# original report

# 21-Gene Recurrence Score Adds Significant Value for Grade 3 Breast Cancers: Results From a National Cohort

J. Bryan lorgulescu, MD<sup>1,2,3</sup>; Rachel A. Freedman, MD, MPH<sup>2,3</sup>; Susan C. Lester, MD, PhD<sup>1,2</sup>; Elizabeth A. Mittendorf, MD, PhD<sup>1,2</sup>; and Jane E. Brock, MBBS, PhD<sup>1,2</sup>

**PURPOSE** The 21-gene recurrence score (RS) is used to identify patients with hormone receptor–positive earlystage breast cancer who may benefit from the addition of chemotherapy to endocrine therapy. We hypothesized that many women with poor prognostic histopathologic grade 3 disease may be offered chemotherapy irrespective of RS results, of whom a subset may not benefit from adjuvant chemotherapy.

**PATIENTS AND METHODS** A total of 30,864 women in the National Cancer Database were diagnosed with pT1c to pT2, pN0 to pN1, grade 3 estrogen receptor–positive, human epidermal growth factor receptor 2–negative invasive breast carcinoma from 2010 to 2015. RS was stratified as low (less than 18), intermediate (18 to 30), and high (31 or more). Overall survival by RS was evaluated by Kaplan-Meier, log-rank, and multivariable proportional hazards, with adjustment for relevant clinical and demographic variables.

**RESULTS** RS testing in grade 3 cancers increased between 2010 and 2015 (pN0, 53% to 72%; pN1, 16% to 36%). Among the 13,558 women with pN0 and the 2,840 with pN1 disease with RS testing, 27.1% and 30.0%, respectively, had low scores (less than 18). The 5-year overall survival rate for patients with a high RS, but not low RS, was significantly higher with chemotherapy (v no chemotherapy; absolute differences: high RS pN0 = 12.2% and pN1 = 25.5%, both P < .001; low RS pN0 = 2.5%, P = .07; and pN1 = 1.0%, P = .27), findings that were reinforced in multivariable analyses risk adjusted by clinicopathologic characteristics.

**CONCLUSION** Increased use of RS may help to better tailor treatment recommendations by stratifying patients with grade 3 disease into those who will and will not derive survival benefit and should be considered in all patients with estrogen receptor–positive/human epidermal growth factor receptor 2–negative T1c to T2, N0 to N1 disease.

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# INTRODUCTION

The 21-gene Oncotype DX Breast Recurrence Score (RS; Genomic Health, Redwood City, CA) is a validated, predictive biomarker that helps to identify patients with breast cancer who benefit from the addition of adjuvant chemotherapy to endocrine therapy for estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative early-stage breast cancer.<sup>1-11</sup> The RS has been incorporated into clinical guidelines, including the National Comprehensive Cancer Network (version 1.2018; to be considered in patients with pNO and pN1 status) and ASCO (to be considered in patients with pNO status) guidelines.<sup>5,6</sup> The American Joint Committee on Cancer (AJCC) eighth edition cancer staging system also includes RS testing to downstage disease as part of the new pathologic prognostic staging system.<sup>7-9</sup> Specifically, patients with pT1 to 2 node-negative, ER-positive, HER2-negative breast cancer of any grade and a low RS (less than 11) are reduced to

prognostic stage group IA as a result of their favorable prognoses, which reflects the utility of a low RS to identify luminal A-type invasive breast cancers (ie, those with a low proliferation rate and high levels of ER and progesterone receptor [PR] expression) that do not benefit from chemotherapy.

The Trial Assigning Individualized Options for Treatment (TAILORx) (ClinicalTrials.gov identifier: NCT00310180) and Rx for Positive-Node, Endocrine-Responsive Breast Cancer (RxPONDER) (Clinical-Trials.gov identifier: NCT01272037) trials were designed to validate the RS prospectively and to determine the benefit of adjuvant chemotherapy for tumors with intermediate-range RS (ie, 11 to 25, not 18 to 30) in patients with pN0 and pN1 status, respectively.<sup>10,11</sup> TAILORx results have shown that the majority of tumors with low and intermediate RS do not benefit from chemotherapy,<sup>12</sup> and the results from RxPONDER are forthcoming.

Author affiliations and support information (if applicable) appear at the end of this article. Accepted on July 18, 2019 and published at

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## CONTEXT

# **Key Objective**

Although grade 3 is considered a poor prognostic factor in estrogen receptor–positive, human epidermal growth factor receptor 2–negative breast cancer, the predictive benefit of multigene recurrence score (RS) testing in this subgroup remains unclear.

# **Knowledge Generated**

Our analysis of the National Cancer Database that comprises more than 70% of all newly diagnosed cancers in the United States reveals that RS results in grade 3 T1c/T2 N0 and N1 breast cancer provide important discriminatory information with regard to chemotherapy benefit. In addition, our findings reveal significant variability in national patterns of RS testing and chemotherapy use for grade 3 tumors.

# Relevance

Expanding national clinical guidelines with regard to the value of RS testing and increasing use of RS testing in grade 3 tumors may facilitate de-escalation of therapy in those with a low RS.

Tumor grade is prognostic and independently associated with risk for recurrence; however, histopathologic high grade may not correlate well with the risk provided by the RS. In the PlanB trial (ClinicalTrials.gov identifier: NCT01049425), approximately 50% of grade 3 tumors had an RS less than 31.13 The correlation of histologic grade with the predictive benefit of RS has not been assessed comprehensively. The proportion of grade 3 tumors in the TAILORx trial, although low, reflects the typical grade distribution, which accounts for 17.8% of all included tumors across scores, and it was 22% in the original cohort for the development of the RS.<sup>1</sup> As a result, the predictive benefit of RS and its potential for preventing overtreatment in grade 3 invasive breast carcinomas may be underappreciated. This study was undertaken to determine the national practices for ordering RS, treatment choices, and survival outcomes in patients with grade 3 breast cancer in a large, national data set.

# PATIENTS AND METHODS

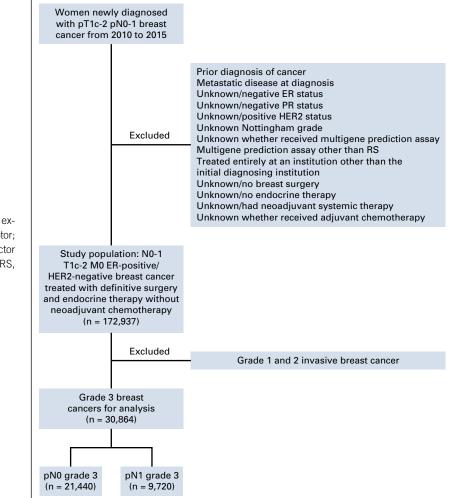
## **Data Source and Cohort Selection**

The registry-derived, hospital-based National Cancer Database (NCDB) curated by the American College of Surgeons and American Cancer Society incorporates more than 70% of newly diagnosed cancers in the United States.<sup>14</sup> The NCDB routinely collects information on patient, tumor, demographic, and hospital characteristics in addition to information on any treatments administered within the first year of diagnosis. Patients newly diagnosed with invasive breast cancer (ie, third edition of the WHO International Classification of Diseases for Oncology morphologic codes 8500 and 8520 to 8524, with invasive behavior code 3, and breast topographic codes C50.0 to 50.9) from 2010 to 2015 were identified.<sup>15</sup> The NCDB began incorporating HER2 (using the 2007 ASCO/College of American Pathologists grading guidelines) and multigene prediction assay data as of 2010.<sup>16-18</sup> Women with

invasive ductal, lobular, or mixed carcinoma histologies; Nottingham grade data; and hormone receptor-positive, HER2-negative, pT1c to 2, and pN0 to 1 resected cancers without neoadjuvant systemic therapy, as determined from collaborative staging, breast cancer-specific site factors, were included (Fig 1).<sup>19</sup> Patients were excluded if they were younger than 20 years of age, had a prior diagnosis of cancer, were diagnosed at an index institution but treated entirely elsewhere, had evidence of distant metastasis, or did not receive surgery or hormonal therapy. Patients also were excluded if they lacked data about whether they received adjuvant chemotherapy or had RS testing. RS risk groups were categorized as low (less than 18), intermediate (18 to 30), and high (31 or higher) as originally defined by Paik et al.<sup>1</sup> Variables were coded according to the Facility Oncology Registry Data Standards Manual revised for 2013.20

### Variables of Interest

Our primary outcomes of interest were receipt of RS testing (yes/no; with no defined as multigene signature testing neither ordered nor performed) and overall survival (OS) using National Death Index data provided by the NCDB and defined as the time from date of diagnosis to death, with patients censored at the date of last follow-up available in the NCDB (December 31, 2015). Because of limited followup, the NCDB does not include survival information for patients diagnosed in the most recent year, which for this release was 2015. Our independent variables of interest for survival analyses were adjuvant chemotherapy receipt (yes/ no) and RS score (low, intermediate, high). Adjuvant chemotherapy and radiotherapy receipt was defined as therapy documented postoperatively within 1 year of diagnosis. Control clinicopathologic variables were age, year of diagnosis, race/ethnicity, insurance status, Charlson-Deyo comorbidity index,<sup>21</sup> histology, AJCC pT classification, PR status, geographic location, Commission on Cancer-designated hospital type, and additional



**FIG 1.** Flow diagram of inclusion and exclusion criteria. ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor; RS, recurrence score.

treatments received beyond chemotherapy (ie, surgery type [breast conserving surgery/mastectomy], adjuvant radiotherapy [yes/no]).

# Statistical Analyses

RS testing by clinicopathologic characteristics for all patients was compared using  $\gamma^2$  tests and t tests, as appropriate. Multivariable logistic regression for receipt of RS testing was then performed, with stratification by pN status. To examine unadjusted differences in OS by chemotherapy receipt and RS, Kaplan-Meier method and log-rank test were used. The OS associated with adjuvant chemotherapy also was evaluated with multivariable Cox proportional hazards regression, after adjustment for all clinicopathologic variables of interest. Potential interaction effects of RS testing with adjuvant chemotherapy were explored using a previously described methodology.<sup>22</sup> To evaluate the accuracy of RS testing and Nottingham/Bloom-Richardson grade encoding, patients treated for breast cancer from 2010 to 2015 were queried from the cancer registrysubmitted data from Brigham and Women's Hospital and Dana-Farber Cancer Institute. The concordance between registry-submitted encoded data and the corresponding Oncotype DX-reported RS and breast pathologist-assigned grade were evaluated for each patient. Statistical analyses were performed using Stata 14.2 software (StataCorp, College Station, TX), with a two-sided  $\alpha$ -level of 0.05 selected as significant. This study was approved by the Partners Healthcare institutional review board (2019P000950).

# RESULTS

A total of 172,937 women with pT1c to 2 invasive breast carcinoma were included in our analysis. Of 126,827 patients with pN0 disease, 16.7% had grade 3 tumors (n = 21,144), and of the 46,110 patients with pN1 disease, 21.1% had grade 3 tumors (n = 9,720). Clinicopathologic characteristics are listed in Table 1.

# Characteristics Associated With RS Testing for pNO Disease

In patients with pN0 grade 3 tumors, 64.1% (n = 13,558) had RS testing compared with 59.2% (n = 22,267) and 65.7% (n = 44,708) with grade 1 and 2 tumors, respectively (P < .001). There was increasing use of RS testing between 2010 to 2015 in grade 3 disease (from

Improvements         Approvements         Approvement         Approvement <th cols<="" th=""><th></th><th></th><th></th><th></th><th></th><th></th><th></th><th></th><th></th><th></th><th></th></th>	<th></th>											
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11,44         6,41         NA         2,720         232         NA           14,00         5,520         706         6,81         2,493         2,69         2,64         1,66         1,70         1,50         1,	Characteristic	Total (No.)		OR	95% CI	ط	Total (No.)	Had RS Testing (%)	N	95% CI	٩	
4,940         6.56         0.81         0.74         2.86         2.86         0.80         0.70         0.50           5,562         706         Ref         2.900         24.4         Ref         1.36         1.56         1.46         1.36         1.56         1.46         1.36         0.501         5           6,501         712         1.05         0.97         0.401         0.71         1.46         0.56         1.46         1.36         1.16         1.36         1.16<	No. of patients	21,144	64.1	NA			9,720	29.2	NA			
4,940         636         0.71         0.74         0.86         0.71         0.86         0.71         0.86         0.71         0.86         0.71         0.86         0.71         0.86         0.71         0.86         0.71         0.86         0.71         0.86         0.71         0.86         0.71         0.86         0.71         0.86         0.71         0.86         0.71         0.86         0.71         0.86         0.86         0.71         0.86         0.71         0.86         0.71         0.86         0.71         0.86         0.71         0.86         0.71         0.86         0.71         0.86         0.71         0.86         0.71         0.86         0.71         0.86         0.71         0.86         0.71         0.86         0.71         0.86         0.71         0.86         0.71         0.86         0.71 <th0.71< th="">         0.71         0.71         <th< td=""><td>Age, years</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></th<></th0.71<>	Age, years											
552         706         Ref	< 50	4,940	63.6	0.81	0.74 to 0.89	< .001	2,865	22.8	0.80	0.70 to 0.92	.002	
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2671         53.2         Ref	≥ 70	4,451	46.7	0.41	0.37 to 0.46	< .001	1,816	29.6	1.14	0.96 to 1.36	.15	
2671 $532$ $Ref$	Year of diagnosis											
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$3337$ $647$ $166$ $148 \mbox{ black}$ $< \mathbf{c01}$ $1336$ $315$ $231 \mbox{ black}$ $310 \mbox$ $310 \mbox$ $310 \$	2012	3,567	63.1	1.54	1.38 to 1.73	< .001	1,670	28.9	1.99	1.64 to 2.40	< .001	
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dek         3/21         6.52         Ref         2.33         Ref         2.34         6.52         Ref         2.34         8.115         2.33         Ref         2.34         2.3	2015	3,904	72.3	2.46	2.19 to 2.75	< .001	1,675	36.0	2.90	2.41 to 3.49	< .001	
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1,046         58.0         0.76         0.66 to 0.88         <.001         572         23.1         0.75         0.60 to 0.95           nm         297         61.3         0.76         0.59 to 0.99         .04         158         23.9         1.14         0.79 to 1.66           nm         235         56.1         Ref          224         22.8         Ref            rance         12,072         68.9         1.50         1.17 to 1.90         .001         5,729         29.0         1.26         0.80 to 1.79           rance         12,072         68.9         1.50         1.17 to 1.90         .001         5,729         29.0         1.26         0.80 to 1.79           rance         13,32         60.2         1.50         1.17 to 1.90         .001         5,729         29.0         1.26         0.80 to 1.79           rance         1,332         60.2         1.50         0.71 to 1.65         .08         789         24.0         1.02         0.69 to 1.51           rance         1.36         0.86 to 1.74         .02         2.784         31.4         1.14         0.79 to 1.66           nment         185         62.2         1.36 <td< td=""><td>Asian/Pacific Islander</td><td>873</td><td>65.2</td><td>0.95</td><td>0.80 to 1.11</td><td>.50</td><td>412</td><td>27.7</td><td>0.99</td><td>0.77 to 1.26</td><td>.93</td></td<>	Asian/Pacific Islander	873	65.2	0.95	0.80 to 1.11	.50	412	27.7	0.99	0.77 to 1.26	.93	
own         297         61.3         0.76         0.59 to 0.99         04         158         329         1.14         0.79 to 1.66           I         335         56.1         Ref         224         228         Ref         223           I         1,302         68.9         1.50         1.17 to 1.90         001         5,729         29.0         1.25         0.88 to 1.79           I         1,302         60.2         1.27         0.97 to 1.65         .08         789         24.0         1.02         0.69 to 1.51           I         0.948         56.9         1.35         1.05 to 1.74         02         2,784         1.14         0.79 to 1.66           I         1.36         0.86 to 1.97         02         2,784         1.14         0.79 to 1.66           I         1.36         0.86 to 1.97         02         2,784         1.14         0.79 to 1.66           I         1.36         0.86 to 1.97         22         2,784         1.14         0.79 to 1.66           I         1.31         1.02 to 2.23         04         82         26.1         1.07         0.98 to 2.96	Hispanic	1,046	58.0	0.76	0.66 to 0.88	< .001	572	23.1	0.75	0.60 to 0.95	.02	
noise         335         56.1         Ref         224         22.8         Ref           rance         12,072         68.9         1.50         1.17 to 1.90 <b>001</b> 5,729         29.0         1.25         0.88 to 1.79           rance         1,392         60.2         1.27         0.97 to 1.65         .08         789         24.0         1.02         0.69 to 1.51           nment         6,948         56.9         1.35         1.05 to 1.74 <b>.02</b> 2,784         31.4         1.14         0.79 to 1.66           nment         185         62.2         1.30         0.86 to 1.97 <b>.02</b> 2,784         31.4         1.14         0.79 to 1.66           nment         185         62.2         1.30         0.86 to 1.97         .22         112         0.51 to 1.91         0.98 to 2.96           212         66.0         1.51         1.02 to 2.23 <b>.04</b> 82         28.1         1.03         0.55 to 1.91	Other/unknown	297	61.3	0.76	0.59 to 0.99	.04	158	32.9	1.14	0.79 to 1.66	.48	
335         56.1         Ref $224$ $22.8$ Ref           ance         12,072         68.9         1.50         1.17 to 1.90 <b>OO1</b> 5,729         29.0         1.25         0.88 to 1.79 $1,392$ 60.2         1.27         0.97 to 1.65         .08         789         24.0         1.02         0.69 to 1.51 $6,948$ 56.9         1.35         1.05 to 1.74 <b>.02</b> 2,784         31.4         1.14         0.79 to 1.66           ment         185         62.2         1.30         0.86 to 1.97         .22         112         35.7         1.70         0.98 to 2.96           ment         185         62.0         1.51         1.02 to 2.23         .04         82         28.1         1.03         0.55 to 1.91	Primary payer											
Burance         12,072         68.9         1.50         1.17 to 1.90 <b>.001</b> 5,729         29.0         1.25         0.88 to 1.79           1,392         60.2         1.27         0.97 to 1.65         .08         789         24.0         1.02         0.69 to 1.51           6,948         56.9         1.35         1.05 to 1.74 <b>.02</b> 2,784         31.4         1.14         0.79 to 1.66           enment         185         62.2         1.30         0.86 to 1.97         .22         112         35.7         1.70         0.98 to 2.96           ernment         185         65.0         1.51         1.02 to 2.23 <b>.04</b> 82         28.1         1.03         0.55 to 1.91	Not insured	335	56.1	Ref			224	22.8	Ref			
1,392         60.2         1.27         0.97 to 1.65         .08         789         24.0         1.02         0.69 to 1.51           6,948         56.9         1.35         1.05 to 1.74 <b>.02</b> 2,784         31.4         1.14         0.79 to 1.66           emment         185         62.2         1.30         0.86 to 1.97         .22         112         35.7         1.70         0.98 to 2.96           212         66.0         1.51         1.02 to 2.23 <b>.04</b> 82         28.1         1.03         0.55 to 1.91	Private insurance	12,072	68.9	1.50	1.17 to 1.90	.001	5,729	29.0	1.25	0.88 to 1.79	.21	
6,948         56.9         1.35         1.05 to 1.74 <b>.02</b> 2,784         31.4         1.14         0.79 to 1.66           ernment         185         62.2         1.30         0.86 to 1.97         .22         112         35.7         1.70         0.98 to 2.96           212         66.0         1.51         1.02 to 2.23 <b>.04</b> 82         28.1         1.03         0.55 to 1.91	Medicaid	1,392	60.2	1.27	0.97 to 1.65	.08	789	24.0	1.02	0.69 to 1.51	.91	
ernment         185         62.2         1.30         0.86 to 1.97         .22         112         35.7         1.70         0.98 to 2.96           212         66.0         1.51         1.02 to 2.23         .04         82         28.1         1.03         0.55 to 1.91	Medicare	6,948	56.9	1.35	1.05 to 1.74	.02	2,784	31.4	1.14	0.79 to 1.66	.48	
212 66.0 1.51 1.02 to 2.23 <b>.04</b> 82 28.1 1.03 0.55 to 1.91	Other government	185	62.2	1.30	0.86 to 1.97	.22	112	35.7	1.70	0.98 to 2.96	.06	
	Unknown	212	66.0	1.51	1.02 to 2.23	.04	82	28.1	1.03	0.55 to 1.91	<u>.93</u>	

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Interface         Interface <t< th=""><th></th><th></th><th></th><th>Multiva</th><th>ariable Logistic Re</th><th>gression</th><th></th><th></th><th>Multiv</th><th>ariable Logistic Re</th><th>gression</th></t<>				Multiva	ariable Logistic Re	gression			Multiv	ariable Logistic Re	gression
Month year         Sign of the sector propertition of the sector propertite propertition of the sector propertite propertitien	Characteristic	Total (No.)		OR	95% CI	Ρ	Total (No.)	Had RS Testing (%)	OR	95% CI	Ρ
Contruit univ concircation         123         579         Ref         289         279         Ref         289         271         1076         133         231           Control treated concretencie         546         640         124         108         125         108         0.88         133         201           Control treated concretencie         546         640         124         108         108         0.88         133         106         0.88         133         0.90         88         0.00         0.88 <th>Hospital type</th> <th></th>	Hospital type										
Compatibatione concrete         9,56         633         123         109         1,25         109         1,25         109         105 </td <td>Community cancer program</td> <td>1,923</td> <td>57.9</td> <td>Ref</td> <td></td> <td></td> <td>869</td> <td>27.9</td> <td>Ref</td> <td></td> <td></td>	Community cancer program	1,923	57.9	Ref			869	27.9	Ref		
Actional Creation         Each         Bit         127         128	Comprehensive cancer center	9,565	63.3	1.22	1.09 to 1.35	< .001	4,282	28.8	1.03	0.87 to 1.22	.72
Ingented circer network program         2190         647         124         108 to 142         629         129         029         129         026         126         126           Hexklin         100         100         101         101         100	Academic/research	6,264	69.0	1.42	1.27 to 1.60	< .001	2,875	32.9	1.27	1.07 to 1.52	.01
mergane         mergane           New Figure         100         No         100         No           New Figure         1.266         6.88         N         N         N         N         N           New Figure         1.266         6.88         1.13         131         135         2.00         133         166         131         166         133         166         133         166         133         166         133         166         133         166         133         166         133         166         133         166         133         166         133         166         133         166         133         166         133         166         133         166         133         166         133         166         133         166	Integrated cancer network program	2,180	64.7	1.24	1.08 to 1.42	.003	923	29.9	1.09	0.88 to 1.35	.43
Mot Englend         1266         668         Ref	Hospital location										
Midla Martic         310/2         70/7         131         113 to 152         600         1556         332         133         106 to 166         01           South Matric         4/37         6.63         112         03% to 125         73         061         127         050         137         050         137         050         137         050         137         050         132         050         137         136         137         136         137         136         137         136         137         136         137         136         137         136         137         136         137         136         136         137	New England	1,266	66.8	Ref			540	27.0	Ref		
South Hantic         4.247         6.68         1.12         0.37 to 1.29         1.24         0.26         0.30         1.25         0.30 to 1.26         0.30           East North Central         1.127         64.3         0.39         0.34         1.33         1.040 to 1.64         0.3           East North Central         1.127         64.3         0.37         0.37         0.61 to 1.87         5.3         1.33         0.390 to 1.77         0.63           West South Central         1.127         64.8         0.73         0.61 to 0.87         4.36         2.36         1.33         0.890 to 1.77         0.65         3.55           West South Central         1.222         56.9         0.74         0.61 to 0.87         4.36         3.26         1.36         0.890 to 1.77         0.86         3.55           West South Central         1.222         56.9         0.74         0.61 to 0.87         4.36         3.26         1.36         0.86         0.87         5.67         2.66         0.95         0.86         0.85         5.95         5.95         1.06         0.85         0.85         5.95         5.95         1.06         0.85         0.85         5.95         1.06         0.85         0.85         5.	Middle Atlantic	3,107	70.7	1.31	4	< .001	1,556	33.2	1.33	1.06 to 1.66	.01
East North Central         3/36         66.3         103         0.40         1.51         1.04         1.22         0.90         1.71         0.40         0.51         0.50         0.60         0.51         0.51         0.51         0.51         0.51         0.50         0.60         0.51         0.51         0.65         0.52         0.61         0.53         0.53         0.53         0.53         0.55         0.51         0.66         0.55         0.55         0.50         0.51         0.55 <td>South Atlantic</td> <td>4,247</td> <td>65.8</td> <td>1.12</td> <td>to</td> <td>.14</td> <td>1,846</td> <td>30.1</td> <td>1.25</td> <td>0.99 to 1.56</td> <td><u>.06</u></td>	South Atlantic	4,247	65.8	1.12	to	.14	1,846	30.1	1.25	0.99 to 1.56	<u>.06</u>
East South Central         1.127         6.42         0.96         0.80 to 1.15         0.83         2.20         1.32         0.89 to 1.77         0.67           West Noth Central         1.736         6.43         0.97         0.80 to 1.14         .70         833         2.95         1.13         0.89 to 1.71         0.65           West Noth Central         1.732         6.60         0.73         0.61 to 0.87         6.00         1.13         0.88 to 1.45         0.65         0.67 to 1.24         0.67 to 1.24         0.65         0.67 to 1.24         0.67         6.67         7           Mountain         922         643         0.74         0.641 to 0.87         6.001         1.32         0.65         0.651 to 0.75         6.67         7           VEC         9457         641         0.66         0.621 to 0.75         6.01         1.32         0.65         0.690 to 0.75         6.67         7           VEC         9437         643         0.67         6.01         0.67         2.92         0.65         0.690 to 0.75         6.61         7           VEC         826         616         0.67         6213         <	East North Central	3,736	66.3	1.08	<u>р</u>	.29	1,634	32.1	1.31	1.04 to 1.64	.02
west Neutri Central         1796         643         027         028         013         028         013         028         013         028         013         028         013         028         026         037         051         133         088         133         088         134         088         134         088         134         088         134         038         036         037         051         133         088         134         038         036	East South Central	1,127	64.2	0.96	0.80 to 1.15	.67	438	32.0	1.32	0.99 to 1.77	<u>.06</u>
wetsouth central         1.22         6.0         0.23         0.61 b 0.87         5.00         0.67 b 1.20         6.46         0.10         0.67 b 1.20         0.67	West North Central	1,796	64.3	0.97	t	.70	833	29.5	1.13	0.88 to 1.45	.35
Mountain         92         648         1.07         0.86 to 1.30         4.35         2.56         1.45         1.06 to 1.34         0.1           Pacific         2.489         56.9         0.74         0.64 to 0.87         <.001	West South Central	1,232	56.0	0.73	t	< .001	535	23.6	06.0		.46
Pactic         2,480         6.63         0.74         0.64 to 0.87         <.001         1.132         2.65         1.08         0.86 to 1.38         5.3           ACC PT         11.687         690         Ref         3507         361         Ref         <.001	Mountain	932	64.8	1.07	0.88 to 1.30	.48	435	32.6	1.45	1.08 to 1.94	.01
ALICE pT         35.07         36.1         Ref            1         11.687         69.0         Ref	Pacific	2,489	56.9	0.74	0.64 to 0.87		1,132	26.5	1.08	0.85 to 1.38	.53
1c         11,687         690         Ref         551         661         651         761         601 </td <td>AJCC pT</td> <td></td>	AJCC pT										
2         9,457         58.1         0.66         0.62 to 0.70	lc	11,687	69.0	Ref			3,507	36.1	Ref		
Histology           DC         18,854         642         Ref         Ref           DC         18,854         642         Ref         335         1.26         0.96 to 1.61         0.7           UC         826         616         0.99         0.85 to 1.16         89         325         1.26         0.96 to 1.15         0.7           MC         1,464         648         1.01         0.90 to 1.15         .82         767         292         0.97         0.82 to 1.15         .74           MC         1,464         648         1.01         0.90 to 1.15         .82         767         292         0.97         0.82 to 1.15         .74           NG         11/182         661         1.51         1.39 to 1.63         8.265         30.5         1.47         1.28 to 1.69         .601           Status         17,182         661         1.51         1.39 to 1.63         8.265         30.5         1.47         1.28 to 1.69         .601           Status         17,182         661         1.51         1.39 to 1.63         2.01         8.26         .601         1.61         .601         8.26         .601         .601         .708         .601	2	9,457	58.1	0.66	0.62 to 0.70	< .001	6,213	25.3	0.65	0.59 to 0.72	<.001
DC         18,854         64,2         Ref         29.1         Ref           1LC         826         61.6         0.99         0.85 to 1.16         .89         33.5         1.26         0.98 to 1.61         07           MC         1,464         64.8         1.01         0.90 to 1.15         .82         767         292         0.97         0.82 to 1.15         74           MC         1,464         64.8         1.01         0.90 to 1.15         .82         767         292         0.97         0.82 to 1.15         74           MC         1,464         64.8         1.01         0.90 to 1.15         .82         767         292         0.97         0.82 to 1.15         74           MC         3,341         55.4         Ref         1.51         1.39 to 1.63         <.001	Histology										
ILC         826         61.6         0.99         0.85 to 1.16         .89         33.5         1.26         0.98 to 1.61         0.7           IMC         1,464         64.8         1.01         0.90 to 1.15         .82         767         292         0.97         0.82 to 1.15         .74           IMC         1,464         64.8         1.01         0.90 to 1.15         .82         767         292         0.97         0.82 to 1.15         .74           IR status         3,941         55.4         Ref          1,439         22.1         Ref           6.01         1.51         1.39 to 1.63         <.001	IDC	18,854	64.2	Ref			8,625	29.1	Ref		
MC         1,464         64.8         1.01         0.90 to 1.15         32         767         29.2         0.97         0.82 to 1.15         74           R status         3,341         55.4         Ref         1,439         22.1         Ref         1         1         866         50.1         8.26         30.5         1,47         1.28 to 1.69         5.01           Negative         17,182         66.1         1.51         1.39 to 1.63         <.001	ILC	826	61.6	0.99	0.85 to 1.16	89.	328	33.5	1.26	0.98 to 1.61	.07
P status	IMC	1,464	64.8	1.01	0.90 to 1.15	.82	767	29.2	0.97	0.82 to 1.15	.74
Negative         3,941         55.4         Ref         1,439         22.1         Ref            Positive         17,182         66.1         1.51         1.39 to 1.63         <.001	PR status										
Positive         17,182         66.1         1.51         1.39 to 1.63         <.001         8,265         30.5         1.47         1.28 to 1.69         <.001           Standard surgery/RT         Yes (lumpectomy with RT or lasses)         18,898         65.5         Ref         7,085         32.6         Ref         <.001	Negative	3,941	55.4	Ref			1,439	22.1	Ref		
Standard surgery/RT           Yes (lumpectomy with RT or mastectomy only)         18,898         65.5         Ref         7,085         32.6         Ref         7.001         Ref           No (lumpectomy only)         832         38.2         0.44         0.38 to 0.51         <.001	Positive	17,182	66.1	1.51	.39 to	< .001	8,265	30.5	1.47	1.28 to 1.69	< .001
Yes (tumpectomy with RT or mastectomy only)18,898 B65.565.5 RefRefRefMastectomy only)83238.20.440.38 to 0.51 $<01$ 23821.90.530.38 to 0.75 $<01$ No (tumpectomy with RT)51552.80.690.57 to 0.84 $<01$ 2,31719.30.550.48 to 0.62 $<01$ NOTE. Boldface indicates significance at $P < .05$ .Note. Boldface indicates significance at $P < .05$ .Abbreviations: AJCC, American Joint Committee on Cancer; IDC, invasive ductal carcinoma; ILC, invasive mixed carcinoma; IMC, invasive mixed carcinoma; IAC, and	Standard surgery/RT										
No (lumpectomy only) $832$ $38.2$ $0.44$ $0.38$ to $0.51$ $<$ .001 $238$ $21.9$ $0.53$ $0.38$ to $0.75$ $<$ .001No (mastectomy with RT) $515$ $52.8$ $0.69$ $0.57$ to $0.84$ $<$ .001 $2,317$ $19.3$ $0.55$ $0.48$ to $0.62$ $<$ .001NOTE. Boldface indicates significance at $P < .05$ . $0.69$ $0.57$ to $0.84$ $<$ .001 $2,317$ $19.3$ $0.55$ $0.48$ to $0.62$ $<$ .001NOTE. Boldface indicates significance at $P < .05$ . $0.69$ $0.57$ to $0.84$ $<$ .001 $2,317$ $19.3$ $0.55$ $0.48$ to $0.62$ $<$ .001Abbreviations: AJCC, American Joint Committee on Cancer; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; IMC, invasive mixed carcinoma; NA, not applicable; OR, odds ratio; PR, or explored procession in the committee on Cancer; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; IMC, invasive mixed carcinoma; NA, not applicable; OR, odds ratio; PR, or explored procession in the carcinoma; IRC, invasive mixed	Yes (lumpectomy with RT or mastectorny only)	18,898	65.5	Ref			7,085	32.6	Ref		
No (mastectomy with RT) $515$ $52.8$ $0.69$ $0.57$ to $0.84$ <b>&lt; .001</b> $2$ ,317 $19.3$ $0.55$ $0.48$ to $0.62$ <b>&lt; .001</b> NOTE. Boldface indicates significance at $P < .05$ . Abbreviations: AJCC, American Joint Committee on Cancer; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; IMC, invasive mixed carcinoma; NA, not applicable; OR, odds ratio; PR,	No (lumpectomy only)	832	38.2	0.44	0.38 to 0.51	< .001	238	21.9	0.53	0.38 to 0.75	< .001
NOTE. Boldface indicates significance at <i>P</i> < .05. Abbreviations: AJCC, American Joint Committee on Cancer; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; IMC, invasive mixed carcinoma; NA, not applicable; OR, odds ratio; PR,	No (mastectomy with RT)	515	52.8	0.69	0.57 to 0.84	< .001	2,317	19.3	0.55	0.48 to 0.62	< .001
Abbreviations: AJCC, American Joint Committee on Cancer; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; IMC, invasive mixed carcinoma; NA, not applicable; OR, odds ratio; PR,	NOTE. Boldface indicates significance	at <i>P</i> < .05.									
	Abbreviations: AJCC, American Joint Co	ommittee on Car	ncer; IDC, invasive ductal	carcinom	ia; ILC, invasive lo	bular carcin	noma; IMC, inva	isive mixed carcinoma; N	NA, not ap	plicable; OR, odds	ratio; PR,

TABLE 1. Characteristics Associated With RS Testing for Grade 3 Disease, Stratified by pN Status (Continued)

5

# Multigene RS for Grade 3 Breast Cancer

53.2% to 72.3%; P < .001). In multivariable logistic analyses, receipt of RS testing for grade 3 disease was significantly associated with ages 50 to 59 years; a more recent (*v* earlier) diagnosis; lower comorbidity score; white race; private or Medicare insurance (*v* uninsured); and tumors that were pT1c, PR positive, or treated with standard local therapy (*v* nonstandard; Table 1).

# Characteristics Associated With RS Testing for pN1 Disease

In patients with pN1 grade 3 tumors, 29.2% (n = 2,840) had RS testing compared with 47.4% (n = 4,937) and 42.7% (n = 11,083) with grade 1 and 2 tumors, respectively (P < .001). We observed an increasing use of RS testing between 2010 and 2015 in pN1 grade 3 disease (from 16.9% to 36.0%; P < .001). In multivariable logistic analyses, receipt of RS testing was significantly associated with ages 50 to 69 years; a more recent diagnosis; lower comorbidity score; non-Hispanic race/ethnicity; and tumors that were pT1c, PR positive, or treated with standard local therapy (Table 1).

# Associations of Chemotherapy and OS for pNO Grade 3 Disease by RS

In multivariable logistic regression analyses, intermediate RS (odds ratio [OR], 15.23; 95% CI, 13.20 to 17.58; P < .001) and high RS (OR, 141.55; 95% CI, 118.58 to 168.97; P < .001) were associated with receipt of adjuvant chemotherapy compared with low RS (Table 2). Adjuvant chemotherapy receipt also was associated with younger patients; patients who were diagnosed earlier in the study period (*v* more recently); patients without comorbidity, pT2 tumors, invasive ductal carcinoma, and PR-negative status; and patients who received standard local therapy (*v* non-standard; Table 2).

The median follow-up for patients with pN0 grade 3 disease was 41.1 months (interquartile range, 28.8-56.3 months), and 5.3% of patients died during the study period. In the group of patients without RS testing, 52.2% received chemotherapy in addition to endocrine therapy, which demonstrated an unadjusted absolute improvement in 5-year OS rate of 10.3% (P < .001; Table 3; Fig 2A). For patients with low RS, 9.1% received chemotherapy, which was not associated with a significantly increased 5-year unadjusted OS rate (P = .07; Table 3; Fig 2A). In contrast, 54.9% of patients with intermediate RS and 89.4% of patients with high RS received chemotherapy, with both groups demonstrating associations with an improved unadjusted 5-year OS rate of 2.5% (P = .002) and 12.2% (P < .001), respectively (Table 3; Fig 2A).

The OS improvements associated with adjuvant chemotherapy in patients with pNO grade 3 disease also were assessed in multivariable Cox proportional hazards regression analyses (Table 4). In patients with grade 3 disease with high RS or who had no RS testing, adjuvant chemotherapy demonstrated significantly improved OS in multivariable analyses compared with those who did not receive chemotherapy (hazard ratio [HR], 0.63 [95% CI, 0.43 to 0.90; P = .01] and 0.51 [95% CI, 0.40 to 0.64; P <.001], respectively), whereas low and intermediate RS were not associated with an OS benefit from adjuvant chemotherapy (reference no chemotherapy; HR, 0.50 [95% CI, 0.16 to 1.61; P = .25] and 0.71 [95% CI, 0.49 to 0.90; P =.07], respectively). Increasing age at diagnosis, comorbidity index, pT classification, and nonstandard lumpectomy-only management all demonstrated worse OS, whereas Asian/ Pacific Islander and Hispanic race (reference white), management at an academic/research institution (reference community cancer program), invasive lobular carcinoma histology, and PR-positive status were associated with improved OS (Table 4).

# Associations of Chemotherapy and OS for pN1 Grade 3 Disease by RS Testing

In multivariable logistic analyses, intermediate (OR, 6.62; 95% CI, 5.28 to 8.30; P < .001) and high (OR, 36.92; 95% CI, 26.73 to 50.99; P < .001) RS were associated with receiving adjuvant chemotherapy compared with low RS (Table 2). Treatment with adjuvant chemotherapy also was associated with patients who were younger, privately insured, without comorbidity, and PR negative and who had received standard local therapy (Table 2).

The median follow-up of patients with pN1 grade 3 disease was 41.9 months (interquartile range, 29.0-56.7 months), and 8.0% of patients died during the study period. In the group of patients without RS testing, 82.8% received chemotherapy in addition to endocrine therapy, which was associated with an absolute improvement in 5-year OS rate of 20.1% (P < .001; Table 3; Fig 2B). For patients with low RS, 25.9% received chemotherapy, and this was not associated with a significantly increased unadjusted 5-year OS (P = .27; Table 3; Fig 2B). In contrast, 64.4% of patients with intermediate RS and 88.3% with high RS received chemotherapy, with both groups demonstrating absolute improvements in 5-year OS rate of 7.5% (P = .02) and 25.5% (P < 0.001), respectively (Table 3; Fig 2B).

The OS benefits of adjuvant chemotherapy in patients with pN1 grade 3 disease also were assessed in multivariable Cox proportional hazards regression analyses (Table 4). As in pN0 disease, patients with pN1 grade 3 disease with high RS and no RS testing showed significantly improved OS with adjuvant chemotherapy (HR, 0.24 [95% Cl, 0.13 to 0.47; P < .001] and 0.42 [95% Cl, 0.33 to 0.53; P < .001], respectively), whereas low and intermediate RS did not (HR, 0.81 [95% Cl, 0.33 to 1.98; P = .64] and 0.67 [95% Cl, 0.35 to 1.27; P = 0.22], respectively). In addition to increasing age at diagnosis, comorbidity index, AJCC pT classification, PR-negative status, and nonstandard lumpectomy-only management all demonstrated worse OS. OS also significantly varied by geographical location (Table 4).

			Multi	Multivariable Logistic Regression	ssion			Multi	Multivariable Logistic Regression	gression
Characteristic	Total (No.)	Had CT (%)	OR	95% CI	ط	Total (No.)	Had CT (%)	OR	95% CI	٩
No. of patients	21,144	53.1	NA			9,720	76.0	NA		
RS										
No RS	7,586	52.2	16.66	14.42 to 19.25	< .001	6,880	82.8	21.87	17.87 to 26.77	< .001
Low	3,591	9.1	Ref			821	25.9	Ref		
Intermediate	5,304	54.9	15.23	13.20 to 17.58	< .001	1,188	64.4	6.62	5.28 to 8.30	< .001
High	4,332	89.4	141.55	118.58 to 168.97	< .001	726	88.3	36.92	26.73 to 50.99	< .001
Age, years										
< 50	4,940	74.8	1.83	1.63 to 2.05	< .001	2,865	91.8	1.39	1.13 to 1.71	.002
50-59	5,552	63.1	Ref			2,699	85.7	Ref		
60-69	6,201	49.9	0.57	0.51 to 0.63	< .001	2,340	75.9	0.63	0.53 to 0.76	< .001
≥ 70	4,451	21.1	0.12	0.11 to 0.14	< .001	1,816	37.0	0.09	0.08 to 0.12	< .001
Year of diagnosis										
2010	2,671	56.8	Ref			1,339	78.4	Ref		
2011	3,207	55.0	0.95	0.83 to 1.10	.53	1,495	77.1	1.11	0.88 to 1.40	.37
2012	3,567	52.3	0.93	0.81 to 1.07	.33	1,670	76.9	1.12	0.89 to 1.39	.34
2013	3,937	53.1	0.93	0.81 to 1.07	.33	1,835	76.6	1.12	0.90 to 1.40	.30
2014	3,858	53.1	0.85	0.74 to 0.98	.02	1,706	73.3	0.84	0.67 to 1.05	.12
2015	3,904	49.9	0.74	0.64 to 0.85	< .001	1,675	74.5	1.09	0.87 to 1.36	.45
Comorbidity index										
0	17,494	54.8	Ref			8,115	78.3	Ref		
1	3,021	46.4	0.89	0.80 to 1.00	<u>4</u>	1,280	67.9	0.83	0.70 to 0.99	.03
2	478	38.9	0.79	0.62 to 1.01	.06	249	57.0	0.57	0.41 to 0.79	.00
S	151	34.4	0.65	0.42 to 1.02	.06	76	36.8	0.31	0.18 to 0.55	< .001
Race/ethnicity										
White	16,551	51.5	Ref			7,380	74.9	Ref		
Black	2,377	58.4	0.99	0.87 to 1.12	.82	1,198	78.6	0.89	0.73 to 1.07	.22
Asian/Pacific Islander	873	61.5	1.17	0.97 to 1.42	.11	412	80.3	1.04	0.75 to 1.45	.81
Hispanic	1,046	58.4	1.08	0.90 to 1.29	.42	572	82.5	1.27	0.95 to 1.71	.11
Other/unknown	297	57.9	1.04	0.76 to 1.43	.81	158	76.0	1.29	0.78 to 2.14	32

# Multigene RS for Grade 3 Breast Cancer

P         Total (No.)         Had CT (%)         0           23         5,729         84.8         1.           .73         5,729         85.8         1.           .16         2,784         52.5         1.           .18         1112         82.1         1.           .18         1112         82.1         1.           .32         869         75.8         1.           .32         869         73.5         8           .20         4,282         75.3         0.           .26         2,875         75.3         0.           .35         1,846         74.2         0.           .30         4,282         75.3         0.           .316         1,634         74.2         0.           .330         1,634         74.3         0.           .310         1,634         74.3         0.           .320         1,634         74.3         0.           .330         438         76.1         1.           .44         535         74.8         0.           .320         1,132         74.1         8           .3507         74.	Total (No.)       India (No.)       Indindia (No.)       India (No.)	MUL	Multivariable Logistic Regression	-			Multiv	Multivariable Logistic Regression	ession
····································		B	95% CI	٩	otal (No.)	Had CT (%)	ß	95% CI	٩
und         335         612         Ref $\sim$ 224         848         Ref $\sim$ instance         12/072         632         120         0890 106         23         5/29         858         1.70         1100.261 $\sim$ instance         12/072         6348         330         0890 109         1.6         2744         525         1.01         0660 102 $\sim$ memmer         186         61.6         1.41         085 10.25         1.6         1.71         821         1.38         0660 102 $\sim$ memmer         186         61.6         1.41         085 10.25         2.6         4.28         7.3         0.9         0.70 11.0 $\sim$ 0.660 10.2         1.26         0.660 10.2         1.28         0.660 10.2         0.7         0.6         0.7         0.6 <td< td=""><td>tured 35 tured 35 insurance 35,072 insurance 12,072 and 1,392 are 6,948 government 1,392 wn 212 wn 212 wn 212 bype 1,205 wn 2,180 0,565 wn 2,180 0,565 1,926 1,22</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></td<>	tured 35 tured 35 insurance 35,072 insurance 12,072 and 1,392 are 6,948 government 1,392 wn 212 wn 212 wn 212 bype 1,205 wn 2,180 0,565 wn 2,180 0,565 1,926 1,22								
interaction         12072         632         120         088 bit 13         73         789         686         170         1100 261           interaction         1392         616         141         086 bit 33         73         789         649         131         081 bit 214         0           intermetic         1365         616         141         086 bit 232         18         217         138         066 bit 53           intermetic         136         616         141         086 bit 23         18         217         138         066 bit 53           intermetic         136         616         131         046 bit 124         26         136         071 bit 13         157           intermetic         156         523         106         056 bit 13         26         28         071 bit 10         107           intermetic         556         523         103         056 bit 134         26         071 bit 10         107         101         107         101         107         101         107         101         107         101         107         101         101         101         101         101         101         101         101         101	insurance 12,072 aid 1,392 are 6,948 are 6,948 avernment 185 win 212 win 212 win 212 win 212 win 212 win 212 win 21,22 win 21,22 win 2,180 win 1,266 win Central 1,266 with Central 1,266 with Central 1,276 with Central 1	.2			224	84.8	Ref		
idial         1,382         632         094         058 lo 23         123         081 lo 214         086 lo 182         133         081 lo 214           ine         138         616         130         086 lo 133         13         081 lo 214         133         086 lo 182         133         086 lo 182         134         086 lo 182         134         086 lo 133         134         086 lo 133         134         086 lo 133         134         086 lo 133         133         086 lo 133         134         086 lo 134         135         Ref         135         136         056 lo 134         136         051 lo 134         136         136         136         136         136         136         136         136	id 1,392 are 6,948 6,948 6,948 8overnment 185 wm 212 wm 212 Wpe 1,923 hot 1,923 ehensive cancer program 1,923 hensive cancer renter 9,565 mic/research 6,264 ted cancer network program 2,180 2,180 bot cancer network program 2,180 in/research 1,226 Atlantic 3,107 Atlantic 3,736 outh Central 1,266 Atlantic 2,180 0 outh Central 1,276 outh Central 1,275 outh Central 1,275 outh Central 1,275 outh Central 2,489 outh Central 2,489 in 0,457 ain 2,489	.2	0.89 to 1.62	.23	5,729	85.8	1.70	1.10 to 2.61	.02
met         548         330         080         056106         16         2784         52.5         104         05610.62           poerment         185         61.6         141         08510.23         18         112         133         05610.288         1           poerment         121         50.9         0.78         0.49 tb.126         32         123         0.75 tb.321         1           mily ametire program         1.923         50.2         1.08         0.49 tb.124         2.6         2.875         75.3         0.89         0.70 tb.10         0.75 tb.133         1           mily ametire program         1.923         50.2         1.08         0.94 tb.124         2.6         2.875         75.3         0.89         0.70 tb.10         0.75 tb.133         1           mily ametire program         2.80         5.1         1.08         0.94 tb.124         2.6         2.875         75.3         0.89         0.70 tb.10         0.75 tb.133         1         1         0.75 tb.113	are         6,948           government         185           wm         212           wpe         212           wpe         1,923           unity cancer program         9,565           unity cancer program         2,180           unity cancer network program         2,180           wic/research         6,264           mic/research         6,264           mic/research         3,107           ted cancer network program         2,180           ocation         1,266           ngland         1,266           Atlantic         3,107           netation         1,266           outh Central         1,266           outh Central         1,266           outh Central         1,127           outh Central         1,232           outh Central         2,489           outh Central         2,489           outh Central	.2	0.68 to 1.31	.73	789	84.9	1.31	0.81 to 2.14	.27
guernment         186         616         1.41         085 to 2.32         1.8         112         82.1         1.38         066 to 2.88           wim<	government         185           wn         212           wn         212           wype         212           ytype         1,923           ehensive cancer program         1,923           ehensive cancer center         9,565           mic/research         6,264           fed cancer network program         2,180           off cancer network program         2,180           location         1,266           ngland         1,266           Atlantic         3,736           orth Central         1,266           outh Central         1,796           outh Central         1,232           ain         932           ain         932           ain         2,489           outh Central         1,245           ain         9,457	0.	0.59 to 1.09	.16	2,784	52.5	1.04	0.66 to 1.62	.87
mt         212         50.9         0.78         0.49 tb 1.26         32         76.8         1.52         0.72 tb 3.21           We         No         No         869         73.5         Ref         1.923         48.5         Ref         1.923         1.923         1.923         1.923         1.923         1.923         1.923         1.923         1.923         1.923         1.923         1.923         1.923         1.923         1.923         1.94         1.924         1.92         1.924         1.92         1.924         1.92         1.924         1.92         1.924         1.92         1.924         1.92         1.924         1.92         1.924         1.92         1.924         1.92         1.924         1.92         1.924         1.92         1.924         1.92         1.924         1.92         1.924         1.92         1.924         1.92         1.924         1.92         1.92         1.924         1.92         1.924         1.924         1.924         1.92         1.924         1.924         1.924         1.924         1.924         1.924         1.924         1.924         1.924         1.924         1.924         1.924         1.924         1.924         1.924         1.924	wn     212       type     1,923       unity cancer program     1,923       ehensive cancer center     9,565       mic/research     6,264       mic/research     6,264       ted cancer network program     2,180       ocation     1,266       Atlantic     3,736       Atlantic     3,736       outh Central     1,796       orth Cen	.6	0.85 to 2.32	.18	112	82.1	1.38	0.66 to 2.88	.39
Ope         Number of the second of the	type     1,923       unity cancer program     1,923       ehensive cancer center     9,565       mic/research     6,264       ted cancer network program     2,180       ted cancer network program     2,180       ocation     2,180       nalantic     3,107       Atlantic     3,107       Atlantic     3,736       orth Central     1,266       outh Central     1,217       outh Central     1,232       ain     9,32       ain     9,457       9,457     11,687	6	0.49 to 1.26	.32	82	76.8	1.52	0.72 to 3.21	.27
unity carcer program         1,223         845         Ref $735$ Ref $735$ Ref           ehreise carcer carler         9,565         502         109         0.96 to 125 $20$ 4.282         734         0.91         0.73 to 113 $100$ ehreise carcer carler         9,565         502         109         0.96 to 124 $26$ $2.87$ $76$ $0.91$ $0.77$ $0.73$ to 113 $0.77$ to 123 $0.77$ to 123 <th< td=""><td>unity cancer program     1,923       ehensive cancer center     9,565       mic/research     6,264       ted cancer network program     2,180       ted cancer network program     2,180       ocation     1,266       Atlantic     3,107       Atlantic     3,736       orth Central     1,127       orth Central     1,796       outh Central     1,796       outh Central     1,232       outh Central     1,232       ain     9,32       ain     9,32       ain     9,457       9,457     9,457</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></th<>	unity cancer program     1,923       ehensive cancer center     9,565       mic/research     6,264       ted cancer network program     2,180       ted cancer network program     2,180       ocation     1,266       Atlantic     3,107       Atlantic     3,736       orth Central     1,127       orth Central     1,796       outh Central     1,796       outh Central     1,232       outh Central     1,232       ain     9,32       ain     9,32       ain     9,457       9,457     9,457								
ehensive carrect center         5,56         502         109         0,56 (12)         209         1,26         2,37         0,39         0,710 (13)         1           indresearch         6,264         5,32         1,03         0,34 (12,4)         26         2,875         75,3         0,88         0,710 (10)         1           indresearch         6,264         5,32         1,13         0,55 (13,4)         1,6         2,875         75,3         0,88         0,710 (10)         1         0,0         0,710 (13)         1         0,1 <t< td=""><td>ethensive cancer center     9,565       mic/research     6,264       ted cancer network program     2,180       ted cancer network program     2,180       ocation     1,266       Atlantic     3,107       Atlantic     3,736       Atlantic     3,736       orth Central     1,127       orth Central     1,796       outh Central     1,732       outh Central     1,232       orth Central     1,235       orth Central     1</td><td>5</td><td></td><td></td><td>869</td><td>73.5</td><td>Ref</td><td></td><td></td></t<>	ethensive cancer center     9,565       mic/research     6,264       ted cancer network program     2,180       ted cancer network program     2,180       ocation     1,266       Atlantic     3,107       Atlantic     3,736       Atlantic     3,736       orth Central     1,127       orth Central     1,796       outh Central     1,732       outh Central     1,232       orth Central     1,235       orth Central     1	5			869	73.5	Ref		
mic/resarch         6,264         532         108         034 01.24         26         2875         75.3         0.08         0.70 01.10           led cancer network program         2.180         5.23         1.13         0.95 01.34         .16         9.23         0.70         0.71 01.34         0.71           ded cancer network program         2.180         5.23         1.13         0.95 01.34         .16         923         766         1.02         0.77 10.134         0.71           death         3.107         496         1.03         0.86 to 124         .72         156         786         0.63 01.14         1.7           Allentic         3.107         496         1.03         0.86 to 124         .72         156         786         0.63 01.14         1.7           Allentic         3.736         52.9         1.10         0.92         0.71 to 1.12         1.43         0.86 to 1.14         1.4         1.4         0.66 to 11.14         1.7           Allentic         1.127         53.1         1.12         0.92         0.92         0.92         0.63         0.66 to 11.14         1.7           Allentic         1.127         53.1         1.122         0.88         0.53         0	mic/research     6,264       ted cancer network program     2,180       location     1,266       ngland     1,266       Atlantic     3,107       Atlantic     3,107       Atlantic     1,266       Atlantic     3,736       orth Central     1,127       outh Central     1,127       outh Central     1,232       outh Central     1,232       ain     932       ain     2,489       11,687     9,457       11,687     9,457	.2	0.96 to 1.25	.20	4,282	73.4	0.91	0.73 to 1.13	39
ted carcer retwork program         2,180         5,23         1,13         0,56 1,13         1,16         1,13         0,51 1,134         1,13           dende         1,266         51.1         Ref         7.2         540         791         Ref         7.7 1, 134           dende         3,107         496         1,03         0.86 to 124         7.2         1,566         7.26         0.85         0.63 to 114         2           Athenic         3,736         52.9         1,10         0.92         0.77 to 11,0         35         1,846         742         0.86         0.63 to 114         2           Athenic         3,736         52.9         1,10         0.92         0.77 to 11,0         35         1,846         742         0.86         0.63 to 113         2           Athenic         1,726         53.1         1,12         0.90 to 114         .30         1,634         742         0.86         0.63 to 1136         2           Athenic         1,232         50,1         1,12         0.90 to 11,12         1.94         1.94         1.94         1.94         1.94         1.94         1.94         1.94         1.95         1.96         0.75         0.68         0.61 to 1126	ted cancer network program     2,180       location     1,266       ngland     1,266       Atlantic     3,107       Atlantic     3,736       Atlantic     1,127       orth Central     1,796       orth Central     1,796       outh Central     1,796       orth Central     1,796       orth Central     1,232       ain     9,32       ain     9,457       ain     11,687       9,457     11,687	.2	0.94 to 1.24	.26	2,875	75.3	0.88	0.70 to 1.10	.27
decidion         1266         511         Ref         791         Ref         791         Ref           Allantic         3,107         496         103         086 to 124         72         1,566         726         0.85         0.63 to 114         1           Allantic         3,107         496         103         086 to 124         72         1,566         726         0.85         0.63 to 114         1           Altantic         3,736         529         1,10         092         0.70 to 110         35         1,846         743         0.85         0.62 to 111         1         1         0         0         0.0114         1         0         0         0.0114         1         0         0         0.0114         1         0	ocation       1,266         ngland       1,266         Atlantic       3,107         Atlantic       3,107         Atlantic       3,736         Atlantic       1,127         outh Central       1,127         outh Central       1,796         outh Central       1,232         outh Central       1,232         outh Central       1,232         ain       9,32         ain       2,489         11,687       9,457         9,457       11,687	¢.	5	.16	923	76.6	1.02	p	<u> 66</u>
ngland         1,266         51.1         Ref         7.2         540         79.1         Ref           Allantic         3,107         49.6         1.03         0.86 b 1.24         7.2         1.56         7.26         0.85         0.63 b 1.14         7           Allantic         3,107         49.6         1.03         0.86 b 1.24         7.2         1.56         0.85         0.63 b 1.14         7           Attantic         3,736         52.9         1.10         0.92         0.77 b 1.10         35         1,846         742         0.85         0.65 b 1.14         7           Orth Central         1,127         53.1         1.12         0.90 b 1.30         30         438         75.1         1.05         0.65 b 1.26         7           Orth Central         1,127         53.1         1.12         0.90 b 1.32         30         438         76.1         1.06         0.75 b 1.46         7           Orth Central         1,232         50.7         0.82         0.74 b 1.12         30         76.3         76.3         0.65         0.65 b 1.126         7           Orth Central         1,232         50.7         74.3         74.3         76.3         0.74         0.	ngland     1,266       Atlantic     3,107       Atlantic     3,107       Atlantic     1,247       orth Central     1,126       outh Central     1,796       outh Central     1,796       outh Central     1,232       ain     932       ain     2,489       ain     9,457       11,687     9,457								
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orth Central         3,736         5,29         1.10         0,92 to 1.31         3.0         1,634         74,9         0,94         0.69 to 1.26           outh Central         1,127         531         1.12         0,90 to 1,40         .30         438         75.3         0,22         0.63 to 1.35           outh Central         1,22         50.7         0,92         0,74 to 1.14         .44         535         74.8         0.65         0.61 to 1.26           outh Central         1,222         50.7         0,92         0,74 to 1.12         .30         435         76.3         0.28         0.61 to 1.26           outh Central         1,222         50.7         0.92         0,74 to 1.12         .30         435         70.3         0.68         0.61 to 1.26           outh Central         1,232         60.1         0.88         0,70 to 1.12         .30         73.3         0.68         0.61 to 1.26           outh Central         1,232         136         1,132         73.4         0.53         0.68         0.64 to 0.99           otto 1,168         60.1         1.66         1.54 to 1.80         71         1.13         77.1         1.28         1.24           otto 1,168         54<	orth Central     3,736       outh Central     1,127       lorth Central     1,796       outh Central     1,796       outh Central     1,796       ain     932       ain     2,489       11,687     11,687       9,457     9,457		0.77 to 1.10	.35	1,846	74.2	0.83	0.62 to 1.11	.21
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orth Central         1,796         52.2         1.08         0.89 to 1.32         4.2         833         76.1         1.05         0.75 to 1.46           outh Central         1,232         50.7         0.92         0.74 to 1.14         4.4         535         7.48         0.63         0.61 to 1.26           outh Central         932         49.1         0.88         0.70 to 1.12         30         435         70.3         0.68         0.61 to 1.26           oith Central         932         49.1         0.88         0.70 to 1.12         30         435         70.3         0.68         0.61 to 1.26           in         2,489         50.1         0.86         0.72 to 1.04         1.12         1,132         73.6         0.74         0.54 to 1.02           in         2,489         50.1         1.66         0.72 to 1.04         1.12         1,132         73.6         0.74 to 1.02           in         9,457         59.1         1.66         1.54 to 1.80         6.01         6.21         0.74         0.74         0.74           in         9,457         59.1         1.66         1.54 to 1.80         6.01         0.50         0.55         0.51         1.26         1.2	Iorth Central     1,796     52       outh Central     1,232     50       ain     9,32     49       2,489     50       11,687     48       9,457     59       18,854     50		0.90 to 1.40	.30	438	75.3	0.92	0.63 to 1.35	.67
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11,687       48.3       Ref       3,507       74.1       Ref         9,457       59.1       1.66       1.54 to 1.80 <b>&lt;.001</b> 6,213       77.1       1.08       0.95 to 1.22         9,457       59.1       1.66       1.54 to 1.80 <b>&lt;.001</b> 6,213       77.1       1.08       0.95 to 1.22       .         1       .       .       .       .       .       .       .       .       .       .       .       .       0.95 to 1.22       .	11,687 48 9,457 59 18,854 54		0.72 to 1.04	.12	1,132	73.6	0.74	0.54 to 1.02	.07
$11,687$ $48.3$ Ref $3,507$ $74.1$ Ref $9,457$ $59.1$ $1.66$ $1.54 \tan 1.80$ $\boldsymbol{<.001}$ $6,213$ $77.1$ $1.08$ $0.95 \tan 1.22$ $1.8,854$ $54.8$ Ref $\mathbf{<.001}$ $\mathbf{ 6},213$ $77.1$ $1.08$ $0.95 \tan 1.22$ $1.8,854$ $54.8$ Ref $\mathbf{ 6},213$ $76.5$ Ref $\mathbf{ 6},213$	11,687 48 9,457 59 18,854 54								
9,457     59.1     1.66     1.54 to 1.80 <b>&lt;.001</b> 6,213     77.1     1.08     0.95 to 1.22       1     1     1     1     1     1     1     1     1       1     1     1     1     1     1     1     1     1     1       1     1     1     1     1     1     1     1     1     1     1       1     1     1     1     1     1     1     1     1     1     1     1     1       1     <	9,457 59 18,854 54	c.			3,507	74.1	Ref		
18,854     54.8     Ref     8,625     76.5     Ref       826     30.8     0.61     0.50 to 0.74     <.001	18,854 54			<.001	6,213	77.1	1.08	0.95 to 1.22	.27
18,854         54.8         Ref         8,625         76.5         Ref           826         30.8         0.61         0.50 to 0.74         <.001	18,854 54								
826         30.8         0.61         0.50 to 0.74         <.001         328         66.8         0.93         0.69 to 1.26         .           1,464         44.4         0.84         0.72 to 0.97         .02         767         74.8         0.93         0.74 to 1.16         .		8 <u>.</u>			8,625	76.5	Ref		
1,464 44.4 0.84 0.72 to 0.97 <b>.02</b> 767 74.8 0.93 0.74 to 1.16	826 30	œ		<.001	328	66.8	0.93	0.69 to 1.26	.64
	1,464 44	4.	0.72 to 0.97	.02	767	74.8	0.93	0.74 to 1.16	.53

TABLE 2. Characteristics Associated With Adjuvant Chemotherapy for Grade 3 Disease, Stratified by pN Status (Continued)

			DNQ					pN1		
			Multiva	Multivariable Logistic Regression	ssion			Multiva	Multivariable Logistic Regression	ession
Characteristic	Total (No.)	Had CT (%)	S	95% CI	٩	Total (No.)	Had CT (%)	ß	95% CI	٩
PR status										
Negative	3,941	75.0	Ref			1,439	83.7	Ref		
Positive	17,182	48.1	0.44	0.40 to 0.49	< .001	8,265	74.7	0.62	0.51 to 0.75	< .001
Standard surgery/RT										
Yes (lumpectomy with RT or mastectomy only)	18,898	54.5	Ref			7,085	73.1	Ref		
No (lumpectomy only)	832	21.9	0.36	0.28 to 0.44	< .001	238	47.1	0.51	0.37 to 0.71	< .001
No (mastectomy with RT)	515	71.7	2.06	1.60 to 2.66	< .001	2,317	88.2	2.30	1.94 to 2.74	< .001
NOTE. Boldface indicates significance at <i>P</i> < .05. Abbreviations: AJCC. American Joint Committee on Cancer: CT. chemotherapy: IDC. invasive ductal carcinoma: ILC. invasive lobular carcinoma: IMC. invasive mixed carcinoma: NA. not applicable: OR.	at $P < .05$ . mmittee on Canc	er: CT, chemothers	apy: IDC, inve	isive ductal carcinom	a: ILC. invasiv	e lobular carcino	oma: IMC, invasive	mixed carci	noma: NA. not appl	cable: OR.

TABLE 2. Characteristics Associated With Adjuvant Chemotherapy for Grade 3 Disease, Stratified by pN Status (Continued) ONa 5 2 odds ratio; PR, progesterone receptor; Ref, reference; RS, recurrence score; RT, radiotherapy.

# Multigene RS for Grade 3 Breast Cancer

**TABLE 3.** Kaplan-Meier Estimates of Overall Survival Associated With Adjuvant Chemotherapy in Patients With Grade 3 Invasive Breast Cancer, Stratified by pN Status and RS

			5-Year Overall Surviv	val Rate, % (95% CI)	
RS*	Total (No.)	Had Chemotherapy (%)	No Chemotherapy	Chemotherapy	Р
pN0					
Low	3,591	9.1	96.3 (95.0 to 97.2)	98.8 (94.9 to 99.7)	.07
Intermediate	5,304	54.9	93.0 (90.8 to 94.7)	95.5 (94.0 to 96.6)	.002
High	4,332	89.4	79.6 (72.4 to 85.1)	91.8 (90.2 to 93.1)	< .001
No RS	7,586	52.2	83.3 (81.3 to 85.0)	93.6 (92.4 to 94.7)	< .001
pN1					
Low	821	25.9	92.0 (86.9 to 95.2)	93.0 (80.7 to 97.6)	.27
Intermediate	1,188	64.4	85.7 (77.5 to 91.1)	93.2 (88.4 to 96.1)	.02
High	726	88.3	66.9 (48.6 to 79.9)	92.4 (88.1 to 95.2)	< .001
No RS	6,880	82.8	70.6 (66.5 to 74.3)	90.7 (89.5 to 91.8)	< .001

NOTE. Boldface indicates significance at P < .05.

Abbreviation: RS, recurrence score.

\*In 2.4% of patients (n = 331) with pN0 and 3.7% (n = 105) with pN1 grade 3 tumors who underwent RS testing, the RS score was not available.

# Evaluation of Grade 3 and RS Coding Accuracy

We also examined our multi-institutional cohort to validate registry-submitted grade and RS encoding. Of 351 adults with invasive breast carcinoma who had RS testing between 2010 and 2015, 74.7% (n = 259) were encoded and submitted for inclusion into cancer registries. Nottingham/ Bloom-Richardson grade was missing or incorrectly encoded in 6.6% of patients (n = 17), including 8.1% (n = 3) with grade 3 disease. The numerical RS was missing in 15.4% of registry-submitted patients (n = 40) and incorrectly encoded in 3.9% (n = 10). In particular, of the 37 grade 3 registry-submitted institutional patients with RS testing, 16.2% (n = 6) had missing scores in registry data, and only 3.2% (n = 1) were incorrectly encoded (as no RS instead of an actual RS of 22).

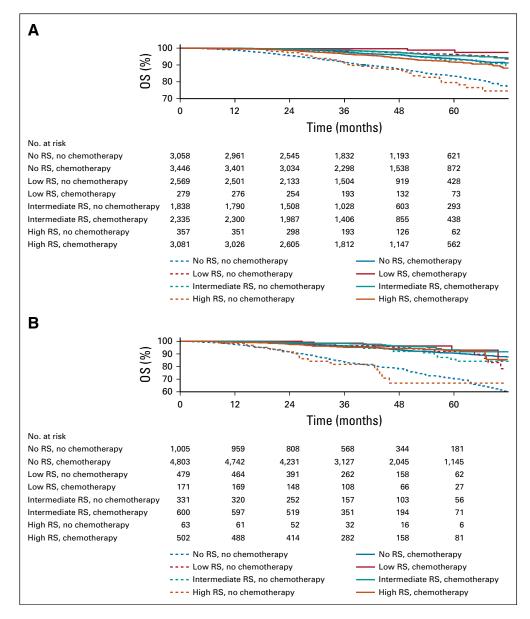
# **DISCUSSION**

In this large national cohort, we evaluated the use of RS, use of adjuvant chemotherapy, and OS for women with breast cancer, with a focus on high tumor grade. We found that 30.0% of pN0 and 27.1% of pN1 grade 3 invasive breast cancers had a low RS, which was not associated with an OS benefit from chemotherapy. Of note, chemotherapy was associated with significant OS improvements in grade 3 invasive breast cancers with high RS, and although associated with improved OS in univariable analyses, intermediate RS was not predictive of significant chemotherapy OS benefit when risk adjusted for clinicopathologic characteristics. The incorporation of RS testing into the clinical decision making for grade 3 invasive breast cancers may help to tailor treatment recommendations for these patients. To our knowledge, these findings represent the largest analysis to date of the potential impact of RS on the outcomes and management of grade 3 tumors and suggest that the assumption that all pT1c/2 pN0/1, ERpositive histopathologic grade 3 tumors are high risk and will consequently benefit from adjuvant chemotherapy may be unmerited.

Although we await the RxPONDER trial final results, the data presented here suggest that patients with a pT1c/2 NO/1 grade 3 tumor with high RS derive benefit from chemotherapy (92% 5-year OS with chemotherapy v 67% to 79% without), whereas grade 3 tumors with low and intermediate RS do not. Our results further reinforce the utility of broad RS testing in grade 3 tumors and suggest that RS can help to distinguish the anticipated chemotherapy benefit among this heterogeneous group of tumors.

The rate of RS testing is less in pN1 disease than in pN0 disease (36% in 2015 v 72% in pN0) but is expanding in both groups because the importance of tumor biology is increasingly recognized. In our study, the increased use of RS testing in pNO grade 3 disease (64.1%) and lower rate of chemotherapy (9.1%) in patients with low RS suggest that clinical practice is increasingly incorporating RS results into decision trees for pNO grade 3 disease. However, our findings also suggest that a significant proportion of patients with pN1 grade 3 disease who do not undergo RS testing may be overtreated and receive chemotherapy with no added OS benefit. We also find that nationally, significant variability exists in grade 3 RS testing patterns by hospital type and geographic location and even in patient insurance status and race/ethnicity, which suggests opportunities for more-detailed guidance from national guidelines for RS testing, particularly for grade 3 tumors.

We found that a high proportion of patients designated as having a high histologic grade had a low RS (less 18)—27.1% with pN0 and 30.0% with pN1 disease—results that



**FIG 2.** Overall survival (OS) in patients with grade 3 invasive breast cancer, stratified by recurrence score (RS). Adjuvant chemotherapy OS estimated by Kaplan-Meier method for patients with (A) pNO and (B) pN1 grade 3 invasive breast cancer, stratified by RS and adjuvant chemotherapy, with an underlying number at risk table. Adjuvant chemotherapy (solid lines) was associated with significantly better median OS than no adjuvant chemotherapy (dashed lines) for intermediate, high, and no RS.

are notably higher than those reported in the PlanB trial (18% of grade 3 tumors).<sup>13</sup> However, our findings are in keeping with those reported in the Microarray in Node-Negative (or 1-3 Positive Lymph Node) Disease May Avoid Chemotherapy (MINDACT) trial, where patients were stratified by both anatomic and genomic risk using a 70-gene signature. In MINDACT, 28.6% of tumors deemed to be of high clinical risk had low genomic risk and were unlikely to benefit from chemotherapy.<sup>23</sup> In the published TAILORx trial data, intermediate RS (11 to 25) tumors in postmenopausal women did not demonstrate clear benefit

from chemotherapy; however, this trial was in patients with NO disease with mostly small tumors, excluded those with an intermediate RS of 26 to 30, and only included a small proportion (17.8%) of patients with grade 3 disease, all of which are limiting comparisons within our study that included a substantial number of T2 tumors in NO disease.<sup>12</sup>

Our analyses are constrained by several limitations of the NCDB. Of note, despite representing a majority of patients with cancer in the United States and forming the basis of AJCC staging guidelines, the lack of centralized clinical or pathologic review may limit the accuracy of encoded data.

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**TABLE 4.** Multivariable Cox Proportional Hazards Regression for the Overall Survival Associated With Adjuvant Chemotherapy in Patients With Grade 3 Invasive Breast Cancer, Stratified by pN Status

arade 5 invasive breast cancer, Stratilied by privisia	tus	рNO			pN1	
Variable	HR	95% CI	Р	HR	95% CI	Р
RS by chemotherapy						
No RS						
Chemotherapy (Ref no chemotherapy)	0.51	0.40 to 0.64	< .001	0.42	0.33 to 0.53	< .001
Low						
Chemotherapy (Ref no chemotherapy)	0.50	0.16 to 1.61	.25	0.81	0.33 to 1.98	.64
Intermediate						
Chemotherapy (Ref no chemotherapy)	0.71	0.49 to 1.03	.07	0.67	0.35 to 1.27	.22
High						
Chemotherapy (Ref no chemotherapy)	0.63	0.43 to 0.90	.01	0.24	0.13 to 0.47	< .001
Age, years						
< 50	0.90	0.67 to 1.20	.46	0.71	0.53 to 0.96	.03
50-59	Ref			Ref		
60-69	1.29	1.02 to 1.62	.03	1.00	0.77 to 1.30	1.00
≥ 70	2.07	1.59 to 2.70	< .001	1.64	1.20 to 2.23	.002
Year of diagnosis						
2010	Ref			Ref		
2011	1.06	0.88 to 1.28	.55	1.37	1.08 to 1.72	.008
2012	0.96	0.77 to 1.19	.70	1.28	0.99 to 1.66	.06
2013	1.05	0.82 to 1.34	.69	1.33	0.99 to 1.79	.06
2014	1.29	0.95 to 1.75	.11	1.79	1.25 to 2.58	.002
Comorbidity index						
0	Ref			Ref		
1	1.43	1.20 to 1.69	< .001	1.35	1.10 to 1.67	.004
2	2.83	2.15 to 3.73	< .001	1.76	1.20 to 2.58	.004
3	2.95	1.89 to 4.60	< .001	3.68	2.26 to 6.01	< .001
Race/ethnicity						
White	Ref			Ref		
Black	1.02	0.82 to 1.26	.88	1.06	0.83 to 1.35	.65
Asian/Pacific Islander	0.50	0.29 to 0.87	.02	0.66	0.38 to 1.17	.15
Hispanic	0.63	0.40 to 0.99	.045	0.67	0.43 to 1.04	.08
Other/unknown	0.63	0.28 to 1.42	.26	0.59	0.24 to 1.43	.24
Primary payer						
Not insured	Ref			Ref		
Private insurance	0.74	0.40 to 1.36	.34	0.74	0.43 to 1.26	.27
Medicaid	0.92	0.47 to 1.80	.81	0.85	0.47 to 1.57	.61
Medicare	0.99	0.53 to 1.83	.97	0.91	0.52 to 1.57	.72
Other government	1.64	0.69 to 3.88	.26	0.91	0.33 to 2.53	.86
Unknown	0.77	0.29 to 1.99	.58	1.29	0.49 to 3.34	.61
Hospital type						
Community cancer program	Ref			Ref		
Comprehensive cancer center	0.86	0.69 to 1.07	.17	0.74	0.57 to 0.97	.03
Academic/research	0.74	0.59 to 0.94	.01	0.84	0.63 to 1.11	.21

(Continued on following page)

TABLE 4.         Multivariable Cox Proportional Hazards Regression for the Overall Survival Associated With Adjuvant Chemotherapy in Patients With
Grade 3 Invasive Breast Cancer, Stratified by pN Status (Continued)

		pNO			pN1	
Variable	HR	95% CI	Р	HR	95% CI	Р
Hospital location						
New England	Ref			Ref		
Middle Atlantic	1.08	0.78 to 1.51	.64	1.82	1.14 to 2.92	.01
South Atlantic	0.92	0.66 to 1.27	.61	1.84	1.15 to 2.94	.01
East North Central	1.07	0.78 to 1.48	.66	1.57	0.98 to 2.52	.06
East South Central	1.06	0.72 to 1.57	.75	1.95	1.10 to 3.44	.02
West North Central	0.93	0.65 to 1.34	.71	1.79	1.08 to 2.96	.02
West South Central	0.75	0.49 to 1.14	.18	1.94	1.14 to 3.31	.02
Mountain	0.97	0.64 to 1.48	.90	1.55	0.86 to 2.79	.14
Pacific	0.82	0.57 to 1.16	.26	1.70	1.03 to 2.79	.04
AJCC pT						
2 (Ref 1c)	1.99	1.73 to 2.30	< .001	1.45	1.20 to 1.75	< .001
Histology						
IDC	Ref			Ref		
ILC	0.60	0.41 to 0.88	.01	1.26	0.86 to 1.86	.23
IMC	0.81	0.61 to 1.09	.17	0.94	0.69 to 1.29	.71
PR status						
Positive (Ref negative)	0.70	0.59 to 0.82	< .001	0.54	0.45 to 0.66	< .001
Standard surgery/RT						
Yes (lumpectomy with RT or mastectomy only)	Ref			Ref		
No (lumpectomy only)	1.94	1.55 to 2.44	< .001	1.99	1.46 to 2.72	< .001
No (mastectomy with RT)	1.03	0.66 to 1.59	.91	0.97	0.78 to 1.21	.80

NOTE. Boldface indicates significance at P < .05.

Abbreviations: AJCC, American Joint Committee on Cancer; HR, hazard ratio; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; IMC, invasive mixed carcinoma; PR, progesterone receptor; Ref, reference; RS, recurrence score; RT, radiotherapy.

However, in our multi-institutional cohort of registrysubmitted patients, 92% with grade 3 disease demonstrated accurate grade coding of whom only 3% had an incorrectly encoded RS, which suggests that key breast cancer-specific factors are encoded into national registries with encouraging accuracy. In addition, the NCDB only includes OS data, which precludes assessment of breast cancer-specific, progression-free, or recurrence-free survival, end points that may be of greater relevance in the clinical setting. Because of limited follow-up, the NCDB does not incorporate survival data for patients diagnosed in the most recent year. As such, our median follow-up is only 41.3 months and the event rate only 6.2%; nevertheless, we incorporated a large sample size that powered the detection of clinically relevant differences in RS predictive value. Finally, the NCDB lacks detailed information about type, dose, and duration of chemotherapeutic and hormonal treatments and, in particular, has limited granular data about the factors that influence clinical decision making about when to administer adjuvant chemotherapy.

For example, across all patients with grade 3 disease who were not administered chemotherapy, the NCDB only encoded a reason in 27% (21% because chemotherapy was contraindicated and 7% because chemotherapy was recommended but refused by the patient). To help to address the lack of data about patient contraindications, we included Charlson-Deyo comorbidity index data in our riskadjusted analyses, and higher indices were associated with reduced chemotherapy use. The NCDB also lacks patient menopausal status and only began encoding HER2 status as of 2010. Furthermore, the NCDB does not have information on why RS was or was not sent, which introduces the potential for bias in whom is anticipated to benefit or not benefit from chemotherapy on the basis of additional patient and physician factors that were not captured in our data set.

In conclusion, our data show significant clinical value for RS testing in patients with grade 3 breast cancer to predict which patients are likely to show early benefit or not from

the addition of chemotherapy. Furthermore, our findings show significant variability in national patterns of RS testing and chemotherapy use for grade 3 disease, which suggests opportunities for more comprehensive national guidelines for RS testing in high-grade tumors. These results fill a gap

# **AFFILIATIONS**

<sup>1</sup>Brigham and Women's Hospital, Boston, MA <sup>2</sup>Harvard Medical School, Boston, MA <sup>3</sup>Dana-Farber Cancer Institute, Boston, MA

# **CORRESPONDING AUTHOR**

Jane E. Brock, MBBS, PhD, Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, 75 Francis St, Boston, MA 02115; Twitter: @BrighamWomens, @DanaFarber; e-mail: jebrock@ bwh.harvard.edu.

## **EQUAL CONTRIBUTION**

E.A.M. and J.E.B. contributed equally and should be considered cosenior authors.

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#### AUTHOR CONTRIBUTIONS

Conception and design: J. Bryan lorgulescu, Rachel A. Freedman, Jane E. Brock

Administrative support: J. Bryan lorgulescu, Susan C. Lester, Jane E. Brock

Provision of study material or patients: Susan C. Lester

Collection and assembly of data: J. Bryan lorgulescu, Susan C. Lester Data analysis and interpretation: J. Bryan lorgulescu, Rachel A. Freedman, Susan C. Lester, Elizabeth A. Mittendorf

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

### REFERENCES

- 1. Paik S, Shak S, Tang G, et al: A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. N Engl J Med 351:2817-2826, 2004
- 2. Paik S, Tang G, Shak S, et al: Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. J Clin Oncol 24:3726-3734, 2006
- Albain KS, Barlow WE, Shak S, et al: Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: A retrospective analysis of a randomised trial. Lancet Oncol 11:55-65, 2010
- Dowsett M, Cuzick J, Wale C, et al: Prediction of risk of distant recurrence using the 21-gene recurrence score in node-negative and node-positive postmenopausal patients with breast cancer treated with anastrozole or tamoxifen: A TransATAC study. J Clin Oncol 28:1829-1834, 2010
- 5. National Comprehensive Cancer Network: Breast Cancer, version 1.2018. https://www.nccn.org/professionals/physician\_gls/pdf/breast\_blocks.pdf
- 6. Harris LN, Ismaila N, McShane LM, et al: Use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol 34:1134-1150, 2016
- 7. American Joint Committee on Cancer: AJCC Cancer Staging Manual (ed 8). New York, NY, Springer, 2017
- 8. Sanders MA, Wong SM, lorgulescu JB, et al: Changes and clarifications in the eighth edition of the AJCC cancer staging system for breast cancer. AJSP Rev Rep 23:113-117, 2018

as we await the final RxPONDER trial results and provide additional data to the reported results of the TAILORx trial to help clinicians to identify patients who may safely omit chemotherapy without compromising their outcomes.

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- 9. Giuliano AE, Connolly JL, Edge SB, et al: Breast cancer-major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin. 67:290-303, 2017
- 10. Sparano JA, Gray RJ, Makower DF, et al: Prospective validation of a 21-gene expression assay in breast cancer. N Engl J Med 373:2005-2014, 2015
- 11. Wong WB, Ramsey SD, Barlow WE, et al: The value of comparative effectiveness research: Projected return on investment of the RxPONDER trial (SWOG S1007). Contemp Clin Trials 33:1117-1123, 2012
- 12. Sparano JA, Gray RJ, Makower DF, et al: Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. N Engl J Med 379:111-121, 2018
- Gluz O, Nitz UA, Christgen M, et al: West German Study Group Phase III PlanB Trial: First prospective outcome data for the 21-gene recurrence score assay and concordance of prognostic markers by central and local pathology assessment. J Clin Oncol 34:2341-2349, 2016
- 14. Boffa DJ, Rosen JE, Mallin K, et al: Using the National Cancer Database for outcomes research: A review. JAMA Oncol 3:1722-1728, 2017
- 15. Tavassoli FA, Devilee P (eds): World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of the Breast and Female Genital Organs. Lyon, France, IARC Press, 2003
- 16. Orucevic A, Bell JL, McNabb AP, et al: Oncotype DX breast cancer recurrence score can be predicted with a novel nomogram using clinicopathologic data. Breast Cancer Res Treat 163:51-61, 2017
- 17. Roberts MC, Miller DP, Shak S, et al: Breast cancer-specific survival in patients with lymph node-positive hormone receptor-positive invasive breast cancer and Oncotype DX recurrence score results in the SEER database. Breast Cancer Res Treat 163:303-310, 2017
- 18. Bhutiani N, Egger ME, Ajkay N, et al: Multigene signature panels and breast cancer therapy: Patterns of use and impact on clinical decision making. J Am Coll Surg 226:406-412.e1, 2018
- 19. American Joint Committee on Cancer: AJCC Cancer Staging Manual (ed 7). New York, NY, Springer, 2010
- 20. Commission on Cancer. Facility Oncology Registry Data Standards Manual: 2013 Revision. Chicago, IL, American College of Surgeons, 2013
- 21. Deyo RA, Cherkin DC, Ciol MA: Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol 45:613-619, 1992
- 22. lorgulescu JB, Harary M, Zogg CK, et al: Improved risk-adjusted survival for melanoma brain metastases in the era of checkpoint blockade immunotherapies: Results from a national cohort. Cancer Immunol Res 6:1039-1045, 2018
- 23. Cardoso F, van't Veer LJ, Bogaerts J, et al: 70-Gene signature as an aid to treatment decisions in early-stage breast cancer. N Engl J Med 375:717-729, 2016