Uptake of the 21-Gene Assay Among Women With Node-Positive, Hormone Receptor–Positive Breast Cancer

Megan C. Roberts, PhD^a; Allison W. Kurian, MD, MSc^b; and Valentina I. Petkov, MD, MPH^a

ABSTRACT

Background: This study assessed uptake of the Oncotype DX 21-gene assay over time and characterized which sociodemographic and clinical factors are associated with test uptake among women with lymph node–positive (LN+), hormone receptor–positive, HER2-negative breast cancer. **Methods:** Invasive breast cancer cases diagnosed in 2010 through 2013 were included from a SEER database linked to 21-gene assay results performed at Genomic Health's Clinical Laboratory. Factors associated with 21-gene assay uptake were identified using a multivariable logistic regression model. **Results:** Uptake of the 21-gene assay increased over time and differed by race, socioeconomic status (SES), and age. In the multivariable model, when clinical and SES variables were controlled for, racial differences in test uptake were no longer observed. Private insurance status was associated with higher odds of 21-gene assay uptake (Medicaid vs private insurance: adjusted odds ratio, 0.86; $P = .02$), and high area-level SES was associated with an increased odds of uptake (quintile 5 vs 1: adjusted odds ratio, 1.6; $P < .001$). Demographic factors such as age and marital status influenced test uptake, and use varied greatly by geographic region. Uptake of the 21-gene assay increased over time and preceded the assay's inclusion in the NCCN Guidelines for LN+ breast cancer. Differences in uptake by race, SES, and age have persisted over time. However, when clinical and SES variables were controlled for, racial differences in assay uptake were no longer observed. Socioeconomic variables, such as health insurance type and area-level SES, were associated with assay uptake. **Conclusions:** Future research should continue to document practice patterns related to the 21-gene assay. Given variation in testing associated with area-level SES, insurance coverage, and geographic region, interventions to understand and reduce differential uptake are needed to ensure equitable access to this genomic test.

J Natl Compr Canc Netw 2019;17(6):662–668
doi: 10.6004/jnccn.2018.7266

Background

The Oncotype DX Breast Recurrence Score (RS) test is a 21-gene expression assay that became commercially available for clinical use in 2004. In patients with early-stage, hormone receptor–positive (HR+), HER2-negative breast cancer, RS has been validated to be prognostic for distant recurrence and breast cancer–specific survival,^{1,2} and predictive of chemotherapy benefit in retrospective studies of archival tissue.^{1,3,4} Multiple studies have shown that the RS assay influences physician treatment recommendations for women with lymph node–positive (LN+) disease,^{3,5–14} and that those who receive treatment based on RS results have low rates of distant recurrence¹⁵ and excellent 5-year breast cancer–specific survival.^{16–20}

In 2015, the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer included use of the 21-gene assay for select patients with LN+ breast cancer (1–3 positive nodes),²¹ although its use in this population preceded its inclusion. Patients with LN+ disease who underwent RS testing tended to be older and have lower grade and smaller sized tumors,⁴ and black women were significantly less likely to receive the 21-gene assay than nonblack women.^{3,4}

However, previous studies of the 21-gene assay have not been population-based,^{3,4} have not been adequately powered to more deeply characterize racial and socioeconomic disparities over time,⁴ and have not included a reliable measure for whether the test was ordered (vs RS received and reported).^{3,4} Furthermore, examining uptake over time may elucidate how it varies according to key covariates (eg, race) during diffusion of the assay among women with LN+ disease, which may have implications for understanding adoption of tumor gene profiling tests more broadly. Thus, this study aimed to assess uptake of the assay over time and to characterize which sociodemographic and clinical factors are associated with its uptake for the first time

^aNational Cancer Institute, Bethesda, Maryland, and ^bStanford University School of Medicine, Stanford, California.

See JNCCN.org for supplemental online content.

in a population-based study of women with LN+, HR+, HER2-negative breast cancer.

Methods

We performed a secondary data analysis to examine uptake of the 21-gene assay among women with LN+ disease through descriptive analyses and multivariable modeling.

Dataset

21-gene assay results from Genomic Health's Clinical Laboratory (2004–2014) were linked to the NCI's SEER breast cancer cases (diagnosed 2004–2013). SEER registries have been required to collect results from multi-gene assays, including Oncotype DX for breast cancer, since 2010. However, due to a fragmented US healthcare system, this information was not always available to the cancer registrars, resulting in underreporting (40% of Oncotype DX tests provided through the linkage were not captured by the cancer registrars). The linkage was performed to obtain more complete, population-based data. The success rate of the linkage was estimated to be >93% and was based on comparison with data collected from medical records by cancer registrars. After SEER approval, the study investigators used deidentified data.

Sample

Women with LN+, HR+, HER2-negative invasive breast cancer who had no distant metastases were included in the study, and only those diagnosed in 2010 through 2013, because reporting of HER2 receptor status into the SEER registries began in 2010.

Measures

The dependent variable was uptake of the 21-gene assay, which was defined as whether a patient had the assay ordered by a clinician. Sociodemographic and tumor covariates that may be associated with assay uptake were included in descriptive statistics and the primary multivariable analysis. Covariates of interest included age at diagnosis (<45, 45–54, 55–64, 65–74, ≥75 years), year of breast cancer diagnosis (2010–2013), number of positive LNs (1, 2, 3, ≥4, unknown), tumor grade (I, II, III, unknown), tumor size (≤1, >1 and ≤2, >2 and ≤5, >5 cm, unknown), race (black, white, other, unknown), area-level socioeconomic status (SES; Yost quintile 1 [low] to 5 [high], unknown), marital status (married, divorced/separated, single/unmarried, widowed, unknown), insurance status (insured, insured/nonspecific, Medicaid, uninsured, unknown), and state of cancer registry reporting. Our analyses also included the assay orders, the 21-gene assay RS (0–100), and risk group (low: RS <18; intermediate: RS 18–30; high: RS ≥31) from Genomic Health.

Statistical Analysis

The proportion of women who had Oncotype DX testing in 2010 through 2013 was plotted. We stratified these plots by key demographic variables, including race, SES, and age, given the need to more deeply characterize test uptake in these groups over time. Population characteristics were analyzed using chi-square tests. Among those who received the 21-gene assay, kernel density estimates of the RS were plotted by the number of positive LNs. Notably, for a number of women (n=336; 7.9%), we received indication that a test was ordered but assay results were not provided to SEER due to a canceled test, failed test (eg, inadequate tissue sample), multiple tests for a patient, or sample outside analysis criteria (HR-negative and/or HER2-positive by reverse-transcription PCR); these individuals were excluded from the kernel density plots and mean RS calculations. Finally, our primary analysis identified factors associated with test uptake using a multivariable logistic regression model. We used modified Poisson regression to estimate unadjusted and adjusted risk ratios. Data were analyzed using Stata (StataCorp LLC).

Results

Sociodemographic Characteristics

Overall uptake of the 21-gene assay increased over time (Figure 1; Tables 1 and 2). Overall, 14% of women with LN+ breast cancer had an Oncotype DX test ordered. Odds of uptake were higher among patients who were white versus black (unadjusted odds ratio [uOR], 1.35; $P<.001$), those living in higher (Yost quintile 3, 4, and 5) versus low (Yost quintile 1) SES areas ($P<.001$), and older women (all age categories ≥45 years; $P<.001$). Conversely, odds of uptake were lower among patients with Medicaid (uOR, 0.59; $P<.001$) or who were uninsured (uOR, 0.73; $P<.01$), and those who were widowed versus married (uOR, 0.73; $P<.001$).

When adjusting for covariates in multivariable analysis (Table 3), race was no longer associated with uptake of the 21-gene assay (white vs black: adjusted odds ratio [aOR], 1.12; $P=.07$). However, living in a high SES area (quintile 5 vs 1: aOR, 1.60; $P<.001$) was associated with higher odds of receiving the assay after controlling for covariates. Conversely, having Medicaid (vs private insurance: aOR, 0.86; $P=.02$) and being widowed (vs married: aOR, 0.79; $P<.001$) were associated with lower odds of uptake when adjusted for covariates, including age. Rates of uptake greatly varied by state, even when controlling for covariates.

Tumor Characteristics

On average, tumor characteristics of women for whom the 21-gene assay was ordered differed from those

Figure 1. Oncotype DX testing uptake by (A) race, (B) area-level socioeconomic status quintile, and (C) age among patients with lymph node–positive breast cancer.

of women who did not have an assay ordered; for example, those who did not receive testing, on average, had higher grade and larger sized tumors and greater LN involvement than those who did receive the test ($P < .001$) (Table 1). The 21-gene assay was used in 7.3% of patients with ≥ 4 positive nodes.

These associations between clinical covariates and uptake held when controlling for covariates in multivariable analysis (Table 3). Greater LN involvement (≥ 4 vs 1 positive LNs: aOR, 0.14; $P < .001$), higher tumor grade (III vs I: aOR, 0.42; $P < .001$), and larger tumor size (> 5 vs ≤ 1 cm: aOR, 0.36; $P < .001$) were associated with lower odds of uptake.

Among women who received the 21-gene assay, distribution of RS results did not vary greatly by number of positive LNs (supplemental eAppendix 1 and eFigure 1, available with this article at JNCCN.org).

Discussion

Uptake of the 21-gene assay increased over time and preceded its inclusion in NCCN Guidelines for LN+ breast cancer. Differences in uptake by race, SES, and age have persisted during diffusion of the assay during the 4-year study period, and in multivariable models, SES, demographic, and clinical characteristics were associated with assay uptake.

Insurance status was found to be associated with higher odds of 21-gene assay uptake, consistent with previous literature.³ Furthermore, we found that high area-level SES was associated with an increased odds of uptake. Interestingly, when clinical and SES variables were controlled for, racial differences in the uptake of the test were no longer observed, suggesting that these variables may partially explain disparities in the uptake of this genomic innovation. Similar findings were reported in a North Carolina cohort.⁴

In addition to SES and clinical factors, demographic factors such as age and being widowed or having unknown marital status influenced uptake of the test. Similar to previous findings among women with LN-negative disease, those who were widowed were less likely to receive the assay, as were the oldest and youngest women with LN+ breast cancer.²² A previous qualitative study found that low test uptake in the youngest and oldest age groups may result from clinician and patient preferences regarding chemotherapy, including providing compulsory chemotherapy in the youngest group and avoiding chemotherapy due to fragility in the oldest age group.²³ Finally, test use varied greatly by geographic region. In a qualitative study, local practice patterns and peer use of the test were found to influence clinicians' adoption of the assay.²³ Similarly, a recent Kaiser Permanente study found that differences in oncologist factors (eg, sex) and organizational factors (eg, use patterns among practice leaders) explained more variation in testing rates than patient-level characteristics,²⁴ and another study (conducted in a single state) found that the likelihood of testing decreased for women when a clinician's patient volume decreased.²⁵ Thus, clinician- and organizational-level factors may partially explain geographic variation in test uptake. Further investigations should explore this hypothesis explicitly.

We found that mean risk scores did not vary by the number of positive LNs. Recent studies show that women with 1 to 3 positive LNs who received treatment based on RS results had good health outcomes.^{16,19} For example,

Table 1. Demographic and Tumor Characteristics

Characteristic	Proportion (%) ^a		
	Overall (N=30,410)	No Test (N=26,139)	Test (N=4,271)
Year of diagnosis			
2010	24.0	24.9	18.8
2011	25.2	25.6	22.7
2012	25.0	24.6	27.2
2013	25.8	25.0	31.3
Age, y			
<45	15.5	16.5	9.1
45–54	26.5	26.8	24.8
55–64	26.2	25.4	31.1
65–74	19.0	18.0	25.1
≥75	12.8	13.2	9.9
Number of positive lymph nodes			
1	35.7	31.1	63.9
2	17.8	17.5	19.8
3	9.6	10.0	7.0
≥4	29.5	33.1	7.3
Unknown	7.4	8.3	2.0
Tumor grade			
I	15.3	13.6	25.5
II	49.8	49.1	54.6
III	31.0	33.1	17.7
Unknown	3.9	4.2	2.2
Tumor size, cm			
≤1	7.2	6.3	12.4
>1 and ≤2	27.8	25.3	43.1
>2 and ≤5	48.3	49.8	38.9
>5	15.1	16.7	5.2
Unknown	1.7	1.8	0.5
Race			
Black	11.8	12.2	9.5
White	78.6	78.0	82.3
Other	9.0	9.2	7.8
Unknown	0.6	0.6	0.5
Socioeconomic status (Yost quintile)			
1 (low)	15.7	16.3	12.1
2	18.0	18.3	16.3
3	19.7	19.8	18.9
4	21.9	21.7	22.8
5 (high)	23.5	22.7	28.6
Unknown	1.3	1.2	1.4

(continued)

^aAll P values <.001 by chi-square test for binary/categorical variables.**Table 1. Demographic and Tumor Characteristics (cont.)**

Characteristic	Proportion (%) ^a		
	Overall (N=30,410)	No Test (N=26,139)	Test (N=4,271)
Marital status			
Married	55.0	54.3	59.2
Divorced/Separated	12.0	11.9	12.2
Single/Unmarried	16.1	16.4	14.5
Widowed	11.9	12.2	9.8
Unknown	5.0	5.1	4.2
Insurance status			
Insured	69.2	68.4	74.2
Insured/Nonspecific	12.9	12.9	12.9
Medicaid	14.1	14.8	9.5
Uninsured	2.3	2.4	1.9
Unknown	1.5	1.5	1.5
State			
California	41.6	42.5	36.2
Connecticut	4.6	4.6	4.7
Georgia	10.8	10.6	11.8
Hawaii	1.8	1.7	2.3
Iowa	3.5	3.5	3.6
Kentucky	5.0	5.0	5.0
Louisiana	5.5	5.5	5.2
Michigan	5.1	4.9	6.3
New Jersey	10.9	10.5	13.4
New Mexico	2.1	2.0	2.8
Washington	6.4	6.4	7.0
Utah	2.7	2.9	1.6

^aAll P values <.001 by chi-square test for binary/categorical variables.

5-year breast cancer–specific mortality was 1% among women with RS <18 who had micrometastases and up to 3 positive nodes.¹⁹ Outcomes worsen among women with ≥4 positive nodes¹⁶; uptake of the 21-gene assay was low in this group, which aligns with current outcomes data and the lack of clinical guidelines for using the assay in this subgroup. Our findings, along with those showing lower use in higher grade and larger tumors, suggests that clinicians may choose to not order a test in more advanced cases for which chemotherapy has historically been indicated.

Limitations

Because we do not have information on clinician characteristics and patient–clinician communication, we could not determine whether the test was discussed and declined by the patient or whether clinician

Table 2. Unadjusted Odds of Oncotype DX Testing Uptake

Characteristic	Unadjusted Odds Ratio	P Value
Year of diagnosis		
2010	Ref	
2011	1.17	<.01
2012	1.46	<.001
2013	1.65	<.001
Age, y		
<45	Ref	
45–54	1.69	<.001
55–64	2.23	<.001
65–74	2.55	<.001
≥75	1.37	<.001
Number of positive lymph nodes		
1	Ref	
2	0.55	<.001
3	0.34	<.001
≥4	0.11	<.001
Unknown	0.12	<.001
Tumor grade		
I	Ref	
II	0.59	<.001
III	0.28	<.001
Unknown	0.28	<.001
Tumor size, cm		
≤1	Ref	
>1 and ≤2	0.87	.02
>2 and ≤5	0.40	<.001
>5	0.16	<.001
Unknown	0.14	<.001
Race		
Black	Ref	
White	1.35	<.001
Other	1.09	.29
Unknown	0.93	.78
Socioeconomic status (Yost quintile)		
1 (low)	Ref	
2	1.20	<.01
3	1.29	<.001
4	1.42	<.001
5 (high)	1.70	<.001
Unknown	1.57	<.01

(continued)

Table 2. Unadjusted Odds of Oncotype DX Testing Uptake (cont.)

Characteristic	Unadjusted Odds Ratio	P Value
Marital status		
Married	Ref	
Divorced/Separated	0.94	.23
Single/Unmarried	0.81	<.001
Widowed	0.73	<.001
Unknown	0.76	<.01
Insurance status		
Insured	Ref	
Insured/Nonspecific	0.92	.11
Medicaid	0.59	<.001
Uninsured	0.73	<.01
Unknown	0.96	.79
State		
California	Ref	
Connecticut	1.31	<.001
Georgia	0.67	<.01
Hawaii	1.51	<.001
Iowa	1.62	<.001
Kentucky	1.20	.05
Louisiana	1.18	.03
Michigan	1.20	.03
New Jersey	1.12	.15
New Mexico	1.50	<.001
Washington	1.60	<.001
Utah	1.29	<.001

characteristics influenced test uptake. However, recent studies suggested that clinician- and organizational-level factors may drive differential uptake. For example, patients seen within comprehensive cancer centers appear to be more likely to receive the 21-gene assay than those seen in tertiary centers, explaining observed disparities in assay uptake among patients with LN-negative disease.²⁶ We were unable to examine these factors, and future studies should focus on this area. Uptake results to date reflect behavior through 2013. During this study period, use of the 21-gene assay was not included in clinical guidelines. Understanding how clinical guideline inclusion has influenced assay uptake and observed disparities in uptake will be important to monitor across diffusion of the innovation. We plan to perform annual updates to gain additional information regarding uptake and patient outcomes. Finally, the ongoing RxPONDER trial will provide prospective data regarding whether patients with

Table 3. Multivariable Logistic Regression Model of Oncotype DX Testing Uptake

Characteristic	Adjusted Odds Ratio	95% CI
Race (vs black)		
White	1.12	0.99–1.27
Other	0.93	0.78–1.12
Unknown	0.86	0.52–1.43
Socioeconomic status (vs Yost quintile 1; low)		
2	1.20	1.05–1.37
3	1.25	1.10–1.42
4	1.36	1.20–1.55
5 (high)	1.60	1.40–1.82
Unknown	1.37	1.00–1.88
Marital status (vs married)		
Divorced/Separated	1.06	0.95–1.19
Single/Unmarried	1.05	0.95–1.17
Widowed	0.79	0.69–0.89
Unknown	0.77	0.65–0.92
Insurance status (vs insured)		
Insured/Nonspecific	0.99	0.89–1.10
Medicaid	0.86	0.77–0.98
Uninsured	1.05	0.82–1.36
Unknown	1.16	0.87–1.56
State (vs California)		
Connecticut	1.23	1.04–1.46
Georgia	1.47	1.30–1.65
Hawaii	1.74	1.35–2.25
Iowa	1.19	0.98–1.45
Kentucky	1.27	1.08–1.51
Louisiana	1.35	1.14–1.59
Michigan	1.64	1.41–1.92
New Jersey	1.73	1.54–1.95
New Mexico	1.77	1.41–2.21
Washington	1.22	1.06–1.41
Utah	0.60	0.46–0.78
Age (vs <45), y		
45–54	1.47	1.30–1.68
55–64	1.98	1.75–2.25
65–74	2.25	1.97–2.57
≥75	1.33	1.13–1.56
Year of breast cancer diagnosis (vs 2010)		
2011	1.20	1.08–1.33
2012	1.52	1.37–1.69
2013	1.78	1.61–1.97

(continued)

Table 3. Multivariable Logistic Regression Model of Oncotype DX Testing Uptake (cont.)

Characteristic	Adjusted Odds Ratio	95% CI
Number of positive lymph nodes (vs 1)		
2	0.58	0.53–0.63
3	0.39	0.34–0.44
≥4	0.14	0.12–0.15
Unknown	0.18	0.15–0.23
Tumor grade (vs I)		
II	0.72	0.66–0.79
III	0.42	0.38–0.47
Unknown	0.39	0.31–0.49
Tumor size (vs ≤1 cm), cm		
>1 and ≤2	1.00	0.88–1.12
>2 and ≤5	0.65	0.58–0.74
>5	0.36	0.30–0.43
Unknown	0.37	0.23–0.59

LN+, HR+, HER2-negative breast cancer and RS <25 benefit from adjuvant chemotherapy, and will provide further guidance on the use of RS for patients with LN+ disease.

Conclusions

Future research should continue to document practice patterns related to the 21-gene assay and longer term outcomes among women who undergo breast cancer treatment based on RS. Given variation in testing associated with area-level SES, insurance coverage, and geographic region, interventions to understand and reduce differential uptake are needed to ensure equitable access to this genomic test.

Submitted September 12, 2018; accepted for publication on December 21, 2018.

Author contributions: Study concept and design: Roberts, Petkov. Data analysis and interpretation: All authors. Manuscript preparation: Roberts. Critical revisions: All authors.

Disclosures: The authors have not received any financial consideration from any person or organization to support the preparation, analysis, results, or discussion of this article.

Disclaimer: The ideas and opinions expressed herein are those of the author(s) and endorsement by any state, Department of Public Health, NCI, the Centers for Disease Control and Prevention, or their contractors and subcontractors is not intended nor should be inferred. The authors acknowledge the SEER registries for collecting the SEER data. The authors have no conflicts of interest to report. The SEER Program is funded by NCI. Genomic Health performed the work to electronically submit the RS results, but provided no funding for this study.

Correspondence: Megan C. Roberts, PhD, UNC Eshelman School of Pharmacy, 2206 Kerr Hall, 301 Pharmacy Lane, Campus Box 7573, Chapel Hill, NC 27599-7573. Email: megan.roberts@unc.edu

References

- 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* 2010;11:55–65.
- Dowsett M, Cuzick J, Ingle J, et al. Meta-analysis of breast cancer outcomes in adjuvant trials of aromatase inhibitors versus tamoxifen. *J Clin Oncol* 2010;28:509–518.
- Jasem J, Fisher CM, Amini A, et al. The 21-gene recurrence score assay for node-positive, early-stage breast cancer and impact of RxPONDER trial on chemotherapy decision-making: have clinicians already decided? *J Natl Compr Canc Netw* 2017;15:494–503.
- Roberts MC, Weinberger M, Dusetzina SB, et al. Racial variation in the uptake of Oncotype DX testing for early-stage breast cancer. *J Clin Oncol* 2016;34:130–138.
- de Boer RH, Baker C, Speakman D, et al. The impact of a genomic assay (Oncotype DX) on adjuvant treatment recommendations in early breast cancer. *Med J Aust* 2013;199:205–208.
- Yamauchi H, Nakagawa C, Takei H, et al. Prospective study of the effect of the 21-gene assay on adjuvant clinical decision-making in Japanese women with estrogen receptor-positive, node-negative, and node-positive breast cancer. *Clin Breast Cancer* 2014;14:191–197.
- Bargallo JE, Lara F, Shaw-Dulin R, et al. A study of the impact of the 21-gene breast cancer assay on the use of adjuvant chemotherapy in women with breast cancer in a Mexican public hospital. *J Surg Oncol* 2015;111:203–207.
- Eiermann W, Rezai M, Kümmel S, et al. The 21-gene recurrence score assay impacts adjuvant therapy recommendations for ER-positive, node-negative and node-positive early breast cancer resulting in a risk-adapted change in chemotherapy use. *Ann Oncol* 2013;24:618–624.
- Gligorov J, Pivot XB, Jacot W, et al. Prospective clinical utility study of the use of the 21-gene assay in adjuvant chemotherapy in women with estrogen receptor-positive early invasive breast cancer: results from the SWITCH study. *Oncologist* 2015;20:873–879.
- Lee MH, Han W, Lee JE, et al. The clinical impact of 21-gene recurrence score on treatment decisions for patients with hormone receptor-positive early breast cancer in Korea. *Cancer Res Treat* 2015;47:208–214.
- Oratz R, Kim B, Chao C, et al. Physician survey of the effect of the 21-gene recurrence score assay results on treatment recommendations for patients with lymph node-positive, estrogen receptor-positive breast cancer. *J Oncol Pract* 2011;7:94–99.
- Torres S, Trudeau M, Gandhi S, et al. Prospective evaluation of the impact of the 21-gene recurrence score assay on adjuvant treatment decisions for women with node-positive breast cancer in Ontario, Canada. *Oncologist* 2018;7:768–775.
- Sun J, Fenton D, Baxter S, et al. A prospective clinical utility study of the impact of the 21-gene recurrence score (RS) assay in the treatment of estrogen receptor positive (ER+), HER2 negative (HER2-), 1-3 node positive (N+) breast cancer (BC). Presented at the 2017 San Antonio Breast Cancer Symposium; December 5–9, 2017; San Antonio, Texas.
- Kurian AW, Bondarenko I, Jagsi R, et al. Recent trends in chemotherapy use and oncologists' treatment recommendations for early-stage breast cancer. *J Natl Cancer Inst* 2018;110:493–500.
- Stemmer SM, Steiner M, Rizel S, et al. Clinical outcomes in ER+ HER2 -node-positive breast cancer patients who were treated according to the Recurrence Score results: evidence from a large prospectively designed registry. *NPJ Breast Cancer* 2017;3:32.
- Roberts MC, Miller DP, Shak S, et al. Breast cancer-specific survival in lymph node-positive hormone receptor-positive invasive breast cancer and Oncotype DX Recurrence Score results in the SEER database. *Breast Cancer Res Treat* 2017;163:303–310.
- Nitz U, Gluz O, Christgen M, et al. Reducing chemotherapy use in clinically high-risk, genomically low-risk pN0 and pN1 early breast cancer patients: five-year data from the prospective, randomised phase 3 West German Study Group (WSG) PlanB trial. *Breast Cancer Res Treat* 2017;165: 573–583.
- Gluz O, Nitz U, Christgen N, et al. Prospective WSG phase III PlanB trial: clinical outcome at 5-year follow up and impact of 21 Gene Recurrence Score result, central/local-pathological review of grade, ER, PR and Ki67 in HR+/HER2- high risk node-negative and -positive breast cancer. Presented at the 2016 European Breast Cancer Conference; March 9–11, 2016; Amsterdam, the Netherlands.
- Petkov VI, Miller DP, Howlader N, et al. Breast-cancer-specific mortality in patients treated based on the 21-gene assay: a SEER population-based study. *NPJ Breast Cancer* 2016;2:16017.
- Shak SM, Petkov VI. Breast cancer-specific mortality (BCSM) in patients with node-positive (N+) breast cancer (BC) treated based on the 21-gene assay in clinical practice. Presented at the 2017 San Antonio Breast Cancer Symposium; December 5–9, 2017; San Antonio, Texas.
- Gradishar WJ, Anderson BO, Balassanian R, et al. NCCN Clinical Practice Guidelines in Oncology: Breast Cancer. Version 1.2015. Accessed September 12, 2018. To view the most recent version, visit NCCN.org.
- Cronin KPV, Howlader N, Howe W, et al. Dissemination of 21-gene assay testing among female breast cancer patients in the US. Presented at the 2016 American Society of Clinical Oncology Annual Meeting; June 3–7, 2016; Chicago, Illinois.
- Roberts MC, Bryson A, Weinberger M, et al. Oncologists' barriers and facilitators for Oncotype Dx use: qualitative study. *Int J Technol Assess Health Care* 2016;32:355–361.
- Lieu TA, Ray GT, Prausnitz SR, et al. Oncologist and organizational factors associated with variation in breast cancer multigene testing. *Breast Cancer Res Treat* 2017;163:167–176.
- Reeder-Hayes KE, Wheeler SB, Baggett CD, et al. Influence of provider factors and race on uptake of breast cancer gene expression profiling. *Cancer* 2018;124:1743–1751.
- Guth AA, Fineberg S, Fei K, et al. Utilization of Oncotype DX in an inner city population: race or place? *Int J Breast Cancer* 2013;2013: 653805.

See JNCCN.org for supplemental online content.

Supplemental online content for:

Uptake of the 21-Gene Assay Among Women With Node-Positive, Hormone Receptor–Positive Breast Cancer

Megan C. Roberts, PhD; Allison W. Kurian, MD, MSc; and Valentina I. Petkov, MD, MPH

J Natl Compr Canc Netw 2019;17(6):662–668

eFigure 1: Kernel Density Estimates of Recurrence Score by Number of Positive Lymph Nodes

eAppendix 1: Distribution of Oncotype DX Scores

eFigure 1. Kernel density estimates of recurrence score by number of positive lymph nodes (LNs).

^aKernel = epanechnikov; bandwidth = 1.3907.

eAppendix 1. Distribution of Oncotype DX Scores

	Overall (N=4,271)	1 LN (n=845)	2 LNs (n=300)	3 LNs (n=312)	≥4 LNs (n=85)	Low (n=2,345)	Intermediate (n=1,348)	High (n=242)
Mean risk score (SD)	16.8 (8.3)	16.5 (8.1)	16.3 (7.9)	18.0 (9.1)	17.8 (9.4)	11.6 (4.1)	22.1 (3.4)	37.7 (7.1)

Abbreviation: LN, lymph node.