Identifying Patterns and Barriers in OncotypeDX Recurrence Score Testing in Older Patients With Early-Stage, Estrogen Receptor–Positive Breast Cancer: Implications for Guidance and Reimbursement

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ABSTRACT

PURPOSE To evaluate the clinical patterns of utilization of OncotypeDX Recurrence Score (RS) in early-stage, hormone receptor–positive, human epidermal growth factor receptor 2–negative breast cancer (BC) at an academic center with previously established internal reflex testing guidelines.

METHODS RS testing in accordance with preexisting reflex criteria and predictors of utilization outside of reflex criteria were retrospectively analyzed for the years 2019-2021 in a quality improvement evaluation. Patients were grouped according to OncotypeDX testing within (cohort A) or outside (cohort B) of predefined criteria which included a cap at age older than 65 years.

RESULTS Of 1,687 patients whose tumors had RS testing, 1,087 were in cohort A and 600 in cohort B. In cohort B, nearly half of patients were older than 65 years (n = 279; IQR, 67-72 years). For patients older than 65 years, those with RS testing were younger (median age: 69 *v* 73 years), with higher grade cancers (G2-3: 84.9% *v* 54.7%) and were more likely to be treated with chemotherapy (15.4% *v* 4.1%). Issues for implementation of RS testing in older patients were identified, including potential structural barriers related to the current policy on the reimbursements of genomic tests.

CONCLUSION Internal guidelines may facilitate standardized utilization of the RS in early-BC. Our data suggest that clinicians preferred broader utilization of RS across the age spectrum, with therapeutically important consequences. Modifying the current policy for reimbursement of RS testing and in internal reflexive testing criteria for those older than 65 years is warranted.

ACCOMPANYING CONTENT

Appendix

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INTRODUCTION

The OncotypeDX Recurrence Score (RS) (Exact Sciences, Madison, WI) is a gene-expression profiling tool used to guide the choice of adjuvant systemic treatments for patients with estrogen receptor-negative (ER–) and/or progesterone receptor–positive, human epidermal growth factor receptor 2 (HER2)–negative, early breast cancer (BC).[1] RS, expressed as a continuous score (RS: 0-100), assesses the expression of 16 genes related to BC proliferation, ER dependency, and HER2 pathway. Retrospective studies demonstrated an independent prognostic value for RS in patients receiving adjuvant endocrine therapy[2] and predicted benefit from adjuvant chemotherapy in patients with high RS.[3] Prospective clinical trials that determined the benefit of chemotherapy as a function of RS validated its clinical use in patients with ER-positive, HER2-negative early BC with a RS of 0-25 and with 0-3 involved axillary lymph nodes.[4-7] Findings from related studies of other genomic signature assays, including the 70-gene MammaPrint (Agendia, Amsterdam, the Netherlands), have consolidated the role of genomic tools in the adjuvant chemotherapy decision making.[8,9] RS testing to determine treatment for early BCs has become widespread.[10-15] At Dana-Farber Cancer Institute (DFCI), a previously conducted internal review demonstrated that RS testing, typically ordered after final pathology results were available and after multidisciplinary consultation with medical oncology, was associated with a longer time to adjuvant chemotherapy initiation.[16] To shorten the time to chemotherapy initiation, a quality improvement (QI) initiative addressed timelines to care, standardizing ordering criteria

CONTEXT

Key Objective

We reviewed the pattern of utilization of OncotypeDX at our institution to evaluate concordance with a set of internal recommendation for reflex testing previously implemented. We focused on the decision making in the population age 65 years and older to identify potential differences or barriers.

Knowledge Generated

A clinically oriented triage drives the requests for OncotypeDX in older patients with early breast cancer (BC). Potential issue of implementation for testing were identified, including structural barriers related to the current policy on the reimbursements of genomic tests on the basis of an age threshold.

Relevance

Older patients with BC should be managed on the basis of comprehensive, oncogeriatric approaches. Limitations to oncology diagnostics and treatments should not be based on age thresholds, to avoid structural barriers that do not align with person-centric best clinical practice.

and streamlining workflows for testing with an initial internal guidance for reflex testing, implemented in 2016, then expanded in 2019 (Appendix Table A1, online only).[17] Criteria for the pathology-triggered reflex testing was further expanded to include patients younger than 65 years with pT1c pN0 G2-3, pT2 pN0 G1-3, or pT1-T3 pN1 G1-3 BC. The age cap of 65 years in the reflex criteria was specifically set because of Medicare reimbursement constraints, rather than for other clinical reasons.[18] However, clinicians may still order RS testing on an ad hoc basis when clinically desired (for those at any age). In this study, we report the results of additional QI exercises to understand how the reflex criteria mirror the clinical practice, on the basis of an updated review of clinical patterns of RS reflex testing and ad hoc testing conducted between 2019 and 2021 to understand the local patterns of utilization, inform and update the reflex testing criteria, and identify potential constraints for operationalizing testing. This analysis has a specific focus on the findings for those older than 65 years.

METHODS

We reviewed the clinical patterns of RS testing from January 2019, when the reflex criteria were lastly expanded, until December 2021, focusing on whether testing was aligned with preexisting reflex criteria or fell outside of this guidance. The clinical expectation was that in cases falling within reflex criteria, a RS ≤ 25 would prompt endocrine treatment without chemotherapy while a RS ≥ 26 would justify chemotherapy and endocrine therapy. In this analysis, we used process improvement methodologies, as framed in Plan-Do-Study-Act (PDSA) cycles.[19] Data were extracted from the prospectively maintained institutional database, hosted in (REDCap, Vanderbilt University, Nashville, TN), which collects data on all patients who undergo breast surgery within the DFCI breast oncology (BOC) program; all pathology samples were evaluated internally. The database is the institutional clinical database for patients with BC who receive breast surgery, in any setting maintained with the purpose of QI investigation and clinical research. The database collects sociodemographic, pathological, molecular, and clinical data, including cancer treatments and follow-up. Anatomic staging was performed in accord with American Joint Committee on Cancer TNM, 8th edition.[20] Hormone receptors and HER2 assessment were based on ASCO/CAP guidelines.[21,22] In March 2022, we queried the database and identified all consecutive tumors undergoing RS testing from January 1, 2019 to December 31, 2021, to evaluate overall adherence internal guidance, and to understand patient and tumor characteristics associated with testing outside of the reflexive guidelines. The research is a QI, low-risk data set because data were extracted as anonymized, so this study was waived from obtaining informed consent from the patients.[23]

The clinical and tumor pathological features for RS testing in this analysis were categorized as being within reflex criteria (cohort A) or outside of reflex criteria (cohort B) (Fig 1). Demographic and clinicopathological features for all patients whose tumors had undergone RS testing, and were included in the database, were consecutively extracted. RS categorization followed the classifications in the TAILORx and RxPONDER clinical trials: low (RS ≤ 10), intermediate (RS: 11-25), and high risk (RS ≥ 26).[6,7] The data are presented with descriptive statistics as absolute numbers and relative percentages. Comparison across groups was based on the Fisher's exact or χ^2 test for categorical and discrete variables and the Wilcoxon rank-sum test for continuous variables. The results from this QI exercise were presented to all the providers of the DFCI BOC to discuss the findings and come to a consensus on an updated set of the recommendations. Discussions during two online sessions, and follow-up by email, generated a revised consensus document to guide the clinicopathologically triggered request of RS testing.[17]

RESULTS

Between January 1, 2019, and December 31, 2021, 1,687 tumors were tested for RS, and we could extract available data from the database (Table 1 and Fig 1). Nearly two thirds (n = 1,087; 64.4%; cohort A) of instances were within reflex criteria; however, more than one-third was outside of these criteria (ie, ordered on a case-by-case basis by clinicians: cohort B), accounting for 600 (35.6%) patients. Patients with reflex testing indications were all younger than 65 years, with pT1c pN0 G2-3 (n = 469; 43.1% of the within reflex criteria cases), pT2 pN0 G1-3 (n = 239; 22.0%), pT1-2 pN1 G1-3 (n = 343; 31.6%), and pT3 N0-1 G1-3 (n = 36; 3.3%) BC.

Among all cases ordered outside of reflex criteria in cohort B (n = 600), 46.5% (n = 279) were due to older than 65-year criterion. In this group of older patients, the median age was 69 years (IQR, 67-71.5 years) (Fig 2). Only a minority of the patients were older than 75 years (n = 19; 6.8%). Patients older than 65 years presented with pT1b-c pN0 G2-3 (n = 77; 27.6% of all cases discrepant for the age criterion) and pT2 pN0 G1-3 (n = 46; 16.5%) tumors. Of the remaining patients in cohort B, 53.5% (n = 321) were 65 years or younger, and orders outside the reflexive guidance were most often for low-grade, pT1c pN0 tumors (pT1c pN0, G1: n = 104; 32.4% of all discrepancies for patients younger than 65 years) and for 5-10 mm, node-negative cancers (pT1b [6-10 mm]: n = 86; 26.8%). That is, clinicians were ordering RS testing for older patients and patients with lower-grade and/or smaller tumors more frequently than had originally been anticipated.

To better characterize patterns of RS testing among older patients, we compared the cohort of patients older than 65 years who had RS testing with those who did not. Patients who did not have RS testing were older (median age 73 *v* 69 years) and more likely to have grade 1 tumors (43.9% *v* 15.1%) (Table 2). They were also more likely to have not undergone sentinel node biopsy or axillary surgery (48% *v* 9.3%) consistent with our clinical practice to reduce morbidity in patients who may be unfit for chemotherapy or at low probability of axillary nodal involvement and for whom the information on the axillary nodes would not affect the treatment decisions.[24] Untested, older patients also had smaller tumors: pT1b-c pN0 G2-3 (n = 216; 32% of all patients staged with pN determined; Table 2).

We additionally evaluated thet impact of RS on treatment decisions in cohort A and B. In cohort A, RS ranged between 0 and 74 (median RS: 16), distributed as follows: low (205; 18.9%), intermediate (711; 67.5%), and high risk (167; 15.4%). RS ranged between 0 and 62 in cohort B (median RS: 17), and it was distributed as follows: 21.7% (n = 130) had low RS, 59.7% (n = 357) intermediate RS, and 18.6% (n = 111) high RS (Table 1). For patients older than 65 years, the distribution was similar (Table 2). On the basis of RS test results, 78 patients (13.0% of cohort B patients) whose tumors fell outside the reflex parameters received adjuvant chemotherapy, and 53 patients (8.8%) received neoadjuvant chemotherapy. Thus, overall, 21.8% of patients with RS testing ordered outside the criteria (cohort B) received chemotherapy, as compared with 20.5% in patients tested within the established criteria (cohort A). Notably, 90.8% of patients in cohort B (n = 545) received adjuvant endocrine therapy; 6.7% of patients did not receive any (neo)adjuvant endocrine therapy, similar to cohort A. Among the group of patients older than 65 years, 12.9% received adjuvant chemotherapy after RS testing,

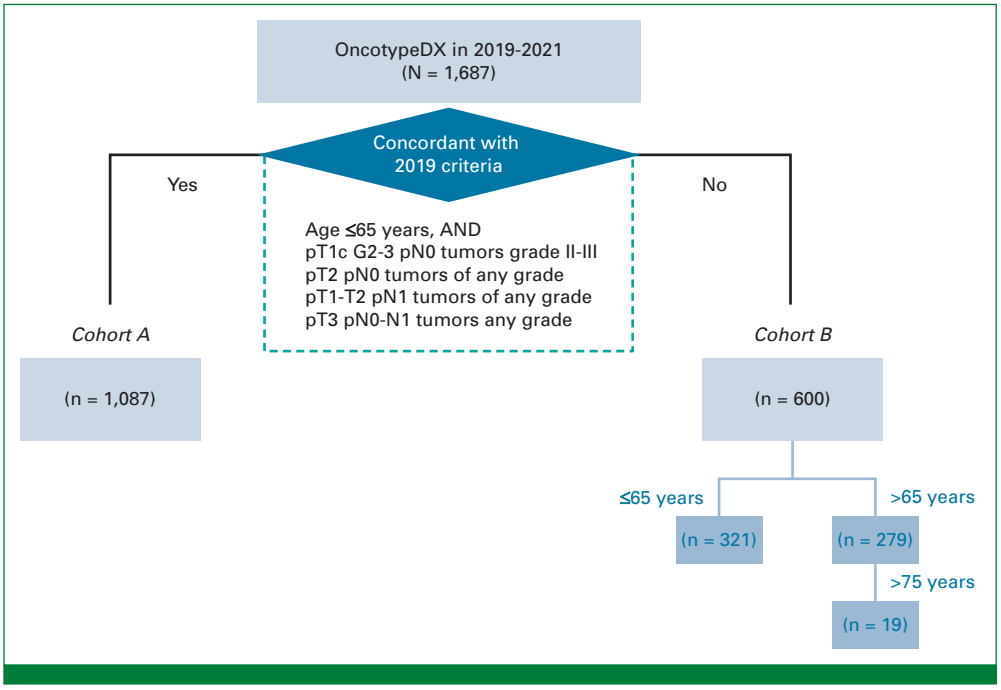

FIG 1. Flow chart of patient selection and inclusion in the two cohorts.

TABLE 1. Characteristics of the Patients Included in the Cohort A (reflex criteria) and Cohort B (ordered outside of criteria)

Characteristic	Cohort A (n = 1,087)	Cohort B (n = 600)	*P*
Age at primary surgery			**< .001**
Median (range), years	52.0 (25.0-65.0)	63.0 (26.0-83.0)	
>65, No. (%)	0 (0.0)	279 (46.5)	
Sex, No. (%)			.636
Female	1,075 (98.9)	591 (98.5)	
Male	12 (1.1)	9 (1.5)	
Race, No. (%)			.265[a]
Caucasian	964 (92.0)	544 (93.6)	
Asian or Pacific Islander	45 (4.3)	17 (2.9)	
African American	38 (3.6)	20 (3.4)	
American Indian, Aleutian, or Eskimo	1 (0.1)	0 (0.0)	
Unknown	39	19	
Menopausal status, No. (%)			**< .001**
Postmenopausal	504 (47.1)	377 (64.1)	
Premenopausal	565 (52.9)	211 (35.9)	
Unknown	18	12	
Pathogenic germline mutation, No. (%)			.412[b]
BRCA1	4 (2.0)	1 (0.8)	
BRCA2	10 (4.9)	4 (3.3)	
Others	14 (6.8)	7 (5.8)	
No	177 (86.3)	109 (90.1)	
Unknown	6	1	
Not done	876	478	
Clinical stage, No. (%)			**< .001[c]**
0	15 (1.4)	9 (1.5)	
I	0 (0.0)	2 (0.3)	
IA	721 (67.3)	355 (59.8)	
IIA	296 (27.6)	140 (23.6)	
IIB	38 (3.5)	64 (10.8)	
IIIA	1 (0.1)	16 (2.7)	
IIIB	0 (0.0)	7 (1.2)	
IIIC	0 (0.0)	1 (0.2)	
Unknown	16	6	
Pathological nodal status, No. (%)			**< .001**
Positive	361 (33.2)	266 (44.3)	
Negative	726 (66.8)	334 (55.7)	
Pathological stage, No. (%)			**< .001[d]**
IA	475 (43.7)	307 (67.3)	
IB	53 (4.9)	10 (2.2)	
II	1 (0.1)	0 (0.0)	
IIA	378 (34.8)	75 (16.4)	
IIB	163 (15.0)	32 (7.0)	
IIIA	17 (1.6)	26 (5.7)	
IIIB	0 (0.0)	1 (0.2)	
IIIC	0 (0.0)	5 (1.1)	
Unknown	0	144	
Tumor histology, No. (%)			.909[e]
Invasive ductal	672 (61.8)	371 (61.8)	
Invasive lobular	171 (15.7)	98 (16.3)	

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TABLE 1. Characteristics of the Patients Included in the Cohort A (reflex criteria) and Cohort B (ordered outside of criteria) (continued)

Characteristic	Cohort A (n = 1,087)	Cohort B (n = 600)	*P*
Mixed (IDC and ILC)	209 (19.2)	109 (18.2)	
Micropapillary	4 (0.4)	6 (1.0)	
Mucinous	20 (1.8)	10 (1.7)	
Tubular	1 (0.1)	4 (0.7)	
DCIS with microinvasion	1 (0.1)	0 (0.0)	
Others	9 (0.8)	2 (0.3)	
Tumor grade, No. (%)			**< .001**
I low grade	119 (11.0)	182 (30.3)	
II intermediate grade	756 (69.6)	304 (50.7)	
III high grade	211 (19.4)	114 (19.0)	
Unknown	1	0	
ER, No. (%)			—
Positive (>9%)	1,084 (99.7)	598 (99.7)	
Positive low (1%-9%)	3 (0.3)	0 (0.0)	
Negative	0 (0.0)	2 (0.3)[f]	
PR, No. (%)			**.021**
Positive (>9%)	928 (85.4)	481 (80.2)	
Positive low (1%-9%)	60 (5.5)	47 (7.8)	
Negative	99 (9.1)	72 (12.0)	
HER2 IHC score, No. (%)			.251
0	412 (37.9)	231 (38.5)	
1+	404 (37.2)	240 (40.0)	
2+ (with negative FISH)	271 (24.9)	129 (21.5)	
HER2-low status, No. (%)			.850
HER2-zero	412 (37.9)	231 (38.5)	
HER2-low	675 (62.1)	369 (61.5)	
ODX risk group [RS], No. (%)			.050
Low risk [0,10]	205 (18.9)	130 (21.7)	
Intermediate risk [11,25]	711 (65.7)	357 (59.7)	
High risk [26,100]	167 (15.4)	111 (18.6)	
Missing	4	2	
ODX numeric (RS), No. (%)			.363
Mean (SD)	17.5 (9.24)	18.1 (10.2)	
Median (range)	16.0 (0-74.0)	17.0 (0-62.0)	
Missing	4	2	
Type of breast surgery, No. (%)			.217
Partial mastectomy	672 (61.8)	397 (66.2)	
Total mastectomy	409 (37.6)	199 (33.2)	
Chest wall excision	3 (0.3)	1 (0.2)	
Wide local excision	3 (0.3)	3 (0.5)	
Axillary management, No. (%)			**< .001**
ALND	28 (2.6)	40 (7.1)	
SLNB	1,001 (92.4)	450 (80.1)	
Both ALND and SLNB	53 (4.9)	72 (12.8)	
Others	1 (0.1)	0 (0.0)	
Missing	4	38	
Received chemotherapy? No. (%)	223 (20.5)	131 (21.8)	.566
Yes adjuvant	223	72	
Neoadjuvant	0	53	

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TABLE 1. Characteristics of the Patients Included in the Cohort A (reflex criteria) and Cohort B (ordered outside of criteria) (continued)

Characteristic	Cohort A (n = 1,087)	Cohort B (n = 600)	*P*
Both adjuvant and neoadjuvant	0	6	
No	864 (79.5)	469 (78.2)	
Received endocrine therapy? No. (%)	1,014 (93.3)	560 (93.3)	1
Yes adjuvant	1,014	483	
Neoadjuvant	0	15	
Both adjuvant and neoadjuvant	0	62	
No	73 (6.7)	40 (6.7)	

NOTE. All *P* values apply to the intercategory comparisons unless otherwise specified. Comparison across groups was based on the Fisher's exact or χ^2 test for categorical and discrete variables and the Wilcoxon rank-sum test for continuous variables. Bold indicates significance at $P < 0.05$.
Abbreviations: ALND, axillary lymph node dissection; DCIS, ductal carcinoma in situ; ER, estrogen receptor; FISH, fluorescent in-situ hybridization; HER2, human epidermal growth factor receptor 2; IDC, invasive ductal carcinoma; IHC, immune-histochemistry; ILC, invasive lobular carcinoma; ODX, OncotypeDX; PR, progesterone receptor; RS, recurrence score; SLNB, sentinel lymph node biopsy.
[a]Caucasian *v* not Caucasian.
[b]Germline *v* nongermline pathogenetic mutations.
[c]0 *v* I *v* II/III: $P = 0.012$.
[d]Stage I *v* stage II *v* stage III.
[e]Invasive ductal *v* invasive lobular *v* mixed (IDC and ILC) *v* other.
[f]Two patients had ER-negative and PR-positive cancer, both were T < 1 cm and node-negative. One patient had metaplastic, G3, and PR < 10% tumor, with RS = 48. The second patient had a ductal-type, G1, an PR 80% cancer, with RS = 20.

compared with only 1.53% for those not tested, suggesting a RS-informed choice and possibly an pretest triage on the basis of oncogeriatric variables (Table 2 and Fig 2). In addition, 53 and 15 patients in cohort B but none in cohort A received neoadjuvant chemotherapy or endocrine therapy, respectively, after RS determination on diagnostic core biopsy samples. For all the other patients, the test was requested on the surgical samples, as per standard clinical practice. The sensitivity analysis of the cohorts with and without patients receiving neoadjuvant treatments only showed minor changes

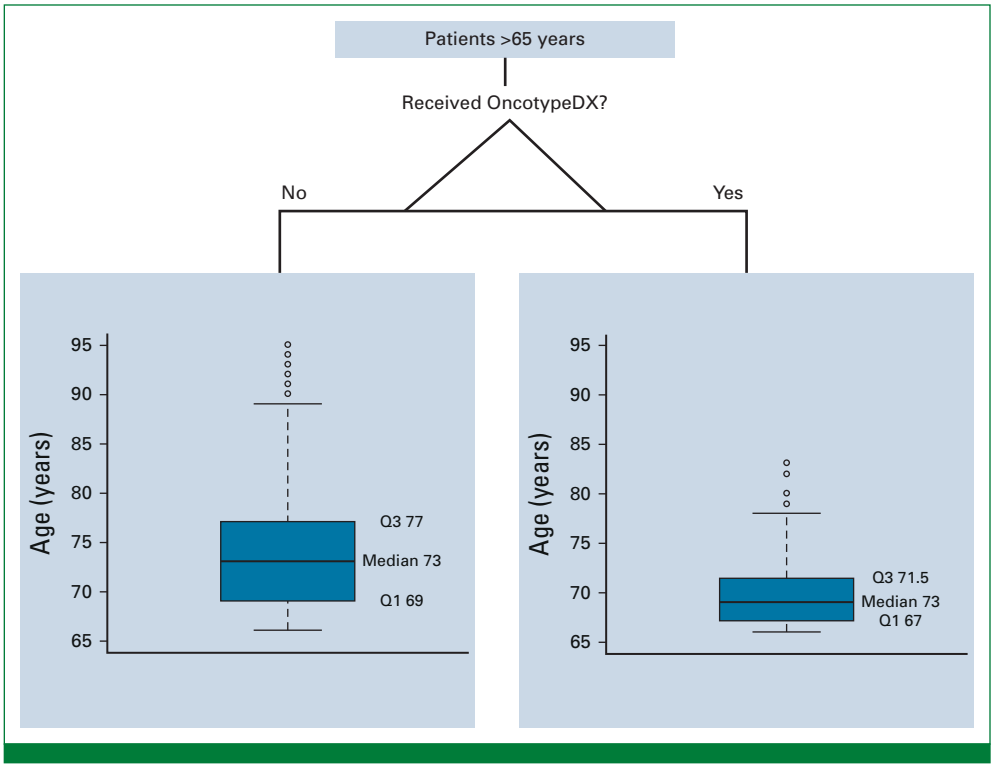

FIG 2. Age distribution of patients in cohort B older than 65 years. Max, maximal age; Min, minimum age; Q1, lower quartile; Q3, upper quartile.

TABLE 2. Characteristics of the Patients Older Than 65 Years Receiving or Not Receiving ODX

Characteristic	No ODX (n = 1,303)	Received ODX (n = 279)	*P*
Age at primary surgery, years			**< .001**
Median (range)	73.0 (66.0-95.0)	69.0 (66.0-83.0)	
Median (IQR)	73.0 (69-77)	69.0 (67-71.5)	
pT, No. (%)			**< .001**[a]
T1a	184 (14.1)	1 (0.4)	
T1b	440 (33.8)	22 (7.9)	
T1c	370 (28.4)	118 (42.3)	
T1mic	27 (2.1)	0 (0)	
T2	125 (9.6)	83 (29.7)	
T3	11 (0.8)	11 (3.9)	
T4b	2 (0.2)	1 (0.4)	
Tx	1 (0.1)	0 (0)	
Missing	143 (11.0)	43 (15.4)	
pN, No. (%)			**< .001**[b]
N0	439 (33.7)	120 (43.0)	
N0(i−)	19 (1.5)	7 (2.5)	
N0(i+)	26 (2.0)	11 (3.9)	
N1	5 (0.4)	20 (7.2)	
N1a	19 (1.5)	24 (8.6)	
N1mi	12 (0.9)	22 (7.9)	
N2	1 (0.1)	0 (0)	
N2a	8 (0.6)	5 (1.8)	
N3	2 (0.2)	1 (0.4)	
N3a	2 (0.2)	0 (0)	
Nx	627 (48.1)	26 (9.3)	
Missing	143 (11.0)	43 (15.4)	
pM, No. (%)			NA
M0	1,160 (89.0)	235 (84.2)	
Missing	143 (11.0)	44 (15.8)	
Received chemotherapy? No. (%)	54 (4.1)	43 (15.4)	**< .001**
Yes adjuvant	20	36	
Neoadjuvant	31	6	
Both adjuvant and neoadjuvant	3	1	
No	1,249 (95.9)	236 (84.6)	
Received endocrine therapy? No. (%)	1,062 (81.5)	262 (93.9)	**< .001**
Yes adjuvant	980	237	
Neoadjuvant	11	4	
Both adjuvant and neoadjuvant	71	21	
No	241 (18.5)	17 (6.1)	
Received neoadjuvant therapy? No. (%)			.283
Yes	111 (8.5)	30 (10.8)	
No	1,192 (91.5)	249 (89.2)	
Grade, No. (%)			**< .001**
I low grade (well differentiated)	572 (43.9)	42 (15.1)	
II intermediate grade (moderately differentiated)	587 (45.0)	172 (61.6)	
III high grade (poorly differentiated)	126 (9.7)	65 (23.3)	
Unknown	18 (1.4)	0 (0)	

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TABLE 2. Characteristics of the Patients Older Than 65 Years Receiving or Not Receiving ODX (continued)

Characteristic	No ODX (n = 1,303)	Received ODX (n = 279)	*P*
ODX risk group, No. (%)			NA
High	NA	52 (18.6)	
Intermediate		156 (55.9)	
Low		70 (25.1)	
Missing		1 (0.4)	
ODX numeric			
Mean (SD)	NA	17.8 (10.2)	NA
Median (min, max)		17.0 (0, 54.0)	
Missing, No. (%)	1 (0.4)		

NOTE. All *P* values apply to the intercategory comparisons unless otherwise specified. Comparison across groups was based on the Fisher's exact or χ^2 test for categorical and discrete variables and the Wilcoxon rank-sum test for continuous variables. Bold indicates significance at $P < 0.05$.
Abbreviation: ODX, OncotypeDX.
[a]T1 *v* T2, T3 *v* T4.
[b]N0 *v* N1 *v* N2 *v* N3 *v* Nx.

in the RS and stage distribution and no difference in the subset older than 65 years (*data not shown*). Although RS testing on core biopsy specimens to determine the choice of neoadjuvant treatment is not routine, the data collection window included the height of the COVID-19 pandemic, when clinical guidelines supported the use of the genomic tools to inform treatments amidst service disruptions and delays and the desire to avoid cytotoxic chemotherapy amid the pandemic.[25,26]

DISCUSSION

We performed a formal, systematic analysis of patterns of RS testing at a large academic institution to understand the pattern of OncotypeDX utilization in the real life and try to identify potential areas to implement previously established reflex criteria. We sought to understand utilization in actual clinical practice and elucidate potential areas where reflex criteria could be refined. Two drivers of testing outside predefined criteria were identified: the age limit for reflex testing and prognostic pathological features of stage I tumors. Grouped together, these encompassed more than three quarters of all ad hoc, case-by-case (non-reflex) RS tests (n = 469 of 600), suggesting potential areas of actionability. Notably, clinical teams recommended chemotherapy at the same rate in all the cohorts (15%-20% of patients tested), including in the older population, suggesting equal clinical value and actionability to RS testing in each cohort, for patients deemed fit to receive chemotherapy. We believed that the findings are sufficiently robust to review our internal practice. We aligned the testing criteria with the eligibility within the pivotal clinical trials of validation of RS, by extending testing to pT1c G1 tumors but not for pT1b pN0 G2-3 cancers, for which the absolute benefit of chemotherapy is still unclear (Appendix Table A1).

Most importantly, we recognized that the reflexive age cutoff of 65 years was leading to insufficient RS testing in older patients. Age was the most common single reason for not pursuing reflex testing. Yet, when older patients did have RS testing, adjuvant chemotherapy was recommended at the same rate as the study group as a whole. This implies that the age cut off of 65 years could result in delays of the treatment start in some older patients eligible for clinically indicated chemotherapy. The practical challenge to reflex testing in women older than 65 years is that the Centers for Medicare & Medicaid Services (CMS) has implemented a 14-day rule: The CMS Date of Service Regulation applies to genomic tests when performed on samples obtained during inpatient (ie, hospital-based as with surgery), but not outpatient, interventions that might be even more common in older patients.[18] Accordingly, the cost for the molecular test will be bound to the costs for hospitalization if the test is ordered within 14 days from the sampling; beyond 14 days, Medicare can be billed directly from laboratories. Ultimately, the CMS regulation represents a potential structural barrier for a surgery-triggered RS request among older patients with BC receiving inpatient surgical care, as well as a reason for delays in adjuvant chemotherapy start.

Guidelines from multinational groups focused on the care of older cancer patients emphasize that treatment restrictions and limitations based on chronological age alone are not appropriate[24] and favor tailored treatment approaches among older patients with ER-positive BC so as to right-size care in light of tumor risk, comorbid conditions, and patient preferences.[27] Accordingly, the International Society of Geriatric Oncology and the European Society of Breast Cancer Specialists[24] note that adjuvant chemotherapy should not be contraindicated ab initio in women older than 65 years, but rather that the decision should be framed in a multidimensional, oncogeriatric approach and informed additionally by tools capable to anticipate the risk of treatment-emergent toxicities.[28,29] Among them, Cancer and Aging Research Group-Breast Cancer toll has been developed specifically for

elderly patients with early BC.[30] Still, there remain relatively few data on the utility of genomic tools to orient treatment decisions in older patients. Evidence on adjuvant chemotherapy is mixed among older patients with ER-positive BC. In TAILORx, 27% of the population with a RS of 11-25 receiving chemotherapy were aged 61-70 years and only 4% were older than 71 years.[31] In RxPONDER, the proportions were 30.6% and 11.6%, respectively.[7] Registry-based studies suggest that adjuvant chemotherapy achieves an improvement in overall survival (OS) up to 33% (hazard ratio, 0.67; 95% CI, 0.48 to 0.93; $P = .02$) for node-positive cancer in women older than 70 years, [32] albeit not consistently reproduced in other series.[33] Recent evidence from the prospective randomized trial ASTER70 using the 97-gene genomic-grade-index to identify high-risk cancers in patients older than 70 years did not demonstrate an OS benefit with adjuvant chemotherapy, although numerical trends may suggest improved outcomes at longer follow-up and among those who received their assigned therapy.[34] These trials are all affected by the inherent clinical bias of only recommending chemotherapy to older patients in greatest need of treatment and highlight the importance of comprehensive prognostic information, including with the use of validated genomic tools. At the same time, we recognized from clinical experience that chemotherapy can affect near-term patient vitality and quality of life particularly among older patients and that comorbid conditions affecting longevity are more prevalent in geriatric patients than others with BC. Chemotherapy can significantly affect quality of life in elderly women, although most patients recover to their basal functioning level within 18-24 months, after a nadir at 6 months.[35,36] In addition, a careful assessment of the competing comorbidities can better outline the overall prognosis of patients: The presence of severe comorbidity burden is associated with significantly higher cancer-related mortality in patients older than 70 years.[37] Accordingly, policy restraints that apply to patients, on the basis of the age, alone are not supported by the evidence and can exacerbate disparities through systematic exclusion from best clinical practice, or delays in treatment start, and are insufficiently patient-centric while assuming all elderly patients are the same.[38]

As noted, on the basis of this internal review, we have broadened the criteria for RS testing to include older patients and selected patients with pT1b G2-3 and pT1c G1 tumors. We also believe that changing reimbursement policies for RS testing in patients older than 65 years would mitigate some of the disparities in RS testing and yield a timely delivery of curative treatments. A potential solution to enhance consistent equitable decisions would be to regulate CMS reimbursements for RS testing on inpatient breast surgery samples in the same way as outpatient procedures.[39] A careful re-evaluation of the 14-day CMS rule for RS testing from inpatient interventions could accelerate progress toward older patients' access to gene profiling and more timely initiation of chemotherapy, when indicated. On the basis of our experience, we now offer RS testing to patients younger than 72 years, based on the upper tertile of age for patients older than 65 years getting tested in our institution and cognizant of the results from ASTER70. With patients, we acknowledge the limited evidence on chemotherapy benefits and the impact of chemotherapy treatment on quality of life, recurrence risk, and OS informed by their overall health.[34,38,40]

We acknowledge several limitations of this study. It lacks long-term follow-up and cannot define whether the additional RS ordering achieved the optimal clinical decision in every case. We could not identify how many patients did not access the test for an issue of reimbursement and what proportion received a recommendation against chemotherapy on the basis of competing comorbid conditions. The CMS testing policy could affect the time to adjuvant chemotherapy start more than the likelihood for older patients to be tested because it is our internal practice to review the indication to test older patients, as informed by oncogeriatric variables. However, it is unlikely that more than two thirds of our patients aged between 65 and 72 years did not receive RS testing owing to competitive comorbidities or ineligibility on the basis of a significant clinical frailty alone. Thus, we feel that policy and guidance restraints have been a barrier to more effective diagnostic testing and treatment individualization among older patients with BC, a finding supported in the literature.[41,42] Our QI exercise is framed within a PDSA cycle approach,[19] with a follow-up planned in 2 years to analyze the clinical pattern of RS utilization and related chemotherapy prescription. The effort will also include a reassessment of the time from surgery to initiation of chemotherapy on the basis of the new criteria to understand the impact of reflex testing patterns on treatment delays of >8 weeks, most likely to be detrimental on the outcomes.

In conclusion, the QI analysis at DFCI BOC evaluating the 2019-2021 utilization pattern of OncotypeDX identified discrete recurrent instances of testing outside the criteria internally lastly updated in 2019. With the present focused analysis on the older population, we identified potential structural barriers to the routinary testing of the elderly population and identified gaps in the literature, especially to inform the clinical decision making. On the basis of these data, we have revised our standard practice to include multidimensional geriatric assessment to trigger reflex RS testing in patients aged 65-72 years, including as part of a dedicated program at DFCI for patients older than 70 years. Ongoing study to keep the recommendations updated and locally relevant are included in the QI efforts, continuously informed by emerging evidence.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Identifying Patterns and Barriers in OncotypeDX Recurrence Score Testing in Older Patients With Early-Stage, Estrogen Receptor–Positive Breast Cancer: Implications for Guidance and Reimbursement

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APPENDIX

TABLE A1. Updated Consensus Statements for Surgeon-Triggered OncotypeDX Reflex Testing

Reflex Testing Criteria	
2019-2021	2022-2024
Age ≤65 years, AND pT1c G2-3 pN0 tumors grade II-III pT2 pN0 tumors of any grade pT1-T2 pN1 tumors of any grade pT3 pN0-N1 tumors any grade Pre- and postmenopausal status	Patient's age ≤65 years, AND pT1c-T3, G1-3, pN0-1 tumors Pre- and postmenopausal status
Additional settings to consider RS testing	
Per physician's choice	Recurrent scenarios Patients aged 66-72 years pT1b pN0 G2-3 Per physician's choice

Abbreviation: RS, recurrence score.