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The influence of 21-gene recurrence score assay on chemotherapy use in a population-based sample of breast cancer patients

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Abstract

Purpose—To quantify the influence of RS assay on changing chemotherapy plans in a general practice setting use using causal inference methods.

Methods—We surveyed 3,880 newly-diagnosed breast cancer patients in Los Angeles and Georgia in 2013-14. We used inverse propensity weighting and multiple imputations to derive complete information for each patient about treatment status with and without testing.

Results—Half of the 1,545 women eligible for testing (ER+ or PR+, HER2−, and stage I-II) received RS. We estimate that 30% (95% confidence interval (CI): 10% - 49%) of patients would have changed their treatment selections after RS assay, with 10% (CI: 0%-20%) being encouraged to undergo chemotherapy and 20% (CI: 10% -30%) being discouraged from chemotherapy. The subgroups whose treatment selections would be changed the most by RS were patients with

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Ethical Standards: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study. Consent was assumed when a completed survey was returned.

positive nodes (44%; CI: 24% - 64%), larger tumor (43% for tumor size >2 cm; CI: 23% - 62%) or younger age (41% for <50 years, CI: 23% - 58%). The assay was associated with a net reduction in chemotherapy use by 10% (CI: 4% - 16%). The reduction was much greater for women with positive nodes (31%; CI: 21% - 41%), larger tumor (30% for tumor size >2 cm; CI: 22% - 38%) or younger age (22% for <50 years; CI: 9% - 35%).

Conclusion—RS substantially changed chemotherapy treatment selections with the largest influence among patients with less favorable pre-test prognosis. Whether this is optimal awaits the results of clinical trials addressing the utility of RS testing in selected subgroups.

Keywords

breast cancer; 21-gene recurrence score assay; chemotherapy; population studies

Introduction

Breast cancer is an important paradigm for how advances in precision medicine may reduce overtreatment.[1,2] Results from 4 genomic tests (ER/PR, HER2, 21-gene assay) and pathology largely determine clinician recommendations regarding adjuvant chemotherapy for most patients newly diagnosed with curable invasive breast cancer. The 21-gene recurrence score (RS) assay has rapidly diffused into clinical practice and is markedly influencing treatment decisions. Studies have reported correlates of the use of the RS assay, as well as the association of testing and test results with the use of chemotherapy.[3-8] Although the test results clearly influence clinician recommendations, how testing itself influences the receipt of chemotherapy in different clinical subgroups in a community population has not been quantified. This question is particularly important as gene expression testing diffuses more broadly into the population.[9,10]

Selection effects confound the estimates of how testing influences receipt of chemotherapy because testing is not offered randomly. Patients are largely selected for testing by their physicians based on the pre-test likelihood of getting chemotherapy, which is influenced by clinical factors and patient preferences. Causal inference methods such as inverse propensity weighting can estimate the average causal effect of testing on chemotherapy use by attempting to create comparable groups of tested and un-tested people as in a randomized trial. However, these methods only estimate the net effect of testing on chemotherapy use, which can obscure the degree to which treatment plans are changed if, for a given population, there are changes in both directions in response to testing. It is also not possible to observe every patient's treatment plan both with and without testing in a general practice setting in order to directly estimate the influence of testing.

We developed a method that enables more granular estimates of how the treatment plan would differ depending on whether a patient is tested or not, and for which patient sub-groups RS testing most strongly influences the receipt of chemotherapy. We conducted our analysis using a large, diverse, contemporary population-based sample of patients newly diagnosed with early-stage breast cancer in 2013-14. We quantified 1) the overall change in chemotherapy use if the entire sample were tested with the RS assay and 2) the proportion of

patients whose treatment plan would be changed in each direction by RS testing, both overall and in subgroups of interest.

Methods

Data source

The iCanCare study identified women with early breast cancer who were aged 20 to 79 years, diagnosed with ductal carcinoma in situ or invasive breast cancer, and reported to the Georgia or Los Angeles County Surveillance, Epidemiology, and End Results (SEER) registry. Patients were sent surveys approximately 2 months after surgical treatment between July 2013 and September 2014. Patients were excluded if they had prior cancer, stage III or IV cancer, tumors > 5 cm, or more than 3 positive lymph nodes. In Los Angeles County (only), Non-Hispanic Whites and African Americans under 50 were also excluded because of enrollment in other studies. African Americans and Latinas were oversampled in Los Angeles to ensure sufficient representation of minorities.

The registries identified eligible patients and administered the survey. Patients were sent a packet with a letter, survey materials, postage paid return envelope, and a $20 cash gift. A modified Dillman survey method was used to encourage response and telephone interviews were used when requested (median time from diagnosis to survey completion was 6 months, sd 2.8 months).[11]

A total of 3,880 patients were identified and sent a survey: 249 women were ineligible because they had exclusions noted above or were deceased, too ill to complete, or unable to complete a survey in Spanish or English); 2,587 of eligible patients (71%) completed the survey. Genomic Health, Inc. provided a database with the RS assay results, which was linked with patients in the iCanCare study and SEER data. The analytical sample was limited to 1,545 patients whose breast cancer was ER+ or PR+, HER2−, and stage I or II. The study protocol was approved by the University of Michigan, the University of Southern California, and Emory University.

Measures

The dependent variable was a binary variable that indicated the receipt of adjuvant chemotherapy via patient report. The primary independent variable was a binary variable indicating whether or not a patient received the RS assay. Covariates included patient demographics, clinical factors, and SEER site. Age at diagnosis, education, race/ethnicity, comorbidities, family income, insurance status, partner status, and employment status at diagnosis were obtained from surveys. Additionally, we asked patients how important it was for them to have as extensive treatment as possible and how important it was to have the newest and most advanced treatments. (5-point-response categories from “not at all important” to “very important”). The variables were dichotomized to be 1 if patients rated “quite important” or “very important” and 0 otherwise. Cancer stage, tumor grade, tumor size, lymph node status and progesterone receptor status were obtained from SEER clinical data.

Statistical Analysis

We first used inverse propensity weighting (IPW) to estimate the overall causal effect of the RS assay on the use of chemotherapy in the sample population.[12] The RS assay recipients were weighted by the inverse of the propensity score and the non-recipients were weighted by the inverse of one minus the propensity score. The propensity score was the probability of receiving the RS assay and calculated based on a logistic regression model. We included in the model the missing data patterns in addition to the covariates that affected either the RS assay or chemotherapy usage.[13] The distributions of covariates between the RS assay recipients and non-recipients before and after IPW were compared using the Mantel-Haenszel test.

We then used a potential outcome multiple imputation approach (POMI) developed by us to estimate the causal effect (See Appendix), now including details about whether or not testing would change treatment plans at an individual level and in key clinical sub-groups. For this, we need to know the chemotherapy treatment status for each patient if tested with the RS assay, and if not tested. However, in a general practice setting, for each patient, the treatment status in only one of these two scenarios is available because she may not get tested; even if tested, her pre-test chemotherapy treatment plan is not usually available. Our approach uses sequential regression multiple imputation[14] to impute the unobserved (counterfactual) treatment status for each patient. Thus for patients who received the RS assay, we imputed their chemotherapy treatment status without the assay, and we did the reverse for those who were not tested. The multiple imputation method accounts for uncertainty associated with the prediction. Additionally, the method simultaneously handles missing data that occur in other measures. The imputation models included the same comprehensive set of variables used in the IPW method.

We classified patients into four groups according to how the assay would have influenced their chemotherapy plan: 1) those who would never receive chemotherapy whether tested or not (never-chemotherapy); 2) those who would have been treated without the test but would not if tested (chemotherapy-discouraged); 3) those who would not have chemotherapy without the test but who would if tested (chemotherapy-encouraged); 4) those who would receive chemotherapy with or without the test (always-chemotherapy).

POMI estimates the average causal effect of testing on chemotherapy use and the influence of testing by the direction and by the presence (vs. absence) of the causal effect of testing on treatment decisions. Both IPW and POMI methods minimize selection bias and control for observed confounders.

Results

The sample consists of 1,545 women who met selection criteria and were eligible to receive RS according to practice guidelines.[15] Of these patients, 764 (49.5%) received the RS assay. Table 1 shows that, after IPW, the distribution of patient characteristics appeared to be balanced between those tested and not tested. There was substantial overlap of the propensity scores between tested and non-tested populations. About one quarter (27%) of the sample were predicted to receive chemotherapy if everyone was tested and 37% to

receive chemotherapy if no one was tested. This corresponds to an overall net reduction of 10% (95% CI: 4% - 16%) in chemotherapy use.

Using the POMI method, we show that about 20% (95% CI: 10% -30%) of patients would have been discouraged to receive chemotherapy (chemotherapy-discouraged) and 10% (95% CI: 0%-20%) encouraged to receive it (chemotherapy-encouraged) because of the influence of the RS assay (Figure 1). Thus, RS assay would have changed chemotherapy plan of 30% of patients (95% CI: 10% - 49%) and resulted in a 10% (95% CI: 4% - 16%) net reduction. The subgroups whose treatment plans would be changed the most by RS assay were patients with positive nodes (44%; 95% CI: 24% - 64%), larger tumor (43% for tumor size > 2 cm; 95% CI: 23% - 62%) or younger age (41% for < 50 years, 95% CI: 23% - 58%). They were more likely to be “chemotherapy discouraged” and less likely to be “chemotherapy encouraged” than their counterparts. Across almost all subgroups except for tumor size <1 cm, patients were more likely to be chemotherapy-discouraged than chemotherapy-encouraged by RS assay.

Table 2 shows that 54% (95% CI: 44% - 64%) of patients were classified to be in the “never chemotherapy” category and 16% (95% CI: 6% - 27%) in the “always chemotherapy” category, regardless of RS use. Women with older age, smaller tumors, or negative lymph nodes were more likely to be in the “never chemotherapy” group and their counterparts were more likely to be in the “always chemotherapy” group. However, for the remaining substantial 30% of the population, testing appears to have influenced decisions.

Figure 2 displays the causal effect, calculated as the net difference between the proportion of patients who would have been “chemotherapy encouraged” and those who would have been “chemotherapy discouraged”. Testing would reduce chemotherapy use by 22% (95% CI: 9% - 35%) for patients < 50 years old, 19% (95% CI: 10% - 27%) for patients aged 50-59, and 7% (95% CI: 1% - 12%) for patients aged 60-69, but the effect of the RS assay was negligible among patients aged >70 with a reduction of 4% (95% CI: 0% - 9%). Testing led to much lower chemotherapy use among patients with positive lymph nodes (31% less, 95% CI: 21% - 41%), compared with a much smaller effect among patients with negative lymph nodes (5% lower, 95% CI: 2% - 9%). The RS assay effect also varied by tumor size: the largest reduction in chemotherapy use was among patients with a tumor >2 cm (30% lower, 95% CI: 22% - 38%), as compared to 8% (95% CI: 0% - 14%) among those with a tumor of 1-2 cm and no reduction with a tumor <1 cm.

Discussion

The rapid adoption of RS testing into clinical practice underscores the commitment of medical oncologists to adopt the most precise evaluative testing algorithms to direct treatment decisions for patients with breast cancer. However, no study has quantified the causal effect of the dissemination of RS testing on altering chemotherapy plans and usage both in a community population as a whole and in key clinical subgroups.

We show that if the entire population represented by our diverse, contemporary sample of breast cancer patients with favorable prognosis (ER+ or PR+, HER2−, and stage I or II)

were tested, RS testing would change treatment decisions in almost a third of patients. The change comprises 20% who were “chemotherapy-discouraged” by RS (a change in decision against chemotherapy) and 10% “chemotherapy-encouraged” (a change towards chemotherapy). Importantly, the subgroup whose decisions would be most likely to be changed by testing was patients with less favorable prognosis (Figure 2). For example, for node-positive women, testing would change chemotherapy treatment plans of 44%, with a net reduction of 31%. For patients aged < 50 years, the test changed treatment plans in 41%, with a net reduction of 22%; and these numbers were 43% and 30% in patients with tumor size > 2 cm.

This finding is consistent with the observational evidence that the majority of patients tested receive low recurrence scores, even among those with less favorable pre-test prognosis.[16] However, it provides a much better estimate less contaminated by selection effects related to who gets tested. Thus we see patients with less favorable prognostic factors due to demography (e.g., young age) or clinical factors (e.g., larger tumor size or positive lymph nodes) are more likely to receive chemotherapy in the absence of RS, and thus are more likely to be “chemotherapy discouraged” by favorable RS results.

A number of prior studies have looked at the observed relationship of RS test results to chemotherapy use, but have reported only on the observable, RS-tested population. Since RS test is not offered randomly, such estimates are subject to selection bias and cannot be used to measure the population-wide effect of rapidly disseminating RS use both within and outside groups recommended for testing. It is also not feasible to obtain patients’ treatment plans before and after testing in a general practice setting. The two largest observational studies sampled populations from SEER-Medicare (N=44,000) or selected cancer centers (N=7400). Dinan et al. found no effect of testing on chemotherapy in women over 65,[5] and Hassett et al. found an odds ratio of .7 for the association of testing with chemotherapy.[6] These large prior studies, however, are not population based, restricted by age, location or both, and other than the SEER-Medicare study, excluded node-positive women for whom an increasing amount of testing and RS-assay-based decision making is being done.

A number of studies have assessed the effect of RS testing on physician recommendations. Estimates for the proportion of cases in which testing would change the physician recommendation ranged from 33% to 43% of cases.[17,18] These studies help clarify pieces of the decision-making process but cannot estimate the overall effect of testing on chemotherapy use across entire eligible population. Prior results are somewhat higher than the estimates we found for overall rates of change in chemotherapy decisions (30%). These prior studies provide evidence only about the stated preferences of the oncologists rather than the revealed choices, which are imperfectly represented by the chemotherapy received as the end result of the entire decision-making process in all its complexity.

Our study has several advantages: it is large, based on sampling from population-based SEER registry data across all ages, 20-79, and supplemented by comprehensive survey information about the subjects. Our analysis used causal methods to optimally balance our rich set of covariates for comparisons between tested and un-tested subjects. This is done in an effort to create estimates as close as possible to those that would be obtained from a

randomized clinical trial, with virtually no selection bias affecting RS use. Our analyses also obtained more granular information about the direction and presence of the influence of testing on chemotherapy decisions. However, there are some limitations to our study. The results of our study are limited to two large geographic area of the United States. Furthermore, some patient groups were not available for our sample frame because of commitments to other studies (Non-Hispanic Whites and African Americans under age 50 in Los Angeles County). Our study is observational and does not account for unmeasured factors. However, a particular strength of our analysis is the adjustment for a rich set of observed covariates including detailed information about socioeconomic status, patient attitudes, preferences and disease status collected through patient surveys.

Implications for clinical practice

Our findings reinforce that major advances in precision evaluate testing in curable breast cancer have markedly improved targeting of treatment to need. In our study, RS testing influenced the targeting of treatment to need in nearly one third of patients. There is growing recognition of the need to address overtreatment in patients with favorable disease. A vital solution to this problem is to improve evaluative test algorithms in order to more accurately identify patients for whom treatment would have no benefit. Our results suggest that potential overtreatment in patients with the most favorable disease is already low and that the addition of RS testing in this clinical subgroup would yield a very small additional reduction in chemotherapy use. For example, the net effect of testing is about nil for patients over 65 with tumor size <1 cm and negative nodes. That this effect is not bigger, in part reflects the good news that relatively few of these patients would get chemotherapy, given current practice patterns, even in the absence of the more precise targeting that RS testing offers. However, clinicians may favor testing in these patients to identify the very few patients with high RS scores who would benefit by treatment or to assure patients who might be inclined towards chemotherapy that benefit would not outweigh risks.

Our results suggest that the biggest decrease in chemotherapy use as a result of RS testing would occur in patients with less favorable prognosis (e.g., those with demographic or anatomic factors suggesting worse outcome, such as young age or positive lymph nodes). There is mounting evidence that this may represent appropriate re-classification from higher to very low marginal benefit of adjuvant chemotherapy, as clinical trial-based evidence grows of the utility of genomic expression testing in clinical subgroups with less favorable pre-test prognosis.[9,10] However further refinement of the clinical utility of RS in these subgroups awaits the results of the RxPONDER trial,[19] and it is even possible that some patients with node-positive disease who currently undergo testing may be ultimately undertreated as a result of testing. The advantage of the methods used in this paper is that we can start to anticipate how the spread of testing may change treatment patterns across the population, and thus can consider the appropriateness of those changes earlier in the course of dissemination of the test.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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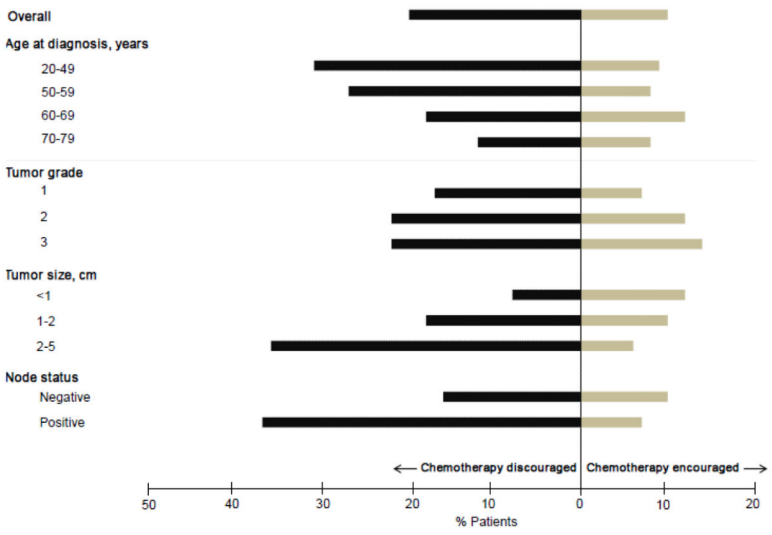

Figure 1. The proportion of patients who would have been either "chemotherapy encouraged" or "chemotherapy discouraged": overall and by clinical subgroups

The "chemotherapy encouraged" refers to patients who would not have received chemotherapy without the RS test but would with the test; the "chemotherapy discouraged" includes patients who would have been treated with chemotherapy without the RS test but would not with the test.

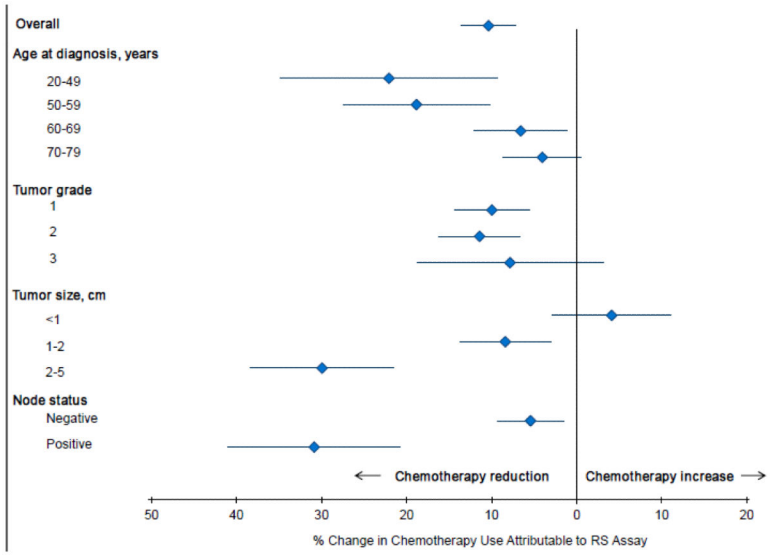

Figure 2. Causal effect, with 95% confidence intervals, of the RS assay on chemotherapy use: overall and by clinical subgroups

The causal effect measures the effect of the RS assay testing on chemotherapy use if the entire sample (or clinical subgroups) was tested compared to the situation when no one in the sample (or clinical subgroups) were tested. It is obtained using the POMI method detailed in the methods section.

Table 1

Patient Characteristics: Overall, Before and After Inverse Propensity Weighting (IPW).

Patient Characteristics	Overall (N=1,545)	Pre-IPW RS Assay§ No (N=781)	Pre-IPW RS Assay§ Yes (N=764)	*P*	Post-IPW RS Assay§ No (N=781)	Post-IPW RS Assay§ Yes (N=764)	*P*
Age at diagnosis, years	%	%	%	<.0001	%	%	0.59
20-49	13.6	11.9	15.3		13.9	13.4	
50-59	27.6	23.6	31.7		26.8	26.6	
60-69	32.3	30.4	34.3		32.7	31.3	
70-79	26.5	34.2	18.7		26.6	28.7	
Node Status				<.0001			0.19
Negative	75.2	66.8	83.8		74.7	71.9	
Positive	17.7	23.9	11.3		18.0	20.5	
Missing	7.1	9.2	5.0		7.3	7.6	
Tumor Grade				<.0001			0.40
1	35.2	37.8	32.6		35.3	34.2	
2	48.7	44.2	53.3		48.0	47.7	
3	15.1	16.1	14.0		15.7	17.4	
Missing	1.0	1.9	0.1		1.0	0.7	
Progesterone receptor				0.35			0.48
Negative	10.4	11.1	9.7		9.9	9.2	
Positive	89.6	88.9	90.3		90.1	90.9	
Cancer Stage				<.0001			0.22
I	68.2	64.2	72.3		68.2	65.4	
II	30.7	34.4	26.8		30.7	33.6	
Missing	1.2	1.4	0.9		1.1	1.0	
Tumor Size, cm				<.0001			0.94
<1	30.1	37.3	22.8		30.6	30.6	
1-2	45.6	36.4	55.1		45.9	45.4	
2-5	23.5	25.5	21.5		22.9	23.5	
Missing	0.8	0.9	0.7		0.7	0.6	
Comorbidities*				0.008			0.84
0 main disease	72.9	70.7	75.3		72.4	71.6	
1 main disease	21.4	21.9	20.8		21.7	22.5	
>1 main diseases	5.7	7.4	3.9		5.9	5.9	
Want Newest and Most Advanced Treatment				0.12			0.92
No	27.1	24.8	29.3		27.9	27.2	

Patient Characteristics	Overall (N=1,545)	Pre-IPW RS Assay§ No (N=781)	Pre-IPW RS Assay§ Yes (N=764)	P	Post-IPW RS Assay§ No (N=781)	Post-IPW RS Assay§ Yes (N=764)	P
Yes	68.6	70.4	66.8		67.9	68.6	
Missing	4.3	4.7	3.9		4.2	4.2	
Want Extensive Treatment				0.17			0.48
No	55.7	53.7	57.9		56.3	54.3	
Yes	38.4	39.7	37.0		38.2	40.4	
Missing	5.9	6.7	5.1		5.5	5.4	
Race/Ethnicity				0.0002			0.62
White	56.8	52.1	61.7		56.3	54.7	
Black	15.3	15.6	14.9		15.5	17.5	
Latina	17.5	21.5	13.5		17.8	17.8	
Asian	7.4	8.1	6.7		7.3	7.3	
Missing	3.0	2.7	3.3		3.0	2.7	
Education				0.015			0.45
High school/GED or less	29.7	33.0	26.3		30.3	29.1	
Some college/technical school	31.9	31.9	31.9		31.1	32.7	
College graduate or higher	37.1	33.8	40.5		37.2	37.2	
Missing	1.3	1.3	1.3		1.5	1.0	
Annual Family Income				0.0007			0.55
<20,000	15.3	15.8	14.9		14.8	14.4	
20,000 - 60,000	27.3	30.1	24.5		27.5	29.7	
>60,000	38.1	33.2	43.1		37.6	36.9	
Missing	19.3	21.0	17.5		20.2	18.9	
Insurance Status				<.0001			0.58
No Insurance	0.5	0.4	0.7		0.4	0.7	
Public Insurance	44.7	50.7	38.6		46.2	44.9	
Private Insurance	51.1	45.2	57.1		49.2	50.7	
Missing	3.7	3.7	3.7		4.2	3.7	
Partner Status				0.006			0.67
No	35.7	39.3	31.9		35.4	35.7	
Yes	62.9	59.7	66.2		62.9	63.0	
Missing	1.4	1.0	1.8		1.7	1.3	
Employment at Diagnosis				0.0016			0.21
Unemployed	21.8	21.5	22.1		21.0	21.2	
Full Time	38.8	34.7	42.9		37.9	38.1	
Part Time	11.8	12.4	11.1		12.3	10.1	

Patient Characteristics	Overall (N=1,545)	Pre-IPW RS Assay§ No (N=781)	Pre-IPW RS Assay§ Yes (N=764)	P	Post-IPW RS Assay§ No (N=781)	Post-IPW RS Assay§ Yes (N=764)	P
Retired or Not working	27.6	31.4	23.8		28.8	30.7	
Site				<.0001			0.87
Georgia	54.9	44.3	65.7		55.1	54.8	
Los Angeles County	45.1	55.7	34.3		44.9	45.2	

*Comorbidities: 0, 1, 2 or more of the four major comorbid conditions: stroke, myocardial infarction, diabetes, or chronic obstructive pulmonary disease

§RS assay: 21-gene recurrence score assay

Table 2

The Percent of Patients, with 95% Confidence Intervals, in Each of the Four Groups * According to How the RS Assay § Influenced Chemotherapy Decisions: Overall, by Age, Tumor Grade, Tumor Size and Node Status.

	Never Chemotherapy	Chemotherapy Discouraged	Chemotherapy Encouraged	Always Chemotherapy
Overall	54.1 (44.0, 64.2)	19.9 (10.0, 29.9)	9.5 (0, 19.6)	16.4 (6.3, 26.5)
Age at diagnosis, years				
20-49	25.9 (15.7, 36.1)	31.4 (23.5, 39.2)	9.3 (0, 22.5)	33.5 (21.8, 45.1)
50-59	43.5 (27.9, 59.1)	27.2 (12.0, 42.4)	8.4 (0, 20.9)	21.0 (8.9, 33.1)
60-69	55.9 (44.4, 67.3)	18.3 (6.1, 30.4)	11.7 (1.6, 21.7)	14.2 (2.8, 25.6)
70-79	74.2 (67.4, 81.0)	11.6 (4.0, 19.1)	7.5 (1.3, 13.7)	6.7 (0, 14.3)
Tumor Grade				
1	71.7 (63.9, 79.6)	16.5 (8.3, 24.7)	6.5 (0.3, 12.8)	5.3 (0, 12.3)
2	53.7 (42.0, 65.4)	21.9 (11.8, 32.0)	10.5 (0, 22.6)	13.8 (2.8, 24.9)
3	14.4 (0.5, 28.4)	21.3 (4.2, 38.5)	13.5 (0, 27.2)	50.7 (33.8, 67.6)
Tumor Size, cm				
<1	75.2 (66.4, 84.0)	7.9 (2.2, 13.5)	12.0 (2.3, 21.6)	5.0 (0, 11.4)
1-2	56.7 (45.7, 67.6)	18.2 (5.2, 31.2)	9.8 (0, 20.7)	15.3 (2.0, 28.6)
2-5	26.2 (14.0, 38.4)	36.3 (25.9, 46.8)	6.4 (0, 17.3)	31.1 (22.1, 40.0)
Node Status				
Negative	63.5 (53.3, 73.7)	15.7 (5.4, 26.0)	10.3 (0.2, 20.3)	10.5 (0.3, 20.7)
Positive	15.1 (5.7, 24.4)	37.3 (25.3, 49.4)	6.5 (0, 17.0)	41.1 (28.3, 54.0)

* Patients were classified into four groups according to the direction and presence of the influence of RS assay on chemotherapy treatment plan: 1) never chemotherapy: those who would never take chemotherapy whether tested or not; 2) chemotherapy discouraged: those who would have been treated without the test but would not if tested; 3) chemotherapy encouraged: those who would not have chemotherapy without the test but who would if tested; and 4) always chemotherapy: those who would take chemotherapy with or without the test.

§ RS Assay: 21-gene recurrence score assay