Chemotherapy Costs and 21-Gene Recurrence Score Genomic Testing Among Medicare Beneficiaries With Early-Stage Breast Cancer, 2005 to 2011

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ABSTRACT

Background: This study examined whether associations between 21-gene recurrence score (RS) genomic testing and lower costs among patients with early-stage, estrogen receptor–positive breast cancer are observable in real-world data from the Medicare population. **Methods:** A retrospective cohort study was conducted using SEER-Medicare data for a nationally representative sample of Medicare beneficiaries diagnosed from 2005 through 2011. The main outcomes were associations between RS testing and overall and chemotherapy-specific costs. The primary analysis was restricted to patients aged 66 to 75 years. **Results:** The primary analysis comprised 30,058 patients. Mean costs 1 year after diagnosis were \$35,940 [SD, \$28,894] overall, \$51,127 [33,386] for clinically high-risk disease, \$33,225 [27,711] for intermediate-risk disease, and \$26,695 [19,532] for low-risk disease. Chemotherapy-specific costs followed similar trends. In multivariable analyses, RS testing was associated with significantly lower costs among high-risk patients in terms of both relative costs (cost ratio, 0.88; 99% CI, 0.82–0.94) and absolute costs (\$6,606; 99% CI, \$39,223–\$9,290). Higher costs among low-risk and intermediate-risk patients were mainly caused by higher non-cancer costs. In sensitivity analyses that included all patients aged ≥66 years (N=64,996), associations between RS testing and costs among high-risk patients were similar but less pronounced because of lower overall use of chemotherapy. **Conclusions:** RS testing was associated with lower overall and chemotherapy-related costs in patients with high-risk disease, consistent with lower chemotherapy use among these patients. Higher overall costs for patients with intermediate-risk and low-risk disease were driven largely by non-treatment-related costs.

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Background

The introduction of genomic tests such as the Oncotype DX 21-gene recurrence score (RS) assay has allowed the omission of adjuvant chemotherapy for patients with estrogen receptor (ER)–positive, node-negative breast cancer who have a low RS.^{1–3} Most economic models used to examine the impact of RS testing on overall and chemotherapy-related costs have suggested that RS testing is cost-saving or cost-effective because of net reductions in the use of adjuvant chemotherapy achieved by limiting treatment to patients most likely to benefit.^{4–12} However, these economic models require numerous assumptions and may be influenced substantially by investigator bias.¹³ Furthermore, patients' treatment decisions can vary depending on personal preferences and priorities, and they may not follow test-based or physician-recommended treatment. Contrary to guideline recommendations, some patients with low-risk disease receive RS testing¹⁴ and have a higher likelihood of undergoing chemotherapy than those who do not receive testing.¹⁵

Given the strong dependence of adjuvant chemotherapy use on patient population characteristics and the focus of prior economic models on clinical trial participants, previous studies may not fully reflect practices in the general patient population. Therefore, we examined associations between 21-gene RS testing and empirically observed costs to Medicare in the form of total payments for overall and cancer-specific care in a nationally representative cohort of patients aged 66 to 75 years diagnosed with incident breast cancer from 2005 through 2011.

Methods

Data Source and Study Population

Data were obtained from the SEER-Medicare linked dataset, a collaborative effort between the NCI and the

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Centers for Medicare & Medicaid Services. SEER data represent approximately 28% of the US population with cancer.¹⁶ The study population included women in the SEER-Medicare dataset with a diagnosis of invasive, ER-positive, nondistant metastatic breast cancer from 2005 through 2011. The analysis was restricted to patients aged 66 to 75 years, because this population is most likely to be considered for adjuvant chemotherapy. It was also restricted to patients with ER-positive tumors, because RS testing was clinically validated and initially recommended for these patients. Although initial studies of RS testing were limited to patients with node-negative disease, the test has also been used in node-positive disease in this population,¹⁴ and may predict disease-free and overall survival in these patients.^{17,18} For these reasons, we included patients with high-risk disease and those with node-positive disease. We used Medicare claims data from 2004 through 2012 to confirm Medicare enrollment, confirm the presence of at least 1 breast cancer claim, and characterize healthcare resource use. We used claims data from the year before diagnosis to identify comorbid conditions. The Institutional Review Board of the Duke University Health System approved the study.

Outcomes

The primary study outcomes were total and chemotherapy-specific costs in the year after diagnosis. Chemotherapy costs included costs for port and/or vascular access placement (CPT codes 36,555–36,598 for port or central access placement, and 76,937 and 77,001 for image guidance for vascular access). Additional end points included costs broken down by costs for cancer-directed surgical procedures, radiation therapy, RS testing, imaging, nonsurgical inpatient, cancer treatment (ie, the sum of surgical and radiation therapy, imaging, and chemotherapy costs), and noncancer treatment. We also calculated overall costs in the year before diagnosis to provide an internal control for overall expenditures. Costs were calculated by summing Medicare payments from all patient claims and adjusting to 2013 US dollars. We identified RS testing in the period from 2 months before to 6 months after diagnosis using CPT code 84,999 associated with the known National Provider Identifier for Genomic Health, Inc. (sole provider of RS testing), and the zip code for Redwood City, California (location of the company).

Control Variables

Clinical variables, including TNM staging, were available in the SEER Patient Entitlement and Diagnosis Summary File (PEDSF). Patients with missing node status were characterized as having node-negative disease and those with microscopic nodal disease (N1mic) as having N1

disease. Current NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) incorporate the use of RS testing to guide adjuvant treatment.³ However, our goal was to determine the impact of RS testing compared with the clinicopathologic risk stratification method that preceded RS testing. Therefore, we categorized patients, as described previously,^{14,15} into 3 risk groups based on histology and T and N stage: low, intermediate, and high. Low-risk disease included node-negative tumors ≤ 0.5 or < 1.0 cm with no unfavorable histologic features as assessed by the site-specific extent of disease (ie, Paget disease, invasive disease, inflammatory disease, G3 or anaplastic histopathology, and T4 disease). Intermediate-risk disease included ER-positive, node-negative tumors 0.6 to 1.0 cm with unfavorable features or > 1.0 cm. High-risk disease included node-positive or T4 disease. HER2 status was unavailable in the data and was not incorporated into risk stratification. The PEDSF was used to obtain demographic variables, including age at diagnosis, sex, race, ethnicity, marital status, and census tract characteristics. SEER registries were grouped by census region. Medicare inpatient, outpatient, and carrier claims from the year before diagnosis were used to identify NCI comorbid conditions.¹⁹

Statistical Analysis

We describe baseline characteristics of the study population using frequencies and percentages for all variables. Chi-square tests were used to test for differences in categorical variables between groups. Costs were analyzed in univariate analyses using the Wilcoxon rank sum test. Costs in univariate analyses are presented as means with SDs to facilitate estimation comparable to the overall total costs in the population. Costs were modeled in multivariable regression analyses using generalized linear modeling with a gamma distribution and log link to separately model relative cost ratios and to calculate the least squares means to estimate absolute cost difference. Multivariable models were adjusted for age, race, marital status, census tract characteristics, tumor grade and size, costs in the year before diagnosis divided by 1,000, receipt of RS testing, and clinical risk group. We used an interaction term between RS testing and risk group to examine differences between subgroups, given prior findings in this population of a differential impact of RS testing on chemotherapy use as a function of risk.⁹ Significance tests and CIs for estimates from all models were 2-sided and used robust standard errors to account for the clustering of patients by registry. Because of the multiple comparisons, we report 99% CIs and used $\alpha = .01$ to establish statistical significance. Statistical analyses were performed using SAS 9.4 (SAS Institute, Inc.).

Sensitivity Analyses

No payments were present for roughly 15% of patients, which can occur for a number of reasons, such as rejection of a claim, credit from a prior overpayment, or beneficiary responsibility that covered the cost of the test (copay, deductible, coinsurance). Additionally, not all patients had a surgical procedure identifiable in the claims data. Therefore, we performed a sensitivity analysis limited to patients with nonzero surgery costs to capture a cohort of patients who received curative therapy and in which all treatment-associated costs were most likely to be captured. An analysis including all patients aged ≥ 66 years ($N=64,996$) was also performed to determine whether older age influenced associated costs.

Results

We identified 30,058 Medicare beneficiaries aged 66 to 75 years diagnosed with ER-positive, nonmetastatic, invasive breast cancer from 2005 through 2011. Among these patients, 17.5% received RS testing as part of their initial workup. Roughly half of the study population had intermediate-risk disease (48.4%), 26.7% had low-risk disease, and 24.9% had high-risk disease (Table 1). More patients who received RS testing were younger (mean age <70 years; 59.6% for ages 65–70 years vs 40.4% for 71–75 years), and those who received testing were more likely to have no comorbid conditions compared with those who did not (68.1% vs 63.4%). Patients who received RS testing were more likely to have intermediate-risk disease (69.5% vs 43.9%) than to have low-risk disease (17.2% vs 28.7%) or high-risk disease (13.3% vs 27.4%) compared with those who did not receive testing.

Patients who received chemotherapy tended to be younger and, compared with those who did not receive chemotherapy, were more likely to have high-risk disease (see supplemental eTable 1, available with this article at JNCCN.org). When patients were stratified by risk group, we observed that those with high-risk disease were more likely to be younger, have multiple comorbid conditions, reside in census tracts with lower socioeconomic status, and receive chemotherapy (supplemental eTable 2). RS testing was most common among patients with intermediate-risk disease (25.1%) compared with low-risk disease (11.3%) and high-risk disease (9.3%). We next stratified receipt of chemotherapy by risk group and RS testing (supplemental eTable 3). Among patients with low-risk or intermediate-risk disease, those who received RS testing were more likely to receive chemotherapy than those who did not receive RS testing. Patients with high-risk disease were less likely to receive chemotherapy if they received RS testing (24.8% vs 41.8%).

Mean costs in the year after diagnosis were \$35,940 overall, \$51,127 for high-risk disease, \$33,225 for

intermediate-risk disease, and \$26,695 for low-risk disease (Table 2). Chemotherapy costs followed a similar trend; in the year before diagnosis, costs were slightly lower by risk group (ie, costs were lower from each risk group, decreasing in order from high to low risk). Patients who received chemotherapy had more than double the costs of those who did not in the year after diagnosis (\$64,302 vs \$28,107), mostly attributable to noncancer costs.

Patients who received RS testing had slightly higher overall costs in the year after diagnosis (\$38,054 vs \$35,491 for no testing), including the costs of RS testing, which averaged \$3,217. Patients who received RS testing had lower chemotherapy costs (\$1,602 vs \$2,473), higher noncancer treatment costs (\$25,187 vs \$22,476), and comparable treatment-related costs (\$12,867 vs \$13,015).

In multivariable analyses, RS testing was associated with lower costs among patients with high-risk disease in terms of both relative costs (relative ratio, 0.88; 99% CI, 0.82–0.94) and absolute costs (\$6,606; 99% CI, \$3,922–\$9,290) (Table 3). Chemotherapy costs for these patients were lower (\$3,622; 99% CI, \$3,035–\$4,210), and noncancer costs were slightly lower (\$2,353; 99% CI, \$32–\$4,674). In contrast, absolute costs were higher among patients with intermediate-risk disease who received RS testing (\$5,568; 99% CI, \$4,271–\$6,864) and among patients with low-risk disease who received RS testing (\$9,462; 99% CI, \$7,076–\$11,848). These higher costs were due almost entirely to higher noncancer costs.

In sensitivity analyses that included all patients aged ≥ 66 years ($N=64,996$), associations between RS testing and costs were similar to those in the primary analysis, but less pronounced because of lower overall use of chemotherapy (Table 4). Chemotherapy costs remained lower among patients with high-risk disease who underwent RS testing (cost ratio, 0.47; 99% CI, 0.37–0.59) and higher among patients with intermediate-risk or low-risk disease (Table 5). In the sensitivity analysis limited to patients with nonzero surgery costs, both overall and chemotherapy costs 1 year after diagnosis followed trends similar to those in the main analysis (supplemental eTable 4); RS testing remained associated with significantly lower costs among high-risk patients (supplemental eTable 5).

Discussion

Results of this study showed that RS testing was associated with roughly \$6,600 lower costs among patients with high-risk disease, of which \$3,600 was attributable to lower direct chemotherapy costs and \$4,300 was attributable to lower noncancer costs. Although RS testing was associated with higher overall costs in intermediate-risk and low-risk disease, these costs were almost entirely attributable to higher noncancer costs, with no differences in mean chemotherapy costs. Our results support

Table 1. Baseline Patient Characteristics by Receipt of RS Testing

Characteristic	All Patients (N=30,058) n (%)	No RS Testing (N=24,798) n (%)	RS Testing (N=5,260) n (%)	P Value
Age group				<.001
65–70 y	15,646 (52.1)	12,512 (50.5)	3,134 (59.6)	
71–75 y	14,412 (47.9)	12,286 (49.5)	2,126 (40.4)	
Black race	2,082 (6.9)	1,773 (7.1)	309 (5.9)	<.001
Comorbid conditions				<.001
0	19,296 (64.2)	15,715 (63.4)	3,581 (68.1)	
1	6,954 (23.1)	5,802 (23.4)	1,152 (21.9)	
≥2	3,808 (12.7)	3,281 (13.2)	527 (10.0)	
Census tract characteristics (bottom quartile)				
Did not complete high school	7,072 (23.5)	5,963 (24.0)	1,109 (21.1)	<.001
Below poverty line	6,962 (23.2)	5,865 (23.7)	1,097 (20.9)	<.001
Percent black	6,859 (22.8)	5,660 (22.8)	1,199 (22.8)	.96
Married	16,361 (54.4)	13,213 (53.3)	3,148 (59.8)	<.001
Urban location	25,158 (83.7)	20,720 (83.6)	4,438 (84.4)	.14
US geographic region				<.001
Midwest	3,316 (11.0)	2,728 (11.0)	588 (11.2)	
Northeast	6,045 (20.1)	4,790 (19.3)	1,255 (23.9)	
South	7,660 (25.5)	6,241 (25.2)	1,419 (27.0)	
West	13,037 (43.4)	11,039 (44.5)	1,998 (38.0)	
Histology				<.001
Ductal	20,955 (69.7)	17,225 (69.5)	3,730 (70.9)	
Ductal and lobular	3,244 (10.8)	2,685 (10.8)	559 (10.6)	
Lobular	3,415 (11.4)	2,719 (11.0)	696 (13.2)	
Unknown	2,444 (8.1)	2,169 (8.7)	275 (5.2)	
Overall cancer stage				<.001
I	17,733 (59.0)	14,428 (58.2)	3,305 (62.8)	
II	8,766 (29.2)	6,936 (28.0)	1,830 (34.8)	
III	2,593 (8.6)	2,532 (10.2)	61 (1.2)	
Other	966 (3.2)	902 (3.6)	64 (1.2)	
Tumor stage				<.001
Tmicro	520 (1.7)	510 (2.1)	NR ^a	
T1a	2,379 (7.9)	2,226 (9.0)	153 (2.9)	
T1b	6,932 (23.1)	5,954 (24.0)	978 (18.6)	
T1c	11,195 (37.2)	8,598 (34.7)	2,597 (49.4)	
T2	6,715 (22.3)	5,351 (21.6)	1,364 (25.9)	
T3	985 (3.3)	899 (3.6)	86 (1.6)	
T4	621 (2.1)	607 (2.4)	NR ^a	
Other	711 (2.4)	653 (2.6)	58 (1.1)	
Node stage				<.001
N0	22,391 (74.5)	17,845 (72.0)	4,546 (86.4)	
N1	5,317 (17.7)	4,655 (18.8)	662 (12.6)	
N2	1,257 (4.2)	1,234 (5.0)	>20 (>0.2)	
N3	722 (2.4)	717 (2.9)	NR ^a	
Other	371 (1.2)	347 (1.4)	24 (0.5)	

(continued on next page)

Abbreviations: NR, not reported; PR, progesterone receptor; RS, recurrence score.

^aIn accordance with the privacy policy of the Centers for Medicare & Medicaid Services, data for cells containing ≤10 observations and data for cells that would allow calculation of cells containing ≤10 observations are not reported.

Table 1. Baseline Patient Characteristics by Receipt of RS Testing (cont.)

Characteristic	All Patients (N=30,058) n (%)	No RS Testing (N=24,798) n (%)	RS Testing (N=5,260) n (%)	P Value
Histologic grade				<.001
I	8,829 (29.4)	7,505 (30.3)	1,324 (25.2)	
II	14,118 (47.0)	11,325 (45.7)	2,793 (53.1)	
III	5,420 (18.0)	4,473 (18.0)	947 (18.0)	
IV	146 (0.5)	137 (0.6)	NR ^a	
Other	1,545 (5.1)	1,358 (5.5)	>180 (>3.0)	
Tumor size, cm				<.001
≤0.5	2,386 (7.9)	2,232 (9.0)	154 (2.9)	
0.5 to <1	6,955 (23.1)	5,977 (24.1)	978 (18.6)	
1 to <2	11,329 (37.7)	8,711 (35.1)	2,618 (49.8)	
≥2	8,164 (27.2)	6,705 (27.0)	1,459 (27.7)	
Other	1,224 (4.1)	1,173 (4.7)	51 (1.0)	
PR status				.07
Positive	25,347 (84.3)	20,874 (84.2)	4,473 (85.0)	
Negative	4,486 (14.9)	3,727 (15.0)	759 (14.4)	
Other	225 (0.7)	197 (0.8)	28 (0.5)	
Unfavorable histology	6,518 (21.7)	5,464 (22.0)	1,054 (20.0)	.001
Year of diagnosis				<.001
2005	4,149 (13.8)	4,024 (16.2)	125 (2.4)	
2006	4,058 (13.5)	3,771 (15.2)	287 (5.5)	
2007	4,221 (14.0)	3,704 (14.9)	517 (9.8)	
2008	4,275 (14.2)	3,477 (14.0)	798 (15.2)	
2009	4,296 (14.3)	3,318 (13.4)	978 (18.6)	
2010	4,468 (14.9)	3,266 (13.2)	1,202 (22.9)	
2011	4,591 (15.3)	3,238 (13.1)	1,353 (25.7)	
Clinical risk group				<.001
High	7,484 (24.9)	6,785 (27.4)	699 (13.3)	
Intermediate	14,553 (48.4)	10,896 (43.9)	3,657 (69.5)	
Low	8,021 (26.7)	7,117 (28.7)	904 (17.2)	
Received chemotherapy	6,505 (21.6)	5,618 (22.7)	887 (16.9)	<.001

Abbreviations: NR, not reported; PR, progesterone receptor; RS, recurrence score.

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the ability of RS testing to reduce chemotherapy costs in patients who would otherwise have received chemotherapy, with a nonsubstantial effect on absolute chemotherapy costs in patients with otherwise low-risk or intermediate-risk disease. However, testing in these lower-risk patients was associated with higher non-cancer costs, indicating that underlying rates of medical resource use are greater among these patients, and suggesting that caution is warranted in interpreting retrospective analyses of total costs associated with receipt of RS testing. Perhaps most important, our study population was limited to Medicare beneficiaries aged >65 years with cancer, supporting the potential value of genomic testing in older populations.

Most studies have found a 10% to 20% reduction in chemotherapy use associated with RS testing.^{19–21} However, not all studies reported declines, and recent critical review of these analyses showed potential biases that may substantially influence study findings.¹³ Previous work found a differential impact of RS testing on chemotherapy use, with significant reductions only among Medicare beneficiaries with high-risk disease.¹⁵ For this reason, we hypothesized that the greatest cost reduction with RS testing would occur among younger, healthier patients with high-risk disease. These results support the notion that RS testing provides the greatest reduction in costs among patients with the highest pretest likelihood of receiving

Table 2. Medicare Payments by Risk Group, Receipt of RS Testing, and Receipt of Chemotherapy in Patients Aged 66–75 Years (N=30,058)

Cost	Clinical Risk Group, Mean (SD)			P Value
	High	Intermediate	Low	
In year before diagnosis	\$10,270 (\$16,847)	\$9,545 (\$14,854)	\$8,546 (\$11,573)	<.001
Overall ^a	\$51,127 (\$33,386)	\$33,225 (\$27,711)	\$26,695 (\$19,532)	<.001
Chemotherapy ^a	\$6,043 (\$9,049)	\$1,526 (\$5,108)	\$290 (\$2,180)	<.001
Surgery ^a	\$3,947 (\$4,735)	\$2,645 (\$3,533)	\$2,304 (\$3,224)	<.001
Radiation ^a	\$4,910 (\$4,864)	\$4,676 (\$5,117)	\$5,573 (\$5,418)	<.001
Imaging	\$3,545 (\$3,189)	\$2,583 (\$2,799)	\$2,562 (\$2,503)	<.001
RS testing ^a	\$312 (\$1,063)	\$848 (\$1,623)	\$388 (\$1,177)	<.001
Nonsurgical inpatient	\$6,382 (\$17,134)	\$3,979 (\$14,439)	\$2,555 (\$10,276)	<.001
Cancer-related	\$18,444 (\$13,480)	\$11,430 (\$9,339)	\$10,729 (\$7,557)	<.001
Noncancer	\$32,683 (\$28,645)	\$21,795 (\$24,052)	\$15,966 (\$17,038)	<.001

Cost	RS Testing, Mean (SD)		P Value
	No	Yes	
In year before diagnosis	\$9,618 (\$15,292)	\$8,708 (\$10,842)	<.001
Overall ^a	\$35,491 (\$30,115)	\$38,054 (\$22,133)	<.001
Chemotherapy ^a	\$2,473 (\$6,516)	\$1,602 (\$4,784)	<.001
Surgery ^a	\$2,829 (\$3,894)	\$3,109 (\$3,607)	<.001
Radiation ^a	\$4,880 (\$5,149)	\$5,411 (\$5,141)	<.001
Imaging	\$2,832 (\$2,904)	\$2,745 (\$2,634)	.04
RS testing ^a	\$35 (\$411)	\$3,217 (\$1,487)	<.001
Nonsurgical inpatient	\$4,548 (\$15,077)	\$2,543 (\$9,570)	<.001
Cancer-related	\$13,015 (\$10,980)	\$12,867 (\$8,682)	.36
Noncancer	\$22,476 (\$25,471)	\$25,187 (\$18,940)	<.001

Cost	Chemotherapy, Mean (SD)		P Value
	No	Yes	
In year before diagnosis	\$9,551 (\$15,198)	\$9,124 (\$12,271)	.04
Overall ^a	\$28,107 (\$22,138)	\$64,302 (\$32,508)	<.001
Chemotherapy ^a	\$642 (\$3,713)	\$8,401 (\$9,154)	<.001
Surgery ^a	\$2,652 (\$3,641)	\$3,697 (\$4,420)	<.001
Radiation ^a	\$4,920 (\$5,186)	\$5,164 (\$5,021)	<.001
Imaging ^a	\$2,491 (\$2,643)	\$3,996 (\$3,271)	<.001
RS testing ^a	\$634 (\$1,451)	\$439 (\$1,240)	<.001
Nonsurgical inpatient	\$3,775 (\$14,043)	\$5,726 (\$15,042)	<.001
Cancer-related	\$10,706 (\$8,448)	\$21,258 (\$13,224)	<.001
Noncancer	\$17,401 (\$19,387)	\$43,044 (\$29,867)	<.001

Abbreviation: RS, recurrence score.

^aOne year after diagnosis.

chemotherapy. However, the potential for RS testing to provide overall reductions in chemotherapy costs or total costs for the health system depends on the extent to which RS testing is performed in patients with high-risk versus intermediate-risk and low-risk disease. Our analysis was necessarily limited to the Medicare

population and raises the question of the impact of RS testing in other settings. Given the lower probability of older patients to both tolerate and benefit from chemotherapy, our findings likely underestimate the potential benefit and cost savings of testing in younger patient populations. We limited our focus to RS

Table 3. Adjusted Associations Between Receipt of RS Testing and Costs by Clinical Risk Group (N=30,058)

Outcome at 1 Year After Diagnosis	Relative Ratio (99% CI)	P Value	Effect, USD (99% CI)	P Value
Overall costs				
Testing vs no testing; high risk	0.88 (0.82–0.94)	<.001	–6,606 (–9,290 to –3,922)	<.001
Testing vs no testing; intermediate risk	1.18 (1.14–1.22)	<.001	5,568 (4,271–6,864)	<.001
Testing vs no testing; low risk	1.37 (1.28–1.46)	<.001	9,462 (7,076–11,848)	<.001
Chemotherapy costs				
Testing vs no testing; high risk	0.43 (0.33–0.55)	<.001	–3,622 (–4,210 to –3,035)	<.001
Testing vs no testing; intermediate risk	1.07 (0.93–1.24)	.22	11 (–273 to 295)	.92
Testing vs no testing; low risk	2.56 (1.63–4.02)	<.001	196 (–326 to 718)	.33
Cancer-related costs				
Testing vs no testing; high risk	0.78 (0.72–0.83)	<.001	–4,250 (–5,264 to –3,236)	<.001
Testing vs no testing; intermediate risk	1.12 (1.08–1.16)	<.001	1,249 (759–1,739)	<.001
Testing vs no testing; low risk	1.15 (1.08–1.24)	<.001	1,595 (693–2,497)	<.001
Non-cancer-related costs				
Testing vs no testing; high risk	0.94 (0.86–1.02)	.05	–2,353 (–4,674 to –32)	.01
Testing vs no testing; intermediate risk	1.21 (1.15–1.26)	<.001	4,322 (3,201–5,444)	<.001
Testing vs no testing; low risk	1.51 (1.38–1.65)	<.001	7,872 (5,808–9,935)	<.001

Models include age, race, marital status, local census tract characteristics, tumor grade and size, dollar amount of prediagnosis costs/1,000, RS testing, clinical risk group, and interaction of testing and risk group. All interactions between testing and risk group were significant. Abbreviation: RS, recurrence score.

testing, given its market dominance in US clinical practice, and did not include other currently available genomic assays.

Our study is the first to examine associations between RS testing and costs in a nationally representative sample of the US population of patients aged >65 years with cancer. Similar work was conducted using the Pennsylvania Cancer Registry for patients with surgically resected breast cancer from 2007 through 2011, which found that RS testing was associated with a 19% decrease in chemotherapy use and \$15,000 in costs among women aged <55 years, and with an increase of 6% and \$3,500 among women aged 75 to 84 years.⁵ These findings are consistent with our observation that women with higher pre-RS probabilities of undergoing chemotherapy were most likely to have a reduction in RS testing and associated costs (eg, younger patients, no comorbid conditions).

Several empirical studies conducted outside the United States, including Ireland,⁶ Germany,⁷ France,⁸ and the United Kingdom,¹⁰ have examined the impact of RS testing in real-world practice. Key cost drivers in these analyses were patients with high clinical risk but low genomic risk, and vice versa. This finding is consistent with our results, in which the most striking differences in costs were driven by patients with high-risk disease. The other studies found that the direct cost of chemotherapy was roughly one-fourth of the overall societal cost, which we did not consider in our study. We did find that

noncancer costs play an important role in total costs for these patients. A study from the United Kingdom found that RS testing was also cost-saving, with a roughly 70% cost reduction among patients with node-positive disease.¹⁰ This finding is similar to our observation of an approximately 60% reduction in chemotherapy costs among patients with node-positive disease. Experience with RS testing in France is similar.⁸

In most published clinical series in which RS testing was available, roughly half of patients had a low-risk score, and the median or mean age was in the mid-50s. It is unknown how distributions of scores from previous clinical series compare with the RS distribution in our study population, in which patients were, on average, at least a decade older. Rates of chemotherapy overall and among patients who received RS testing in our study were significantly lower than previously reported rates of chemotherapy of approximately 40% among patients with ER-positive, node-negative disease who received RS testing. Therefore, we would expect the impact of RS testing on costs to be more favorable in younger, higher-risk patient populations with higher baseline rates of chemotherapy use. Future economic analyses focused on specific patient groups would be well-informed by first determining pretest rates of chemotherapy use.

Our study has limitations. Only RS tests paid for by Medicare could be detected in the data. Our claims-based

Table 4. Medicare Payments Among Patients Aged 66–75 Years (N=64,996)

Cost	Clinical Risk Group, Mean (SD)			P Value
	High	Intermediate	Low	
In year before diagnosis	\$11,354 (\$17,657)	\$10,961 (\$16,968)	\$9,474 (\$13,020)	<.001
Overall ^a	\$45,006 (\$34,504)	\$30,207 (\$27,945)	\$25,881 (\$20,502)	<.001
Chemotherapy ^a	\$4,322 (\$8,203)	\$1,035 (\$4,441)	\$230 (\$2,017)	<.001
Surgery ^a	\$3,874 (\$4,895)	\$2,547 (\$3,640)	\$2,240 (\$3,963)	<.001
Radiation ^a	\$4,212 (\$4,775)	\$3,760 (\$4,936)	\$4,748 (\$5,321)	<.001
Imaging ^a	\$3,051 (\$3,001)	\$2,284 (\$2,586)	\$2,456 (\$2,492)	<.001
RS testing ^a	\$212 (\$880)	\$524 (\$1,336)	\$272 (\$997)	<.001
Nonsurgical inpatient	\$7,498 (\$19,177)	\$5,505 (\$17,197)	\$3,603 (\$12,274)	<.001
Cancer-related	\$15,459 (\$12,950)	\$9,626 (\$8,921)	\$9,674 (\$7,821)	<.001
Noncancer	\$29,547 (\$29,354)	\$20,581 (\$24,674)	\$16,208 (\$18,002)	<.001

Cost	RS Testing, Mean (SD)		P Value
	No	Yes	
In year before diagnosis	\$10,886 (\$16,790)	\$9,213 (\$11,618)	<.001
Overall ^a	\$32,102 (\$29,679)	\$38,317 (\$23,247)	<.001
Chemotherapy ^a	\$1,660 (\$5,562)	\$1,575 (\$4,844)	.21
Surgery ^a	\$2,752 (\$4,157)	\$3,178 (\$3,689)	<.001
Radiation ^a	\$3,968 (\$4,978)	\$5,232 (\$5,123)	<.001
Imaging ^a	\$2,484 (\$2,694)	\$2,760 (\$2,661)	<.001
RS testing ^a	\$24 (\$326)	\$3,220 (\$1,465)	<.001
Nonsurgical inpatient	\$5,860 (\$17,298)	\$2,983 (\$11,093)	<.001
Cancer-related	\$10,863 (\$10,301)	\$12,745 (\$8,762)	<.001
Noncancer	\$21,239 (\$25,534)	\$25,572 (\$19,951)	<.001

Cost	Chemotherapy, Mean (SD)		P Value
	No	Yes	
In year before diagnosis	\$10,877 (\$16,814)	\$9,707 (\$13,064)	<.001
Overall ^a	\$27,077 (\$24,114)	\$64,079 (\$33,673)	<.001
Chemotherapy ^a	\$461 (\$3,253)	\$8,144 (\$9,312)	<.001
Surgery ^a	\$2,620 (\$3,992)	\$3,783 (\$4,572)	<.001
Radiation ^a	\$3,968 (\$4,996)	\$4,892 (\$5,015)	<.001
Imaging ^a	\$2,248 (\$2,487)	\$3,973 (\$3,240)	<.001
RS testing ^a	\$384 (\$1,166)	\$393 (\$1,176)	.50
Nonsurgical inpatient	\$5,342 (\$16,759)	\$6,586 (\$16,574)	<.001
Cancer-related	\$9,297 (\$8,284)	\$20,792 (\$13,412)	<.001
Noncancer	\$17,781 (\$21,572)	\$43,286 (\$30,782)	<.001

Abbreviation: RS, recurrence score.

^aOne year after diagnosis.

approach has been described in detail by our group and others, supporting the validity of using administrative claims data to detect use of the assay.^{14,15} We did not know the results of the assay, only that patients received the test. Efforts are ongoing to link RS assay results to patient data in the SEER-Medicare and other databases. However, from

the payer perspective, it should be noted that decisions to cover a test for a patient population must be made at the population level without knowledge of individual test results. Nonetheless, the extent to which RS testing influences costs for individual patients in the general population remains an important area of ongoing

Table 5. Adjusted Associations Between Receipt of RS Testing and Costs Among Patients Aged ≥66 Years (N=64,996)

Outcome at 1 Year After Diagnosis	Relative Ratio (99% CI)	P Value	Effect, USD (99% CI)	P Value
Overall costs				
Testing vs no testing; high risk	0.94 (0.89–1.00)	.01	–2,578 (–4,813 to –343)	.003
Testing vs no testing; intermediate risk	1.26 (1.22–1.30)	<.001	7,590 (6,510–8,670)	<.001
Testing vs no testing; low risk	1.35 (1.28–1.44)	<.001	8,867 (6,793–10,941)	<.001
Chemotherapy costs				
Testing vs no testing; high risk	0.47 (0.37–0.59)	<.001	–2,365 (–2,791 to –1,938)	<.001
Testing vs no testing; intermediate risk	1.35 (1.18–1.54)	<.001	185 (–21 to 391)	.02
Testing vs no testing; low risk	2.93 (1.96–4.38)	<.001	24 (–372 to 420)	.87
Cancer-related costs				
Testing vs no testing; high risk	0.85 (0.79–0.90)	<.001	–2,287 (–3,073 to –1,501)	<.001
Testing vs no testing; intermediate risk	1.22 (1.18–1.26)	<.001	2,026 (1,646–2,406)	<.001
Testing vs no testing; low risk	1.18 (1.11–1.26)	<.001	1,757 (1,028–2,486)	<.001
Non-cancer-related costs				
Testing vs no testing; high risk	1.00 (0.92–1.07)	.87	–288 (–2,237 to 1,661)	.70
Testing vs no testing; intermediate risk	1.28 (1.23–1.33)	<.001	5,566 (4,625–6,508)	<.001
Testing vs no testing; low risk	1.44 (1.34–1.56)	<.001	7,112 (5,304–8,921)	<.001

Models include age, race, marital status, local census tract characteristics, tumor grade and size, dollar amount of prediagnosis costs/1,000, recurrence score testing, clinical risk group, and interaction of testing and risk group. All interactions between testing and risk group were significant. Abbreviation: RS, recurrence score.

research. Patients in the SEER registry are enriched for nonwhite, low-poverty, and urban areas, which may affect the generalizability of our findings. The study population was limited to patients aged ≥65 years and therefore includes just less than half of all newly diagnosed cases of breast cancer. Younger patients are more likely to undergo chemotherapy, and therefore the impact of RS testing in younger patients was unaddressed by this study. HER2 status was unavailable in the data. Finally, emerging strategies to guide chemotherapy use have been discussed in recent years, including use of surrogate immunohistochemical metrics of risks^{22,23} and even radiomics-based analyses of breast MRI. However, these remain in the realm of research and are not routinely used to supplant RS testing to guide management decisions.

Conclusions

In general clinical practice among patients with newly diagnosed, ER-positive, localized invasive cancer, receipt of RS testing was associated with lower overall and chemotherapy-related costs in patients with high-risk disease consistent with a reduction in chemotherapy use in these patients. No difference in chemotherapy costs was associated with receipt of RS testing in patients with low-risk or intermediate-risk disease, with slightly higher overall and non-chemotherapy-related costs.

Taken together, our results support the ability of RS testing to reduce chemotherapy costs in real-world practice among patients for whom receipt of chemotherapy is the default treatment paradigm.

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