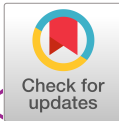


# Substantial Reduction in Adjuvant Chemotherapy With the Use of the 21-Gene Test to Manage Early Breast Cancer in a Public Hospital in Brazil

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**PURPOSE** We evaluated the impact of 21-gene test results on treatment decisions for patients with early-stage breast cancer treated under the public health care system in Brazil, Sistema Único de Saúde.

**METHODS** Eligible patients treated at Hospital Pérola Byington and Santa Casa de Misericórdia de São Paulo in Brazil were required to have the following characteristics: postsurgery with hormone receptor–positive, human epidermal growth factor 2–negative, node-negative and node-positive, and T1/T2 breast cancer and patients with these characteristics were candidates for adjuvant systemic therapy. Treatment recommendations, chemotherapy plus hormonal therapy (CT + HT) or HT alone, were captured before and after 21-gene test results.

**RESULTS** From August 2018 to April 2019, 179 women were enrolled. The mean age was 58 years (29–86 years), 135 (76%) were postmenopausal, and 58 (32%) had node-positive breast cancer. Most patients (61%) had a tumor > 2 cm, including 7% with tumors > 4 cm. Using Recurrence Score (RS) result cut points on the basis of the TAILORx trial, 40 (22%) had RS 0–10, 91 (51%) had RS 11–25, and 48 (27%) had RS 26–100. Before 21-gene testing, 162 of 179 (91%) patients were recommended for CT. After testing, 117 of 179 patients (65%) had changes in CT recommendation: 112 (63%) who were initially recommended CT received HT alone and five (3%) who were initially recommended HT alone received CT + HT. After 21-gene testing, 99% of physicians reported strong confidence in their treatment recommendations.

**CONCLUSION** The change in clinical practice at these public hospitals was greater than expected: 66% of initial treatment recommendations were changed to omit CT with 21-gene test results. Clinicopathologic features did not correlate well with 21-gene test results and did not adequately identify those most likely to benefit from CT.

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## INTRODUCTION

In 1988, a public health care system, Sistema Único de Saúde (SUS), was formed in Brazil to ensure universal free access to health care. About 70%–81% of Brazilians with breast cancer have health care access only through the SUS.<sup>1,2</sup> The formation of the SUS has profoundly affected the epidemiology of breast cancer in Brazil. Incidence rates of breast cancer fell from 177–277 cases per 100,000 women (depending on region) in the early 1980s to 29–66 cases per 100,000 women in the 1990s.<sup>3</sup> The incidence rate of breast cancer in Brazil is lower than those in Europe, Australia or New Zealand, and North America.<sup>4</sup> Yet the mortality rate in Brazil is similar to those of the high-income economies, underscoring the greater relative burden of breast cancer in Brazil.<sup>3,4</sup>

Despite considerable spending on public health care in upper-middle income economies like Brazil—estimated to be at least half of total health

care expenditures<sup>5</sup>—challenges persist in achieving optimal management of breast cancer, from screening to diagnosis to access to therapies.<sup>1–3</sup>

Outcomes of patients with breast cancer in Brazil vary by type of health care coverage, public or private: Patients on public health care are more likely to have more advanced disease at diagnosis, to undergo more mastectomies and fewer lumpectomies, to receive trastuzumab less often for human epidermal growth factor 2–positive (HER2+) breast cancer, and to receive chemotherapy (CT) more often.<sup>2</sup> These observations suggest a role for cost-effective tools with clinical utility to improve outcomes for patients with breast cancer.

The 21-gene test (Oncotype DX Breast Recurrence Score [RS] test; Genomic Health Inc, Redwood City, CA) is a validated prognosticator of 10-year distant recurrence in patients with estrogen receptor (ER)+, HER2–, node-negative, and node-positive early-stage

## 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

We examined how 21-gene test results may affect treatment decisions for 179 women with breast cancer treated at two public hospitals in Brazil. The mean age was 58 years; 135 women were postmenopausal. Regarding high-risk clinicopathologic features, 32% were node-positive and 61% had tumors > 2 cm. Before 21-gene testing, 162 of 179 women (91%) were recommended chemotherapy (CT). Then, samples were sent for 21-gene testing; 22% had Recurrence Score (RS) 0-10, 51% had RS 11-25, and 27% had RS 26-100.

### Knowledge Generated

With these test results available, 117 women (65%) had changes in treatment recommendations. For 112 women, the recommendation changed from CT to no CT, and for five women, from no CT to CT.

### Relevance

With 21-gene test results, CT recommendations were reduced, suggesting the potential for public health care cost savings with routine use of the 21-gene test for early-stage breast cancer.

breast cancer who receive hormonal therapy (HT).<sup>6-12</sup> The test has also been validated to predict CT benefit in patients with node-negative and node-positive breast cancer.<sup>7,9</sup>

The 21-gene test has shown clinical utility in studies conducted worldwide. In studies that compared the proportions of patients who were recommended CT before 21-gene testing (on the basis of risk estimated from clinicopathologic features alone) and prescribed CT after 21-gene testing (on the basis of risk estimated from RS results), the CT use was reduced by 24%-45% among patients with node-negative breast cancer and 30%-37% with node-positive breast cancer.<sup>13-18</sup> Studies of patient outcomes with and without 21-gene testing have shown that patients with testing had fewer distant recurrence events and longer disease-free and overall survival.<sup>19,20</sup>

Although the clinical utility of the 21-gene test has been studied in other countries, it has not been studied well in Brazil. We undertook a survey of physicians in Brazil to better understand how the 21-gene test is used in clinical practice and how RS results may affect adjuvant treatment recommendations made for patients with breast cancer. We report the results of our survey at two public hospitals (SUS) in São Paulo, Brazil.

## METHODS

This was a prospective observational survey of physicians to characterize the use of the 21-gene test in routine clinical practice in Brazil and the impact of 21-gene test results on adjuvant treatment recommendations and physician confidence in those recommendations (Data Supplement). The survey study was reviewed and approved by the Committees on Ethics and Research at the participating sites or by a central review board.

Physicians were eligible if they were medical oncologists or breast surgeons in Brazil who make adjuvant treatment recommendations for patients with breast cancer. Three physicians each at Hospital Pérola Byington and Santa

Casa de Misericórdia de São Paulo fulfilled these criteria. All six physicians were invited to participate in the study, and all six accepted. Physicians had to complete two questionnaires for each of their eligible patients, one before 21-gene testing and the other after. The first questionnaire collected data on treatment decisions (CT, HT, or CT plus HT) made for each patient before samples were sent for 21-gene testing. After 21-gene test results were returned, physicians completed the second questionnaire. Physicians' confidence in treatment recommendations made for each of their patients before testing and 2-3 months after 21-gene test results was also recorded.

Patients were eligible if they were at least age 18 years and diagnosed with early-stage, T1-2, ER+, HER2-, node-negative, or node-positive invasive breast cancer. Patients had to be candidates for systemic CT and agree to have 21-gene testing done as part of routine care. Patients with low performance status who were not candidates for CT were excluded from this study. Patients had to have available data on age, tumor size, tumor grade, tumor histology, nodal status, ER and PR status by immunohistochemistry (IHC), and HER2 status by IHC or fluorescence in situ hybridization. Other clinicopathologic characteristics (menopausal status, lymphovascular invasion, and Ki67 by IHC) were collected if available. Patients were ineligible if they had more than one operable primary breast tumor, multifocal or multicentric tumors, or metastatic breast cancer or had endocrine therapy or CT before 21-gene testing. Participating patients provided written, signed informed consent.

The 21-gene test was performed at the Genomic Health Inc Clinical Laboratory.<sup>6</sup> Briefly, RNA was extracted from formalin-fixed paraffin-embedded breast cancer tissue and used to determine the expression levels of 21 genes (16 cancer-related genes and five reference genes). An RS result was calculated that represents an individualized estimate of the risk of distant recurrence at 10 years and the likelihood of benefit from adjuvant CT treatment.<sup>6-12</sup> RS

groups are RS 0-17, RS 18-30, and RS 31-100.<sup>6</sup> RS groups based on the Trial Assigning Individualized Options for Treatment (TAILORx) for node-negative breast cancer are RS 0-10, RS 11-25, and RS 26-100.<sup>21</sup> RS groups for node-positive breast cancer are RS 0-25 and RS 26-100.

Analyses were descriptive in nature unless otherwise indicated. Descriptive statistics included frequency counts and percentages in contingency tables; means, standard deviations, medians, quartiles, and ranges; Spearman correlation coefficients; and concordance percentages and other measures of association. The association between RS results in five-unit categories and pre- and postassay recommendations was assessed using the Cochran-Armitage trend test. Statistics included point estimates and 95% CIs when appropriate. All hypothesis tests were conducted at a two-sided alpha level of .05.

## RESULTS

Between August 2018 and April 2019, surveys were completed for 179 patients. Patient and disease characteristics are summarized in Table 1. The median age was 58 years (range 29-86 years), and 76% of patients were postmenopausal. Nearly a third of patients (32%) had node-positive breast cancer. Most (61%) had tumors > 2 cm in size, and 12% had grade 3 tumors.

Using RS groups defined by cutoffs of 18 and 31, 59% had RS 0-17, 26% had RS 18-30, and 15% had RS 31-100. Using TAILORx RS groups, 22% had RS 0-10, 51% had RS 11-25, and 27% had RS 26-100. Distribution of RS results varied by nodal status (Fig 1). A larger proportion of patients with  $\geq 4$  positive nodes had higher RS results (RS 31-100 or RS 26-100) than patients with fewer or no positive nodes.

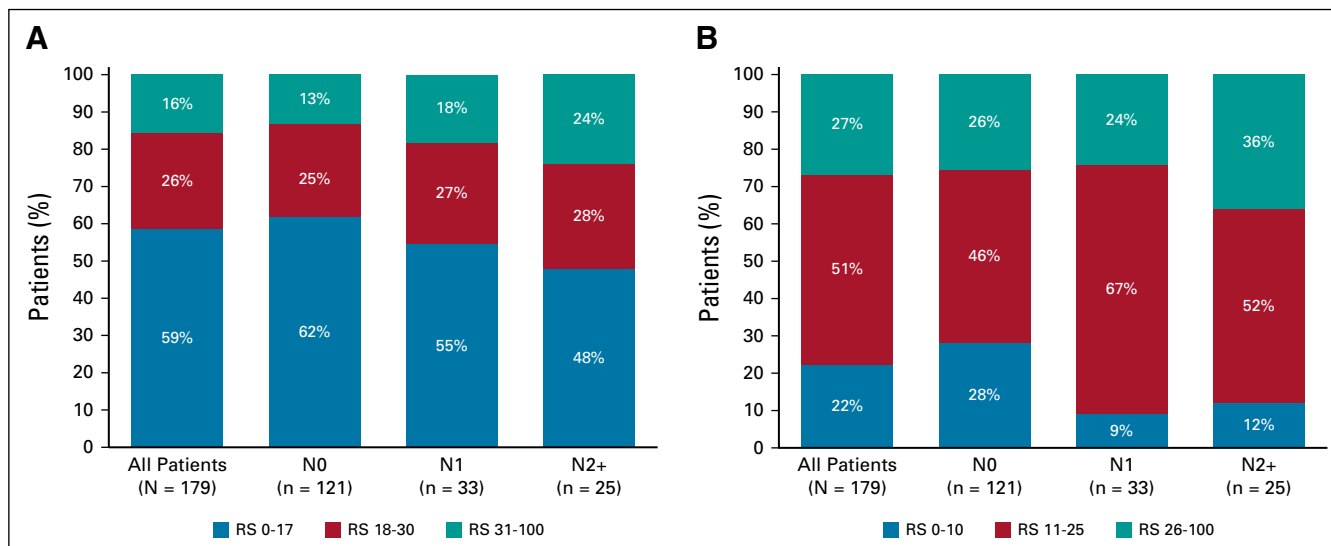
**TABLE 1.** Patient Baseline Clinical and Pathologic Characteristics

Characteristic	Overall (N = 179)	N0 (n = 121)	N1 (n = 33)	N2+ (n = 25)
Age, years, No. (%)				
Mean (SD)	58 (11)			
Median (range)	58 (29-86)			
$\leq 50$	39 (22)	25 (21)	7 (21)	7 (28)
$> 50$	140 (78)	96 (79)	26 (79)	18 (72)
Menopausal status, <sup>a</sup> No. (%)				
Premenopausal	39 (22)	23 (19)	9 (27)	7 (28)
Perimenopausal	4 (2)	3 (2)	0 (0)	1 (4)
Postmenopausal	135 (76)	94 (78)	24 (73)	17 (68)
Tumor grade, No. (%)				
1	31 (17)	23 (19)	5 (15)	3 (12)
2	127 (71)	85 (70)	23 (70)	19 (76)
3	21 (12)	13 (11)	5 (15)	3 (12)
Tumor size, cm, No. (%)				
Mean (SD)	2.6 (1.0)			
Median (range)	3 (1-5)			
$\leq 1$	6 (3)	3 (2)	2 (6)	1 (4)
$> 1$ to 2	63 (35)	45 (37)	12 (36)	6 (24)
$> 2$ to 4	98 (55)	66 (55)	17 (52)	15 (60)
$> 4$	12 (7)	7 (6)	2 (6)	3 (12)
Ki67%, No. (%)				
Mean (SD)	20 (13)			
Median (range)	20 (1-80)			
0-10	69 (39)	50 (41)	10 (30)	9 (36)
11-20	51 (28)	39 (32)	7 (21)	5 (20)
21-30	34 (19)	21 (17)	9 (27)	4 (16)
$> 30$	25 (14)	11 (9)	7 (21)	7 (28)

NOTE. Percentages were subject to rounding.

Abbreviations: N0, node-negative; N1, 1-3 positive nodes; N2+,  $\geq 4$  positive nodes; SD, standard deviation.

<sup>a</sup>One woman was missing data on menopausal status.



**FIG 1.** Distribution of RS results by (A) RS risk groups RS 0-17, RS 18-30, and RS 31-100 and by (B) TAILORx risk groups RS 0-10, RS 11-25, and RS 26-100. Percentages may not sum to 100% because of rounding. N0, node-negative; N1, 1-3 positive nodes; N2+,  $\geq 4$  positive nodes; RS, Recurrence Score.

Stratifying RS results by categories of clinicopathologic factors showed a broad distribution of RS results regardless of the category or the clinicopathologic factor (Fig 2). Both higher-risk (larger tumors, higher grade, younger age, and higher Ki67%) and lower-risk categories of clinicopathologic features included patients with RS results that range from low to high genomic risk. An assessment of the correlation between continuous RS result and continuous Ki67% showed a weak but statistically significant correlation (Spearman correlation 0.33,  $P < .0001$  v no correlation; Data Supplement).

Before 21-gene testing, 162 patients (91%) were recommended for CT. The CT regimens most frequently recommended before testing were six cycles of fluorouracil, doxorubicin, and cyclophosphamide (55%) and four cycles of doxorubicin and cyclophosphamide plus docetaxel (31%) (see the Data Supplement for the full list of recommended CT regimens). After testing, 117 patients (65%) had a change in treatment recommendation. After testing, 55 patients (31%) had a recommendation for CT, representing a 66% relative reduction in CT recommendations overall (Table 2). For these 55 patients, the CT regimens most frequently recommended were four cycles of doxorubicin and cyclophosphamide plus docetaxel (44%) and six cycles of fluorouracil, doxorubicin, and cyclophosphamide (38%) (Data Supplement). Among patients with node-negative breast cancer ( $n = 121$ ), 79 patients (65%) had a change in treatment recommendation after testing. Specifically, 104 patients (86%) had recommendations for CT before testing, and 35 (29%) patients after, representing a 66% relative reduction in CT recommendations in this cohort (Table 2). All patients with node-positive breast cancer ( $n = 58$ ) before 21-gene testing. After testing, 38 patients (66%) had a change in treatment recommendation. Only 20

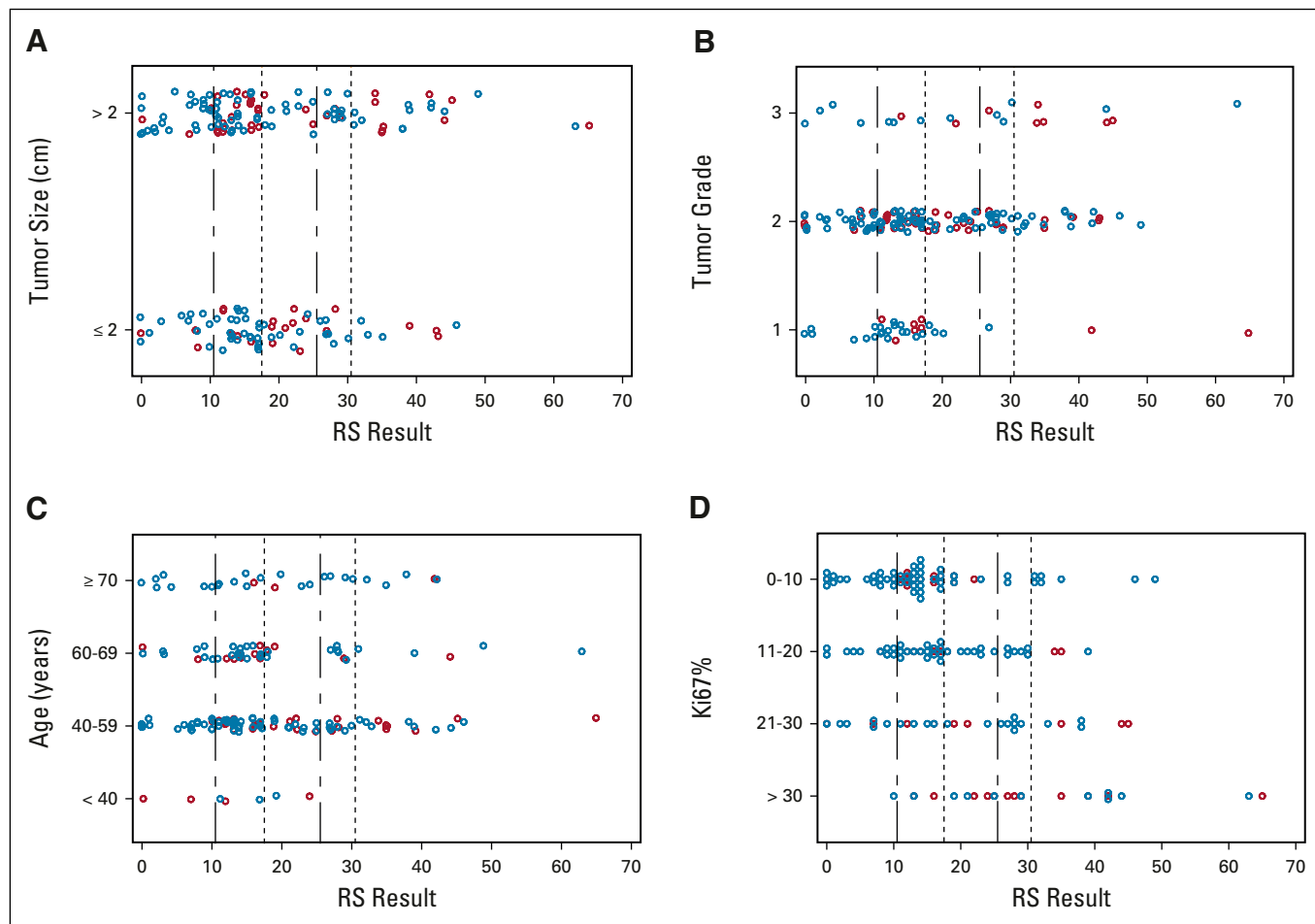
patients (34%) received CT recommendations after testing, representing a 66% relative reduction in this cohort (Table 2).

Treatment recommendations made before 21-gene testing were based on risk estimated by clinicopathologic features. A comparison of treatment recommendations made before and after testing showed that the majority of patients, including those who would have lower RS results (RS 0-17 or RS 0-25 by TAILORx cutoff), had recommendations for CT before RS results were known ( $P_{\text{trend}} = .424$ ), whereas recommended CT aligned with increasing RS result once incorporated into the treatment decision ( $P_{\text{trend}} < .0001$ ; Fig 3). After RS results became known, all or most treatment recommendations for patients with lower RS results, particularly RS 0-25, were changed to omit CT, and some treatment recommendations for patients with RS 26-30 were changed to include CT (Data Supplement).

Both before and after 21-gene testing, physicians rated their level of confidence in the treatment recommendations made for each of their patients (Fig 4). Before testing, physicians reported feeling somewhat confident (78%) or strongly confident (6%) in 84% of their treatment recommendations. After testing, physicians reported feeling strongly confident in 99% of their treatment recommendations.

## DISCUSSION

We have presented results of a survey evaluating the influence of RS results on treatment decisions made by physicians at a public hospital in Brazil for their patients with ER+, HER2-, node-negative, and node-positive breast cancer. Our findings showed that having RS results led physicians to change their treatment recommendations such that recommendations for CT were reduced by 66%, regardless of nodal status. The use of 21-gene testing bolstered



**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) and node-positive (red circles). Vertical solid lines with spaces mark the TAILORx cutpoints of RS 11 and RS 26; vertical broken lines mark the Recurrence Score cutpoints of RS 18 and RS 31. RS, Recurrence Score.

physicians' confidence in their treatment recommendations such that 99% reported feeling strongly confident in recommendations made after testing. Given the influence that RS results had on treatment recommendations and physician confidence, the 21-gene test has demonstrated in this study to have clinical utility for patients with ER+, HER2- breast cancer who are treated in Brazil.

The 66% reduction in CT recommendations observed was higher than expected, on the basis of the results of other, earlier decision impact studies of the 21-gene test. In one such study conducted at a public hospital in Mexico ( $n = 96$ , node-negative and node-positive), 21-gene testing resulted in a 28% reduction in CT recommendations.<sup>22</sup> In a pooled analysis of multiple studies conducted in Europe, a 38% reduction in CT was found for patients with node-negative breast cancer.<sup>23</sup> In two separate studies of patients with node-positive breast cancer, the percent reduction in CT recommendations was 30% in one study<sup>16</sup> and 37% in another.<sup>17</sup> In a companion study that evaluated the impact of RS results on treatment recommendations for patients in

Latin America, the percent reduction in CT recommendations was 39% overall.<sup>24</sup> The current study did not examine reasons for changing treatment recommendations after receiving RS results, but the high level of confidence that physicians expressed in their recommendations after testing suggests a high degree of comfort in applying the RS results in clinical practice. The large reduction in CT recommendations observed may be related in part to the high rates of CT recommendations at baseline on the basis of clinicopathologic features alone. Indeed, 86% of node-negative patients and 100% of node-positive patients were recommended CT before obtaining the 21-gene assay.

Compared with other clinical utility studies, this study included greater proportions of patients with high-risk clinicopathologic features: 32% had node-positive breast cancer, including 14% with  $\geq 4$  positive nodes; 61% had tumors  $> 2$  cm in size, including 7% with tumors  $> 4$  cm in size; and 12% had grade 3 tumors. In the 8th edition of its Cancer Staging Manual, the American Joint Committee on

**TABLE 2.** Change in CT Recommendations From Before to After RS Test Results

		After RS Test Results		
		No CT Recommended	CT Recommended <sup>a</sup>	
<b>All Patients (N = 179)</b>				
Before RS test results	No CT recommended	12	5	17
	CT recommended <sup>a</sup>	112	50	162
		124	55	179
<b>Node-Negative (n = 121)</b>				
Before RS test results	No CT recommended	12	5	17
	CT recommended <sup>a</sup>	74	30	104
		86	35	121
<b>Node-Positive (n = 58)</b>				
Before RS test results	No CT recommended	0	0	0
	CT recommended <sup>a</sup>	38	20	58
		38	20	58

Abbreviations: CT, chemotherapy; RS, Recurrence Score.

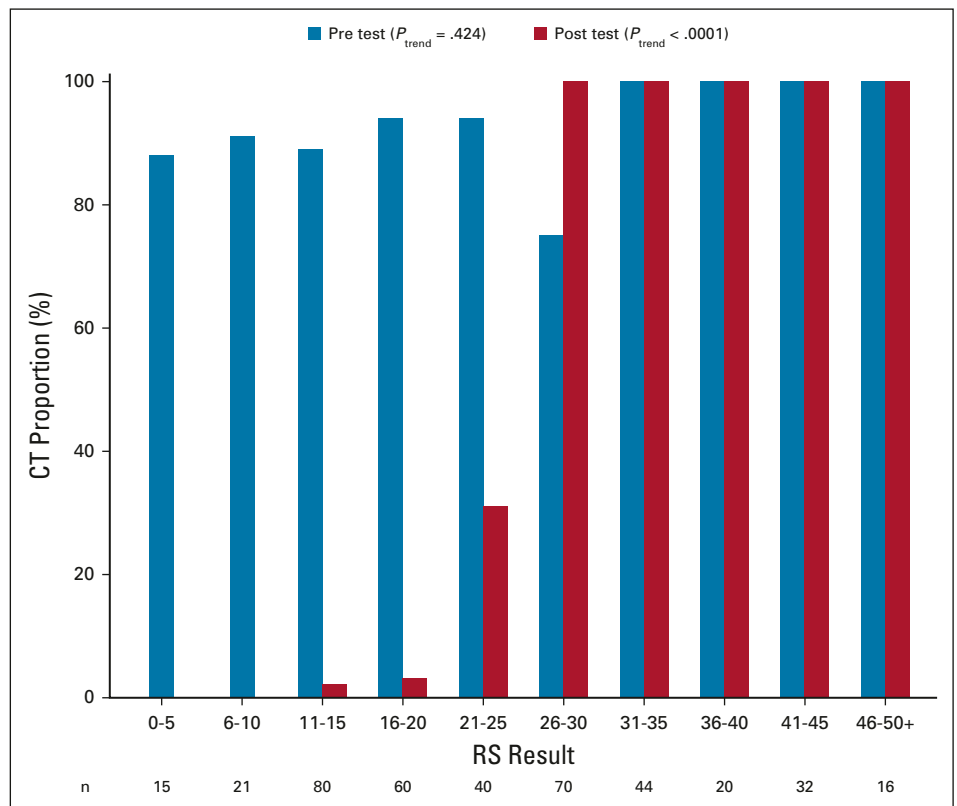
<sup>a</sup>Either CT alone or CT plus hormonal therapy.

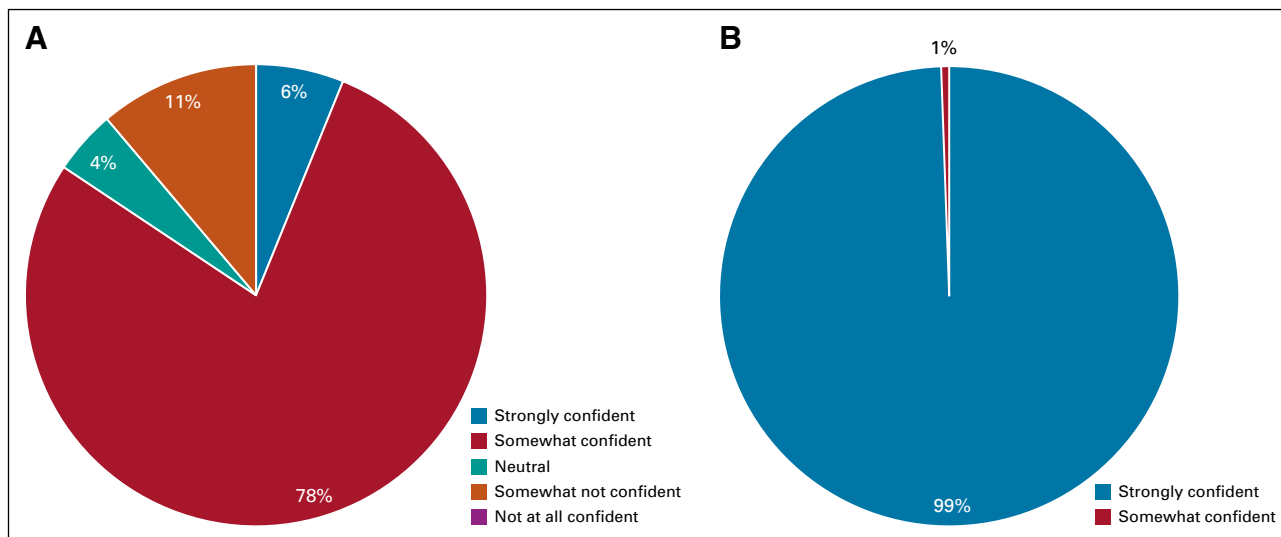
Cancer recommended that patients are classified as prognostic stage IA if they had hormone receptor-positive, HER2-, T1-2N0 breast cancer of any grade, and RS

0-10.<sup>25</sup> Despite the prevalence of high-risk clinicopathologic features, there was a 100% reduction in CT recommendations after 21-gene testing among patients with RS 0-10. This reduction in CT recommendations is consistent with the American Joint Committee on Cancer 8th edition staging criteria for node-negative patients. In addition, this reduction is supported by a recent cohort study of 154,050 patients from the SEER program, in which Kantor et al<sup>26</sup> found that patients with RS 0-10 had a 5-year breast cancer-specific survival of > 98%, regardless of tumor size (T1-3), nodal involvement (N0-3), and tumor grade (grade 1-3).

Among patients in our study with mid-range RS results, we observed 60%-80% reductions in CT recommendations among those with RS 11-15, RS 16-20, and RS 21-25 (Data Supplement). The observed physicians' recommendations to reduce CT for patients with RS 11-25 were consistent with clinical outcome data from the TAILORx trial, which demonstrated that patients with node-negative breast cancer and RS 11-25 did not benefit from adjuvant CT.<sup>11</sup> The RxPONDER (Treatment for Positive Node, Endocrine Responsive Breast Cancer) trial,<sup>27,28</sup> which randomly assigns pre- and postmenopausal patients with 1-3 node-positive breast cancer and RS 0-25 to HT with or without CT, reported its first results.<sup>29</sup> A total of 5,015 patients were included in the analysis (n = 2,506 HT; n = 2,509 CT therapy plus HT). In the primary analysis, the test for interaction between CT and RS results was not significant (P = .30), providing no evidence that the RS

**FIG 3.** Proportion of all patients (node-negative and node-positive) with CT recommendation before and after RS test results by RS result. CT, chemotherapy; RS, Recurrence Score.





**FIG 4.** Physician self-reported level of confidence in treatment decisions made for each patient (A) before and (B) after RS testing. RS, Recurrence Score.

result predicts the relative benefit of CT for invasive disease-free survival for patients with RS 0-25. Notably, a pre-specified analysis by menopausal status showed that premenopausal women, but not postmenopausal women, derived significant benefit from CT ( $P = .0004$ ).<sup>29</sup> Our study was conducted before the RxPONDER results were reported. There were 17 pre- or perimenopausal women in our study who had node-positive breast cancer. Had our study been conducted after RxPONDER results, physicians might have made different treatment recommendations for these patients, but we cannot determine at this time the potential effects of RxPONDER results on the recommendations already made for our patients.

All patients with RS 26-100 were recommended CT in this study, consistent with the results of analyses of the National Surgical Adjuvant Breast and Bowel Project B-20 and SWOG S8814 trials. Both trials indicated substantial CT benefit for the subgroups of patients with high RS results (RS 26-100 in the B-20 trial and RS 31-100 in the S8814 trial) in lymph node-negative and lymph node-positive patients, respectively.<sup>9,21,30</sup>

When the RS results were stratified by categories of clinicopathologic factors (tumor size, tumor grade, age, and Ki67%), we observed a spectrum of RS results within every category, including those traditionally considered high-risk

and low-risk clinicopathologic categories. This observation shows that clinicopathologic risk does not correspond to genomic risk as measured by the 21-gene test. Figure 4 shows that before 21-gene testing, most patients got recommendations for CT. Even patients who received low RS results (RS 0-25) had CT recommendations when risk was estimated on the basis of clinicopathologic factors alone.

In conclusion, this study demonstrated the clinical utility of the 21-gene test to help guide treatment decisions for patients in Brazil with node-negative or node-positive, ER+, HER2- breast cancer. Altogether, the assay allowed physicians to spare CT from a substantial number of patients in the public sector of the Brazilian health care system, reducing overall CT recommendations from 91% to 31%. Although physicians in this study might have selected patients who were clear candidates for adjuvant CT in the first place, the large reduction in CT recommendations—and by inference, CT use—carries implications for the opportunity for improved clinical outcomes and quality of care for patients and for health care utilization in Brazil. Given the disparity in breast cancer outcomes between patients with public and private health coverage,<sup>2</sup> the potential for 21-gene testing to positively affect outcomes of patients under public care warrants further investigations.

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#### PRIOR PRESENTATION

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## SUPPORT

Genomic Health Inc (a wholly owned subsidiary of Exact Sciences Corporation) performed the 21-gene tests free of charge for this study but provided no other support.

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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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