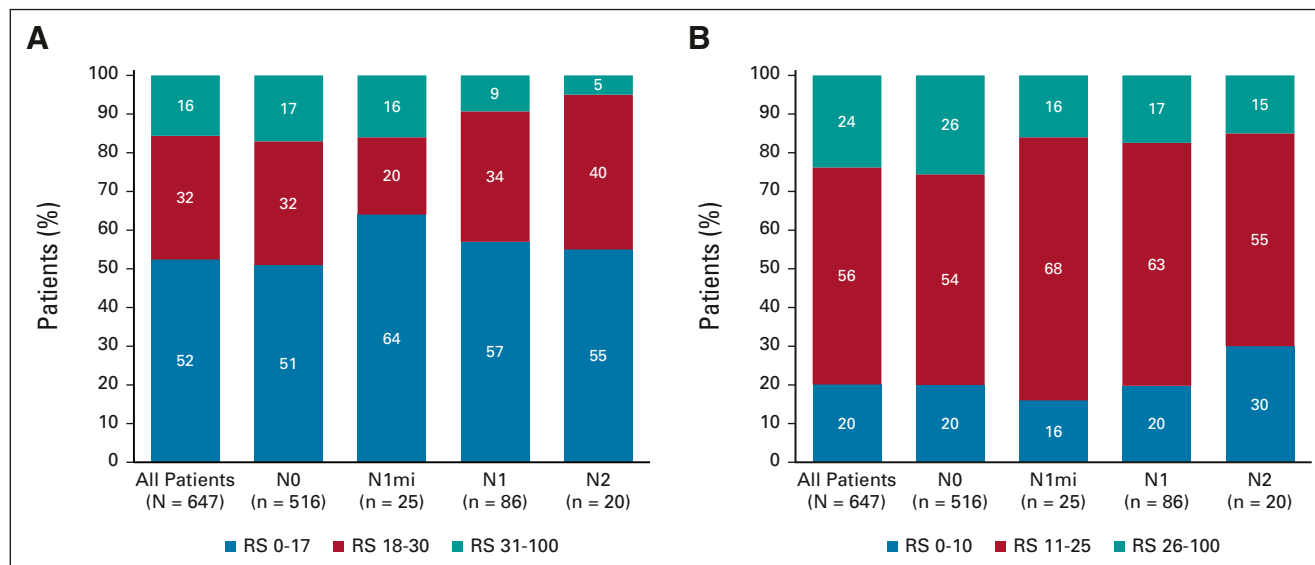


FIG 1. Distribution of RS results by (A) risk groups of RS 0-17, RS 18-30, and RS 31-100 and (B) Trial Assigning Individualized Options for Treatment risk groups of RS 0-10, RS 11-25, and RS 26-100. RS, Recurrence Score.

when appropriate.⁴⁰ CIs calculated below 0% or above 100% were set to the appropriate boundary. All hypothesis tests were conducted at a two-sided α level of .05.

RESULTS

Between March 2015 and December 2019, the survey was completed for 647 patients across 14 sites in Argentina, Colombia, Mexico, and Peru. Patient demographics and disease characteristics are given in Table 1. The mean age was 54 years (SD 12 years), and 55% were postmenopausal. Approximately 20% of patients had node-positive breast cancer (N1mi, N1, or N2). The mean tumor size was 1.9 cm (SD 1.0 cm), and approximately 30% had tumors larger than 2 cm. Almost 20% of patients had grade 3 tumors.

The distribution of RS results by nodal status is shown in Figure 1. Using RS groups defined by RS 0-17, RS 18-30, and RS 31-100, 52% of all patients had RS 0-17, ranging from 51% to 64% depending on nodal status. Using TAILORx RS groups (RS 0-10, RS 11-25, and RS 26-100), 76% of patients had RS 0-25, ranging from 74% to 85% depending on nodal status.

The distributions of RS results by nodal status and several clinicopathologic factors (tumor size, tumor grade, age, and Ki67%) are shown in Figure 2. There was a wide range of RS results for every category of every clinicopathologic factor. For example, patients with high-risk clinicopathologic features (large tumor size, high grade, younger age, and higher Ki67%) or low-risk features (small tumor size, low grade, older age, and lower Ki67%) have RS results that span low to high genomic risk.

After Breast Recurrence Score testing, 37% (n = 240) of all patients, 34% (n = 175) of patients with node-negative

breast cancer, and 50% (n = 65) of patients with node-positive breast cancer had a change in treatment recommendation. Most of the changes in treatment recommendations after Recurrence Score testing resulted in a reduction in chemotherapy recommendations (Table 2). Before Breast Recurrence Score testing, 50% (n = 325) of all patients had a chemotherapy recommendation; after testing, 31% (n = 199) did, which represents a 39% (95% CI, 33.4 to 44.3) relative reduction and a 19% absolute reduction in chemotherapy recommendations. Before testing, 47% (n = 243) of patients with node-negative breast cancer had a chemotherapy recommendation; after testing, 31% (n = 162) did, which represents a 33% (95% CI, 25.3 to 43.7) relative reduction and a 16% absolute reduction in chemotherapy recommendations.

The percent reduction in chemotherapy recommendations for patients with node-negative breast cancer varied by the time period before or after the primary analyses from the TAILORx trial reported: 28% (95% CI, 15.9 to 48.3) before TAILORx reported and 36% (95% CI, 25.8 to 49.1) after (Data Supplement). Before TAILORx, net reductions in chemotherapy recommendations were made in patients with RS 0-20; after TAILORx, net reductions were made in patients with RS 0-25 (Data Supplement). These results remained consistent when assessed by age in patients with node-negative breast cancer. After TAILORx, chemotherapy recommendations were reduced in patients with RS 0-25, regardless of age group (≤ 50 or > 50 years; Data Supplement).

Before testing, 63% (n = 82) of patients with node-positive breast cancer had a chemotherapy recommendation; after testing, 28% (n = 37) did, which represents a 55% (95% CI, 42.1 to 70.7) relative reduction and a 34% absolute

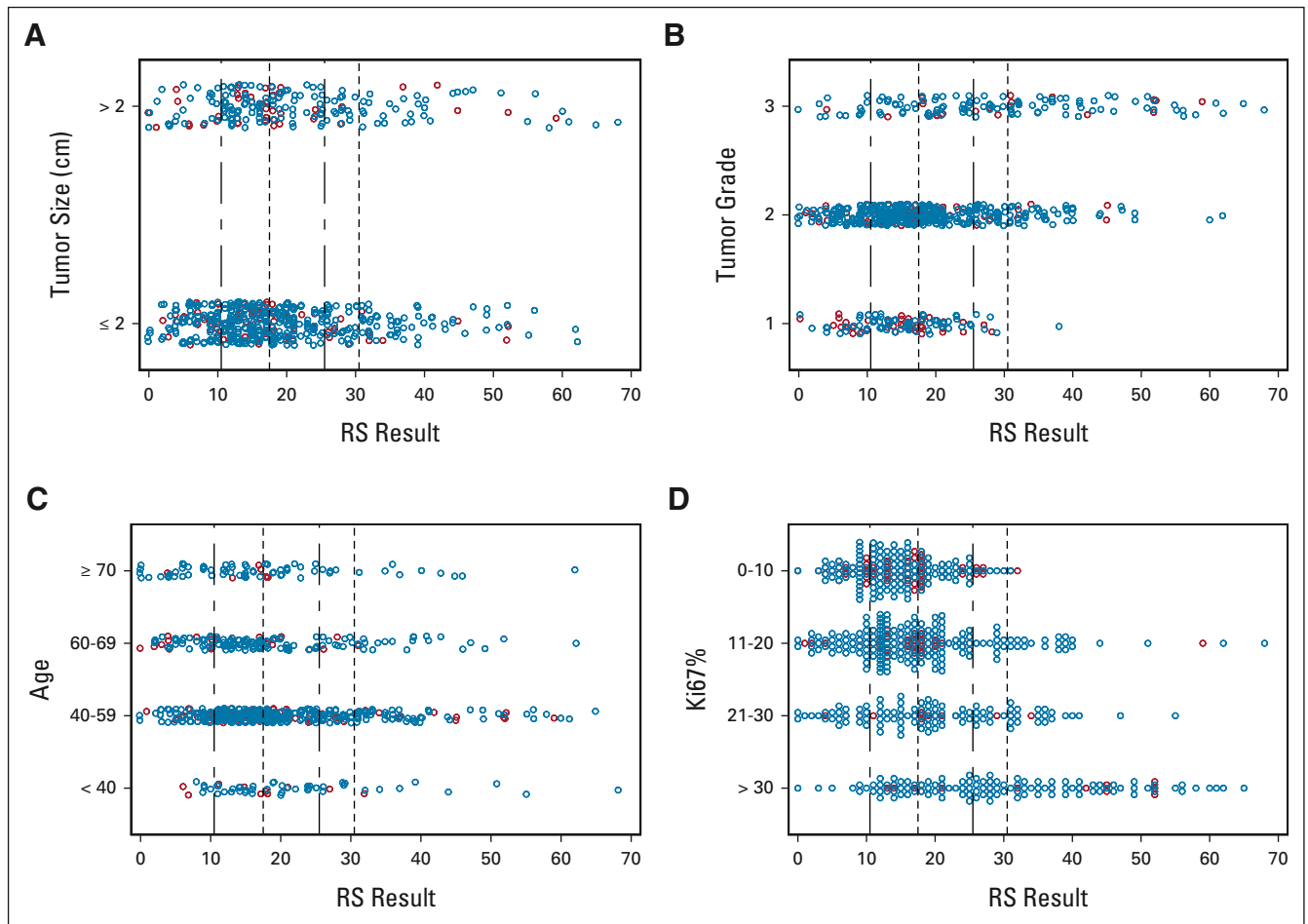


FIG 2. Distribution of RS results by (A) tumor size, (B) tumor grade, (C) age, and (D) Ki67%. Nodal status is marked by color: node-negative (blue circles), micrometastases and 0-3 positive nodes (blue circles), and 4-9 positive nodes (red circles). Vertical dotted-dashed lines mark the Trial Assigning Individualized Options for Treatment cutpoints of RS 11 and RS 26; vertical dotted lines mark the traditional cutpoints of RS 18 and RS 31. RS, Recurrence Score.

reduction in chemotherapy recommendations. The percent reduction varied by extent of nodal involvement: 74% (95% CI, 50.1 to 100 [CI was calculated to exceed 100% and set to the appropriate boundary]) for N1mi, 49% (95% CI, 31.5 to 73.5) for N1, and 50% (95% CI, 20.5 to 97.7) for N2. The percent reduction in node-positive patients was similar before and after TAILORx reported (Data Supplement).

The proportion of patients with chemotherapy recommendations before and after Breast Recurrence Score testing is shown by RS result in Figure 3. Before testing, when only clinicopathologic factors were used to guide treatment recommendations, a considerable proportion of patients with lower RS results had recommendations for chemotherapy and a proportion with higher RS results had no recommendation for chemotherapy. After RS testing, chemotherapy recommendations were reduced for those with lower RS results and increased for those with higher results.

Before RS testing, 322 (50%) of patients had recommendations excluding chemotherapy. After testing, 57

(18%) of these patients had their recommendations changed to include chemotherapy, including 47 patients (17%) with node-negative and 10 patients (20%) with node-positive breast cancer (Table 2).

Physicians rated their level of confidence in the treatment decisions made for each patient before and after RS testing (Fig 4). Before testing, physicians felt strongly confident (45%) or somewhat confident (37%) in 82% of their decisions. After RS testing, physicians felt strongly confident (81%) or somewhat confident (17%) in 98% of their treatment decisions.

DISCUSSION

This survey was the largest prospective study conducted in Latin America to evaluate the clinical utility of the Oncotype DX Breast Recurrence Score test. After the clinical validation of RS results as a predictor of adjuvant chemotherapy benefit in node-negative and node-positive breast cancer,^{11,14} prospective clinical utility studies conducted worldwide showed how physicians

TABLE 2. Change in Chemotherapy Recommendations From Before to After RS Results by Nodal Status

Patient Group	After RS Test Results		Total
	No CT Recommended	CT Recommended ^a	
All patients (N = 647)			
Before RS test results			
No CT recommended	265	57	322
CT recommended ^a	183	142	325
Total	448	199	647
McNemar's test $P < .0001$			
Node-negative (n = 516)			
Before RS test results			
No CT recommended	226	47	273
CT recommended ^a	128	115	243
Total	354	162	516
McNemar's test $P < .0001$			
Node-positive (n = 131)			
Before RS test results			
No CT recommended	39	10	49
CT recommended ^a	55	27	82
Total	94	37	131
McNemar's test $P < .0001$			

Abbreviations: CT, chemotherapy; RS, Recurrence Score.

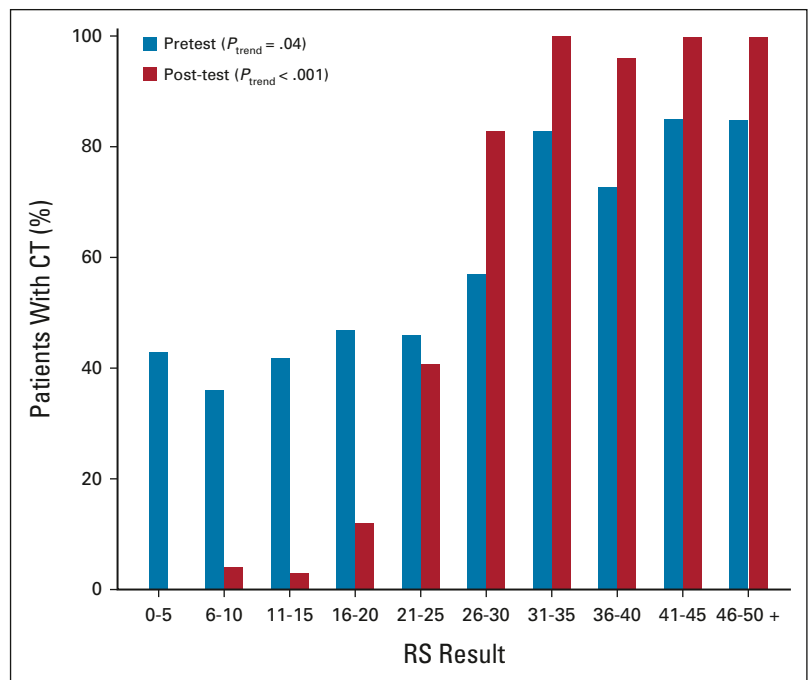
^aEither CT alone or CT plus hormonal therapy.

applied the RS results to recommend and prescribe chemotherapy more judiciously to patients with node-negative and node-positive breast cancer.^{21,22,33,35,41} In

this study, we observed a reduction in chemotherapy recommendations after Breast Recurrence Score testing across all groups, indicating that the clinical utility of the test across nodal status endures in Latin America. Furthermore, the post-TAILORx treatment recommendations observed in our study for node-negative breast cancer were generally reflected clinical practice guidelines that advise chemotherapy for patients with RS 26-100 of any age, consideration of chemotherapy for patients with RS 16-25 who are premenopausal, and no chemotherapy for patients with RS 0-25 who are postmenopausal or RS 0-15 who are premenopausal.^{42,43}

To our knowledge, this was the first clinical utility study to assess physician practice patterns since the publication of the TAILORx results, which further refined the RS cutpoint for prediction of adjuvant chemotherapy benefit.¹⁶ The patient population of this study differed from that of TAILORx,¹⁵⁻¹⁷ with greater proportions of patients who were ≤ 50 years of age (43% v 31%) and who had tumors > 2 cm in size (~30% v 25%), PR-negative status (21% v 10%), and node-positive disease (20% v 0%). Patient differences notwithstanding, physicians made fewer chemotherapy recommendations for patients with node-negative breast cancer after TAILORx reported, especially in patients with RS 0-25 and regardless of age group (≤ 50 or > 50 years), consistent with TAILORx results.^{16,18} This suggests how practice-changing the TAILORx results were to physicians in Latin America and how very comfortable these physicians were in applying the learnings from TAILORx to their clinical practices. Indeed, 98% of physicians reported being strongly or somewhat

FIG 3. Proportion of patients recommended CT before (pretest) and after receiving RS results (post-test), by RS result. CT, chemotherapy; RS, Recurrence Score.



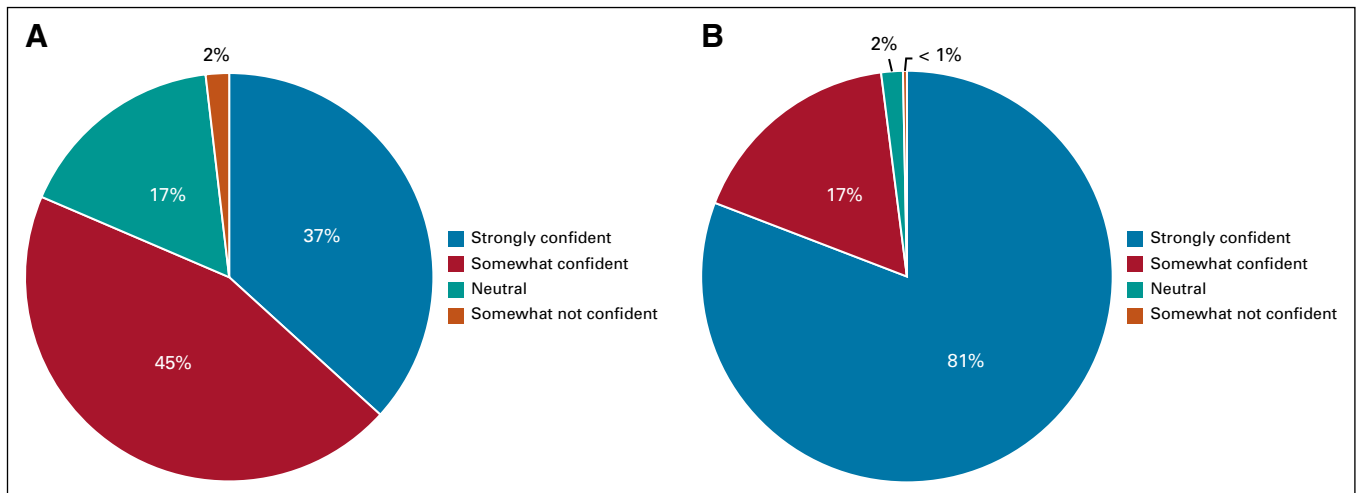


FIG 4. Physician self-reported confidence in treatment recommendations (A) before and (B) after 21-gene testing.

confident in the treatment decisions they made with RS results.

There were 131 patients with nodal involvement (N1mi, N1, or N2) in our study, including 20 (15%) with N2 breast cancer. This proportion was larger than the proportion with ≥ 4 positive nodes in the SEER registry (4%).⁴⁴ Our study did not assess reasons for the higher rate of Breast Recurrence Score testing among patients with more nodal involvement, but we note that many of the patients in this study paid out of pocket for testing, which may account at least in part for this relatively large proportion of patients with N2 breast cancer. In this group with nodal involvement, we observed a 55% relative reduction in chemotherapy recommendations after Breast Recurrence Score testing, which is higher than the percent differences documented in other decision impact studies done with patients with node-positive breast cancer. For example, de Boer et al (n = 50) noted a 32% relative reduction after RS results, Eiermann et al (n = 122) a 38% relative reduction, and Torres et al (n = 67) a 34% relative reduction.^{21,22,37} The reasons for the larger reduction in chemotherapy recommendations observed in this study were not explored but may reflect differences in regional clinical practice, greater clinical utility of Breast Recurrence Score testing in higher risk patient cohorts in Latin America than in other countries, or an evolution of clinical practice over time during which physicians worldwide have sought evidence-based strategies to appropriately de-escalate treatment in selected patients.

A combination of prospective clinical trial results and real-world evidence supports appropriate de-escalation for patients with node-positive breast cancer but low genomic risk as determined by the Breast Recurrence Score test.⁴⁴⁻⁴⁶ In the PlanB clinical trial, patients with 1-3 positive nodes and RS 0-11 who received endocrine therapy alone (n = 110) had 94.4% disease-free survival at 5 years

(compared with 94.2% for 238 patients with node-negative breast cancer).⁴⁵ In the population-based Clalit Health Services registry (n = 709), the 5-year freedom from distant recurrence was 97.3% for 518 patients with node-positive breast cancer and RS 0-17 who were treated with endocrine therapy alone.⁴⁶ In the SEER registry (N = 6,768), the 5-year breast cancer-specific survival ranged from 95.1% to 99.4% for those with RS 0-17, depending on the extent of nodal involvement (micrometastases and 1-3 positive nodes). Adjuvant chemotherapy use was reported in 18%-41% of patients in this SEER cohort, depending on the extent of nodal involvement.⁴⁴ The Breast Recurrence Score test has been validated to predict chemotherapy benefit in the node-positive setting, and multiple clinical utility and registry studies have now demonstrated the opportunity to spare chemotherapy in those with low RS results. The prospective Treatment for Positive Node, Endocrine Responsive Breast Cancer (RxPONDER; SWOG S1007) clinical trial recently reported no evidence that the Breast RS result predicts relative chemotherapy benefit within the RS 0-25 range.⁴⁷⁻⁴⁹ This was not surprising, given that the SWOG S8814 study predicted significant chemotherapy benefit in the RS 31-100 group in an analysis that included the full range of RS results (RS 0-100). RxPONDER did find that relative chemotherapy benefit with RS 0-25 depends on menopausal status, with premenopausal patients deriving benefit from chemotherapy treatment.⁴⁹ These findings could have affected the treatment decisions made by the physicians and patients in our study had they been reported earlier, and further investigations will be needed to understand how the RxPONDER results may affect clinical practice.

We found wide distributions of RS results across all categories of clinicopathologic factors, namely, age, tumor size, tumor grade, and Ki67%. These factors are often used alone without genomic information to estimate risk of recurrence and make chemotherapy decisions. A set of

uniform criteria for low versus high clinicopathologic risk was not prespecified for the participating sites, so pretest treatment recommendations were based on physician-determined estimates of clinicopathologic risk. Our observations suggest that clinicopathologic features and RS results provide complementary information that can be considered together for risk estimation and treatment decision making. As observed in Figure 3, a considerable proportion of patients with low RS results were recommended chemotherapy before testing, on the basis of clinicopathologic factors and/or patient preference. In the National Surgical Adjuvant Breast and Bowel Project B-20 analysis, clinical variables including age, tumor size, and tumor grade did not independently predict chemotherapy benefit in patients with node-negative breast cancer who

had a RS result.¹¹ The RS results therefore provide information beyond what can be gleaned from clinicopathologic factors alone that can be used to guide treatment decisions. Importantly, the RS result is validated to predict chemotherapy benefit for patients with node-negative and node-positive breast cancer.^{11,12,14}

In summary, our study documented a 39% overall reduction in chemotherapy recommendations after Breast Recurrence Score testing, regardless of nodal status. Physicians overall reported increased confidence in treatment recommendations with RS results. This study demonstrates the clinical utility of the Breast Recurrence Score test among patients with higher risk clinical characteristics, including node-positive patients, in Latin America.

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