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The Impact of Genomic Testing on the Recommendation for Radiation Therapy in Patients With Ductal Carcinoma In Situ: A Prospective Clinical Utility Assessment of the 12-Gene DCIS Score™ Result

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Background and Objectives: Twenty percent of breast cancers are ductal carcinoma in situ (DCIS), with 15–60% having a local recurrence (LR) after surgery. Radiotherapy reduces LR by 50% but has not impacted survival. The validated Onco*type* DX® 12-gene assay (DCIS Score) provides individualized 10-year LR estimates. This is the first study to assess whether DCIS Score impacts physicians' recommendations for radiation.
Methods: Ten sites enrolled women (9/2012–2/2014) with DCIS eligible for breast-conserving therapy, excluding patients with invasive carcinoma and planned mastectomy. Prospective data collected included clinicopathologic factors, DCIS Score assay, and treatment recommendation before and after the assay result was known.
Results: In 115 patients (median age: 61 years; 74.8% postmenopausal), median DCIS size was 8 mm; 20% were nuclear grade 1, 46.1% grade 2; 64.4% reported necrosis. 86.1% were ER+, 79.1% PR+ (immunohistochemistry assay). Median DCIS Score: 29 (range: 0–85). Pre-assay, 73% (95%CI: 64.0–80.9%) had radiotherapy recommendations vs. 59.1% (95%CI: 49.6–68.2%) post-assay ($P = 0.008$). Physicians rated DCIS Score as the most impactful factor in planning treatment.
Conclusions: The radiotherapy recommendation changed from pre-assay to post-assay 31.3% (95%CI: 23.0–40.6%) of the time—a clinically significant change. This study supports the clinical utility of the DCIS Score and indicates that the test provides additional, individualized information on LR risk.
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KEY WORDS: **ductal carcinoma in situ; breast cancer; clinical utility; genomics; recurrence risk; adjuvant radiotherapy**

INTRODUCTION

Noninvasive breast cancers include both lobular carcinoma in situ (LCIS) and ductal carcinoma in situ (DCIS), referred to as stage 0 breast cancers [1]. The incidence of DCIS has increased over the past 30 years with routine mammography screening [2]. The rate of invasive breast cancer and related death has not increased in incidence over the same time period [2]. DCIS now comprises 20% of all breast cancers diagnosed by mammography in the United States [3,4].

Treatment of DCIS aims to prevent the occurrence of invasive disease and any local recurrence (LR) of DCIS. In most patients, breast-conserving therapy is an appropriate treatment option [1]. LR rates with surgery alone range from 15% to 60%; half of which are invasive [1]. Adding whole breast irradiation (XRT) following excision reduces the relative LR risk by approximately 50% but has not been shown to impact survival [1,5]. Since studies to date have not identified any subgroups that did not receive some benefit from XRT [5], many patients—with low likelihood of recurrence—continue to be treated with XRT. LR estimates have historically been based on clinicopathologic factors. For instance, young age or higher tumor grade are considered to be associated with higher LR risk, and generally treated more aggressively. However, clinicopathologic factors can only serve as a proxy for the biologic aggressiveness of the disease; an optimal method for determining whether XRT is necessary in an individual patient has not been established.

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The Oncotype DX® Breast Cancer assay for DCIS (DCIS Score) is the first multigene expression assay that generates individualized estimates of 10-year risk of any LR (DCIS or invasive carcinoma) and invasive LR [6]. The DCIS Score is based on the biology of the tumor and is generated from an algorithm that includes 12 of the 21 genes in the Oncotype DX invasive assay. The DCIS Score result and its association with LR was clinically validated in the Eastern Cooperative Oncology Group (ECOG) E5194 study that included patients with DCIS who had been selected for observation (no XRT) after surgical excision based on characteristics associated with a low LR risk [6]. The study showed that there was a range of DCIS scores within the cohort and further categorized patients into risk groups of low, intermediate, or high LR risk [6]. While menopausal status and tumor size were prognostic, other measures (e.g., grade, comedo necrosis, and margin width) were poor predictors of LR, and there was a range of DCIS Score results across any of these measures, indicating that these measures were unable to "predict" the score. Additionally, the DCIS Score was significantly associated with the risk of invasive LR, separate from the overall LR risk [6].

The ability of a given test result to influence patient management is referred to as "clinical utility" [7]. This study is the first to address clinical utility of the DCIS Score assay, initiated shortly after the assay became commercially available. The study aim was to understand the clinical utility of the DCIS Score by assessing the impact of the DCIS Score result on the recommendation for XRT in patients after primary surgical excision of their tumors.

MATERIALS AND METHODS

Study Design and Setting

In this prospectively enrolled observational study, the data were collected from medical records of patients with DCIS at 10 cancer centers in the U.S.: 5 Rocky Mountain Cancer Centers (RMCC), CO; Surgical Clinic of Central Arkansas (SCCA), AR; The Christ Hospital (CH), OH; the University of California-San Francisco (UCSF), Helen Diller Cancer Center, CA; University of Maryland St. Joseph Medical Center (UM), MD; and St. Elizabeth Healthcare (SEH), KY. Study sites were selected based on volume of DCIS patients and geographic location. The majority of these cancer centers were community practices and two were academic centers. The study was approved by Institutional Review Boards for each site.

Patient Population

Each center identified eligible patients from among actively treated patients at the site. Patients enrolled in the study were ≥18-year-old women with histologically proven DCIS eligible for breast-conserving therapy, had surgical excision pathology report available, and had a DCIS Score ordered but the result not yet available. Patients for whom the initial treatment recommendation was mastectomy were excluded, as mastectomy would not be accompanied by XRT. Patients were also excluded if they had LCIS without DCIS or any evidence of invasive carcinoma.

Data

An electronic case report form (eCRF) was designed in conjunction with representative participating physicians (MA, MJS). To ensure consistent data abstraction across sites, all abstractors were trained in applying inclusion/exclusion criteria and data entry. Data were collected using a secure and password-protected web-based application (http://www.project-redcap.org/; supported by grant UL1TR000011 from NCATS/NIH). Trained data coordinators at each site reviewed patient records and prospectively collected data using the eCRF at two different points: once before and once after the DCIS Score result became known to the treating physician. Data collected at the pre-assay assessment included patient demographics, pathology data, physician treatment recommendations, and physician estimates of the 10-year risk of LR (DCIS or invasive cancer). Post-assay data were collected after the DCIS Score report was issued and included the DCIS Score result, physician treatment recommendations post-assay, physician estimates of the 10-year risk of LR, and ratings of the impact of factors on physician treatment recommendations. Regular data quality assurance included checks for content, inconsistencies, and missing fields. De-identified data from each site were combined into a single analytic database.

Statistical Analysis

The sample size was estimated assuming that a change of 15% (the midrange of 10–20% proposed by clinical experts) would be a clinically significant change. Using the Clopper–Pearson exact confidence intervals (CIs), we calculated a sample size of 110 would be required to provide adequate precision in estimation of the change rate, assuming that the true change rate was 15%. We estimated that 10% of patients would be not evaluable (e.g., no DCIS Score result, insufficient tumor, patient withdrawal, etc.); therefore, the final enrollment target was 122.

The analytic sample consisted of all eligible patients for whom pre- and post-assay treatment recommendations were recorded. All analyses are descriptive unless otherwise specified. Data are presented as mean (standard deviation: SD) or median (range) for continuous variables, and as counts and percentages for categorical data. Results are presented for all patients and within pre-defined DCIS Score result risk groups: low (<39), intermediate (39–54), high (≥55). The pre- and post-assay treatment recommendations are reported as the proportion of patients with XRT. McNemar's test was used to compare the pre- and post-assay proportions. Paired *t*-tests were used to compare pre- and post-assay physician estimates of LR. $P < 0.05$ was considered statistically significant.

The primary endpoint was the change in XRT recommendation from pre-assay to post-assay (yes vs. no). We defined change in XRT recommendation as having XRT recommended pre-assay and no XRT recommended post-assay (or the reverse), calculated as the proportion of patients with a change in recommendation divided by all patients eligible for analysis. Two-sided 95% Clopper–Pearson Exact CIs were calculated for percent change in XRT recommendation. A change of 15% was considered a clinically significant impact. All statistical analyses were performed using SAS® version 9.2 (SAS Institute, Cary, NC).

RESULTS

A total of 122 patients were enrolled at 10 centers from September 2012 to February 2014. Of these, seven patients were ineligible and were excluded from the analysis: four patients had no DCIS Score result, one had mastectomy planned, one declined DCIS Score testing, and one was determined not to have DCIS on the final pathology report. The 115 evaluable patients were enrolled by five radiation oncologists (48 patients; 41.7%) and five surgeons (67 patients; 58.3%). Forty-eight patients were enrolled at five RMCC sites, 28 patients at SCCA, 15 patients at CH, 9 patients at UCSF, 9 patients at UM, and 6 patients at SEH.

Clinical and pathologic features are in Table I: median patient age was 61 years (range: 36–83), with 15.7% of patients <50 years old; Ethnicity: 77% white, 8.7% black, 6.1% Asian, 4.3% Hispanic/Latino and 7.8% other or unknown race (more than one ethnicity could be selected); 74.8% of patients were postmenopausal. The median size of DCIS was 8 mm (range: 1–115). Twenty percent of patients had nuclear grade of 1, 46.1% had a grade 2, and 33.9% had a grade of 3. Necrosis was reported as present in 64.4%, with 28.7% described as focal. Forty-

TABLE I. Patient Characteristics, Tumor Characteristics, and Oncotype DX DCIS Score Results

		Total N = 115
Age (years)	n, mean (SD)	115, 60.1 (10.2)
	median (range)	61 (36–83)
<50 years	n (%)	18 (15.7)
50–59 years	n (%)	38 (33.0)
60–69 years	n (%)	41 (35.7)
≥70 years	n (%)	18 (15.7)
Postmenopausal (yes)[a]	n (%)	86 (74.8)
DCIS size (greatest dimension using gross and microscopic evaluation in mm)	n, mean (SD)	115, 13.6 (15.7)
	median (range)	8 (1–115)
≤5	n (%)	42 (36.5)
6–10	n (%)	27 (23.5)
11–20	n (%)	23 (20.0)
>20	n (%)	23 (20.0)
Nuclear grade		
Grade I (low)	n (%)	23 (20.0)
Grade II (intermediate)	n (%)	53 (46.1)
Grade III (high)	n (%)	39 (33.9)
Necrosis		
Not identified	n (%)	25 (21.7)
Not reported	n (%)	16 (13.9)
Present, central (expansive "comedo" necrosis)	n (%)	41 (35.7)
Present, focal (small foci or single cell necrosis)	n (%)	33 (28.7)
Distance from closest margin (mm)	n, mean (SD)	113, 4.2 (4.2)
	median (range)	3 (0–20)
Missing	n (%)	2 (1.7)
<1	n (%)	11 (9.6)
1–1.9	n (%)	27 (23.5)
2–2.9	n (%)	14 (12.2)
3–4.9	n (%)	21 (18.3)
5–9.9	n (%)	20 (17.4)
≥10	n (%)	20 (17.4)
Distance from closest margin <3 mm	n (%)	52 (46.0)

SD, standard deviation; DCIS, ductal carcinoma in situ; ER, estrogen receptor; PR, progesterone receptor.

[a]Menopause, the permanent cessation of menses, status is determined based on any of the following criteria: (1) prior bilateral oophorectomy; (2) age <60 years and amenorrheic for ≥12 months in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression and FSH and estradiol in the postmenopausal range; (3) if taking tamoxifen or toremifene, and age <60 years, then FSH and plasma estradiol level in postmenopausal ranges (NCCN 2015).

six percent of patients (n = 52) had a distance from closest margin <3 mm. Estrogen (ER) and progesterone (PR) receptor testing by immunohistochemistry assay were positive in 86.1% and 79.1%, respectively. ER and PR testing by RT-PCR were positive in 88.7% and 80.9%, respectively. Mean DCIS Score was 30.7 (SD: 22.1) and median was 29, ranging from 0 (n = 11) to 85 (n = 1) (Fig. 1). Distribution of scores: 62.6% (n = 72) low; 20.9% (n = 24) intermediate; 16.5% (n = 19) high. Pre-assay median physician estimate of 10-year LR risk was 20% (range: 6–60%) for any (DCIS or invasive cancer), and for invasive cancer was 10% (range: 3–25%). Post-assay median physician estimate of 10-year LR risk was 16% (5–50%) for any (DCIS or invasive cancer) and 7% (2–25%) for invasive cancer.

Pre-assay, there were 84 patients with recommendation for XRT (73%; 95%CI: 64.0–80.9%). Twenty-six patients had a change to no XRT recommendation post-assay (22.6%; 95%CI: 15.3–31.3%), reflecting a 30.9% change (Fig. 2A). After incorporating the results of the DCIS Score, the percentage of patients who were recommended XRT dropped to 59.1% (95%CI: 49.6–68.2%), a significant reduction from pre- to post-assay ($P = 0.008$) (Fig. 2A). Conversely, of 31 patients with pre-assay recommendation for no XRT (27%; 95%CI: 19.1–36%), 10 patients had a change to recommendation for XRT post-assay (8.7%; 95%CI: 4.2–15.4%)—a 32.2% change. Overall, 31.3% (95%CI: 23–40.6%) of patients had a change in recommendation for XRT from pre-assay to post-assay. The change in XRT recommendation was most pronounced in the DCIS Score low-risk group ($P < 0.001$) and was also significant in the DCIS Score high-risk group ($P = 0.014$) (Fig. 2B).

Additional analyses revealed mean physician estimate of 10-year LR risk of any cancer decreased in the low DCIS Score result group from 19.9% to 14.3% ($P < 0.001$), and there was a trend toward an increase in the high DCIS Score result group from 23.2% to 27.9% ($P = 0.057$) (Fig. 2C). Similarly, mean physician estimate of 10-year LR of invasive cancer decreased in the DCIS Score low-risk group from 10.1% to 6.2% ($P < 0.001$) and insignificantly increased in the DCIS Score high-risk group from 13.1% to 15.2% ($P = 0.124$). Mean physician estimates of any 10-year LR (23.1 to 22.2%) and LR of invasive cancer (11.8 to 11.0%) in the DCIS Score intermediate risk group were similar from pre- to post-assay (both $P > 0.3$). Exploratory analyses revealed there was a range of DCIS Score results within the categories of clinicopathologic factors, e.g., age, margin, size, nuclear grade (Fig. 3). Physicians also rated the impact of various factors on their treatment recommendations on a scale of 1 (no or minimal impact on recommendation) to 5 (mostly or entirely responsible for recommendation). The DCIS Score was rated most impactful (median: 5), followed by pathologic features (median: 4), patient preference (median: 3), patient age (median: 3), patient comorbidities (median: 2), recommendation from a multidisciplinary physicians group (median: 2), and from an individual physician (median: 1).

DISCUSSION

The DCIS Score result was clinically validated in a cohort of patients from the E5194 study and showed a strong and independent association with any LR and invasive LR [6]. This is the first genomic test that provides an individualized likelihood of LR for DCIS patients and differentiates patients with a lower LR risk from those with higher risk. Our study revealed the use of the DCIS Score leads to clinically significant changes in XRT recommendation, indicating that the DCIS Score result adds value beyond traditional clinicopathologic factors.

Recommendations for XRT changed in 31.3% in patients after the DCIS Score was obtained, with XRT recommended for 73.0% of the patients pre-assay compared to 59.1% post-assay. Changes in XRT recommendation were concentrated in patients with low and high DCIS Score results. Almost all (25/27) changes in patients with low scores involved the elimination of previously recommended XRT, while all (6/6) changes in patients with high scores involved the addition of XRT where none was previously recommended. XRT was ultimately recommended for all patients with high DCIS Score results, compared with 36.1% of patients with low scores.

Prior clinical utility studies of genomic tests in cancer have demonstrated comparable changes in treatment recommendations. Oratz et al. [8] used data from patient charts to demonstrate that knowledge of a 21-gene assay changed treatment recommendations and eventual treatment in 21% and 25% of ER-positive lymph node-negative breast cancer patients, respectively. A physician survey showed that medical oncologists changed their adjuvant treatment recommendation in 70 of 138 patients (51%) after obtaining the 21-gene Recurrence Score assay result for patients with lymph node-positive, ER-positive breast cancer [9]. Another physician survey on the clinical

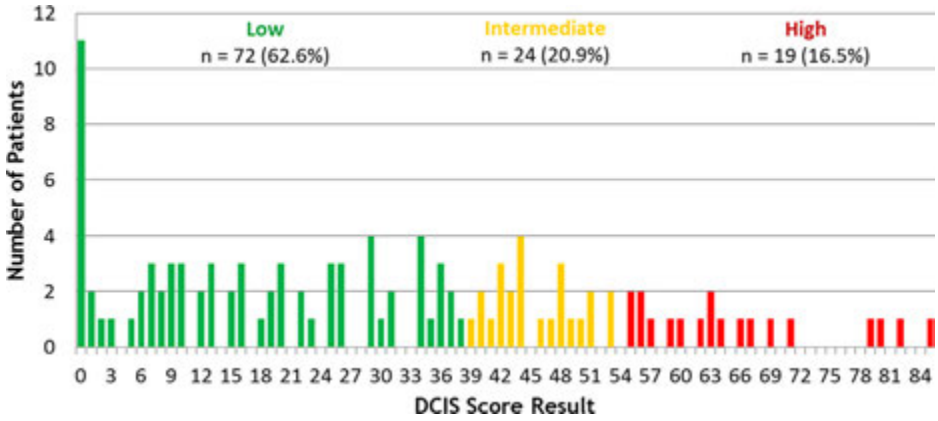

Fig. 1. Range of Onco*type* DX for ductal carcinoma in situ (DCIS) score results.

utility of a 14-gene quantitative RT-PCR test in patients with stage I–III non-small-cell lung cancer revealed that physician chemotherapy recommendations changed due to the assay results in 37 of 120 patients (30.8%, 95%CI: 22.7–39.9%) [10]. A survey of medical oncologists, who ordered the Onco*type* DX 12-gene colon cancer Recurrence Score for their stage II colon cancer patients, revealed that 29% of treatment recommendations changed after the assay [11]. In the second prospective multicenter study of the impact of the 12-gene colon cancer assay results on treatment recommendations in stage II colon cancer patients, recommendations changed for 45% (95%CI: 36–53%) patients, with intensity decreasing for 33% and increasing for 11% [12]. Altogether, the change rate in this study is consistent with prior clinical

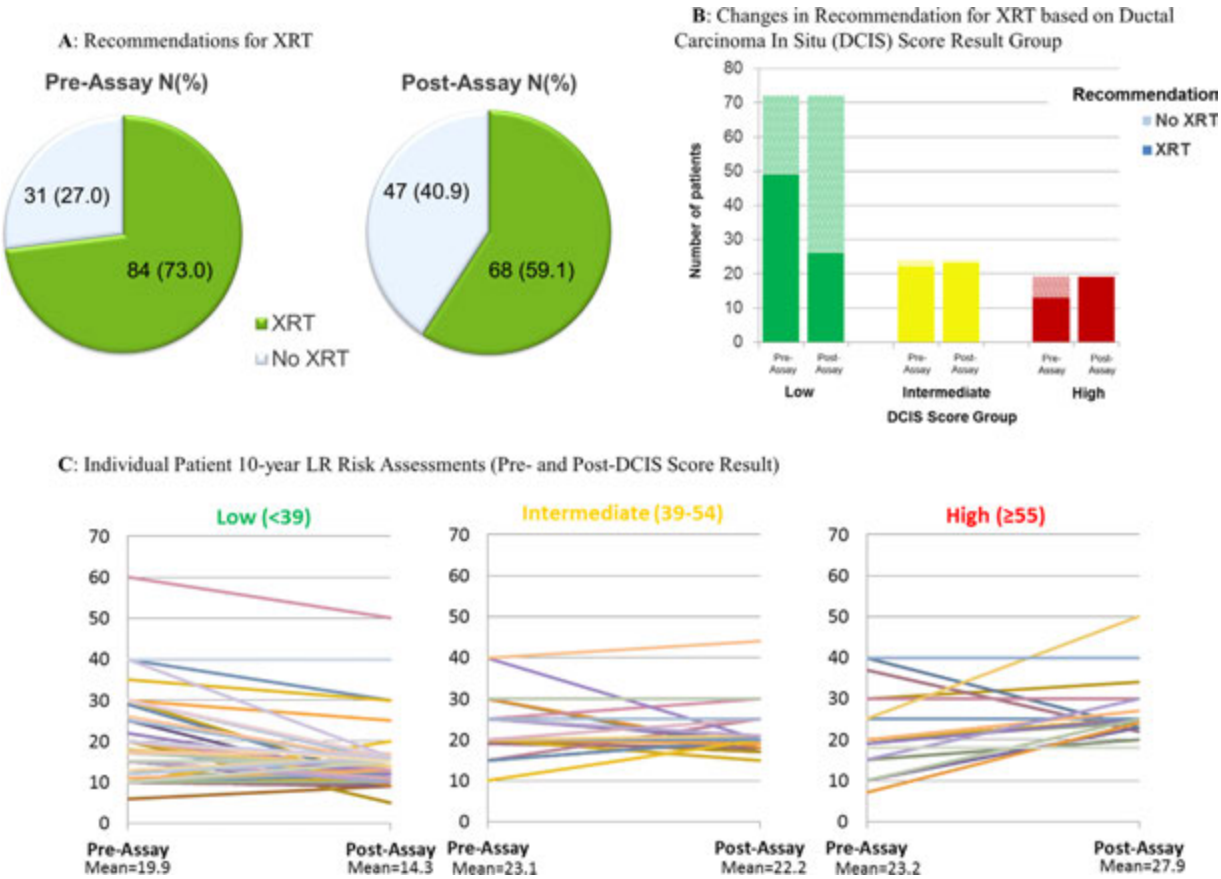

Fig. 2. Recommendations for radiotherapy (XRT) and individual patient 10-year local recurrence risk assessments. **A**: Recommendations for XRT. **B**: Changes in recommendation for XRT based on Ductal Carcinoma In Situ (DCIS) Score Result Group. **C**: Individual patient 10-year LR risk assessments (pre- and post-DCIS score result).

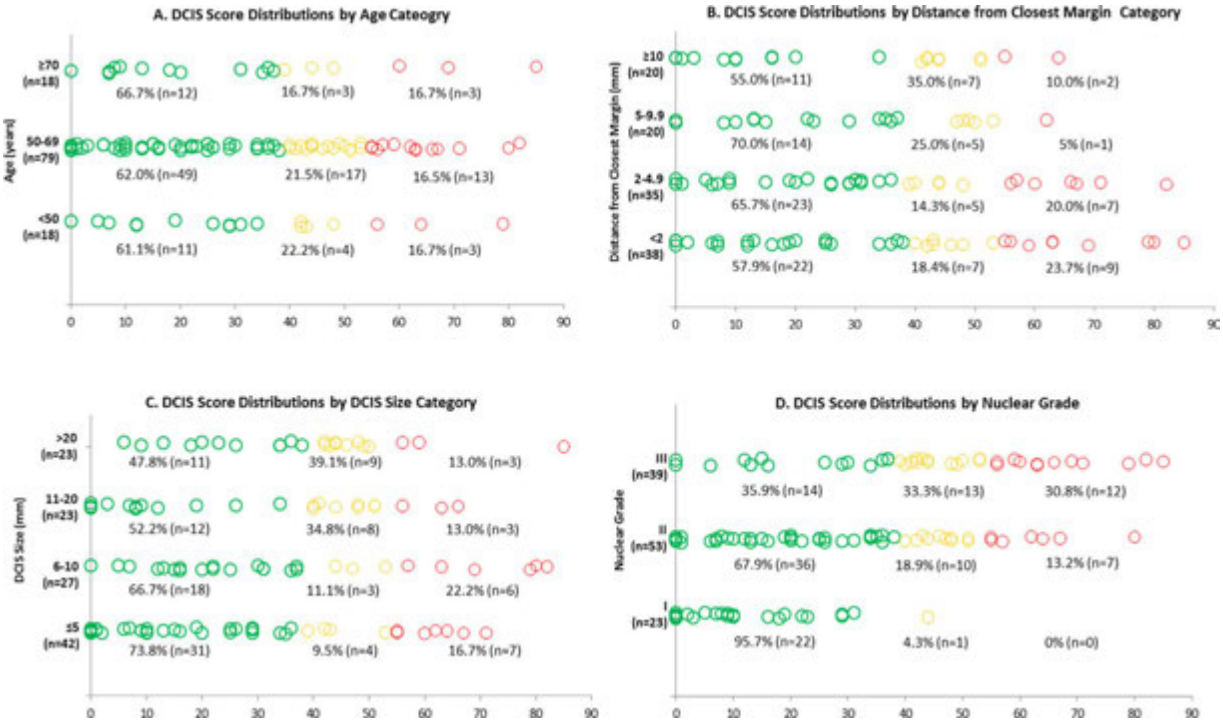

Fig. 3. Figure 3. Distribution of the ductal carcinoma in situ (DCIS) score result by clinical and pathologic (CP) factors. **A**: DCIS score distributions by age category. **B**: DCIS score distributions by distance from closest margin category. **C**: DCIS score distributions by DCIS size category. D: DCIS score distributions by nuclear grade.

utility studies of genomic assays and supports the use of such tests by clinicians when planning treatment recommendations for patients with cancer.

Physicians gave the highest importance to the DCIS score in their treatment recommendations compared with pathologic features, patient preference, patient age, comorbidities, or consultations with other physicians. A prior study on the clinical utility of another assay, the 21-gene assay, used in patients with ER-positive, lymph node-negative breast cancer, reported weak correlation between the assay and both age and tumor size and a moderate correlation between the assay and tumor grade [8]. Considering prior study findings on the topic, our study demonstrates that physicians more frequently identify the DCIS Score result with higher importance than other prognostic measures of risk, such as traditional clinicopathologic factors, in influencing their recommendations.

Our study demonstrated the mean physician estimate of any 10-year LR decreased in the low DCIS Score result group from 19.9% to 14.3% ($P < 0.001$) and trended toward an increase in the high DCIS Score result group from 23.2% to 27.9% ($P = 0.057$). This suggests that the DCIS Score result adds to the physician LR estimates and underscores the importance of understanding the underlying tumor biology as well as providing a more individualized estimate of 10-year risk of invasive LR. This observation is further exemplified by the change in physician estimates of LR risk pre- and post-assay, which decreased in patients with low DCIS Score results and increased in patients with high DCIS Score results.

Additionally, there was a range of DCIS Score results across the clinicopathologic characteristics, indicating that these factors alone could not predict the DCIS score. The DCIS Score reflects the individual patient's underlying tumor biology and provides a quantitative estimate of the risk of any LR and invasive LR. Estimates based on the traditional clinicopathologic factors can only provide group estimates of any LR but not specific estimates of invasive LR risk. The use of the DCIS Score in low-risk patients may provide physicians with sufficient evidence to tailor treatment and potentially recommend foregoing XRT in patients with a low risk of LR.

Strengths and Limitations

This is the first clinical utility study of the recently commercially available Onco*type* DX Breast Cancer assay for DCIS. A major strength of this study is the prospective study design, which eliminates recall bias in physician treatment decisions. The study also reports up-to-date results collected from a geographically dispersed sample of patients, adequately powered to detect changes in the primary outcome.

The primary limitation of this study is that, by design, this study is an analysis of how decisions are made and the impact of the DCIS Score result on the treatment recommendation, but not an assessment of whether those decisions were made appropriately. As such, the study does not provide insight into whether any of the other clinical or pathologic variables related to cancer outcomes, such as local failure, were weighed more or less heavily on the treatment recommendation. A utility study is not designed to assess whether any such decision-making is clinically valid.

A secondary limitation of this study was the collection of treatment recommendations, rather than actual treatment. We have no reason to believe treatment recommendations would change after the data were collected, but we could not confirm this with the current study design. As with any study that is observational or uncontrolled, there are limitations and possible biases that cannot be adjusted for in the analysis. There is likely a selection bias since the sample was not random—e.g., patients with a perceived lower LR risk were approached. Data were collected at centers with a high volume of DCIS patients and focused on breast surgeons and radiation oncologists. The study physicians were early adopters of the assay but our results are consistent with prior findings [8–12]. Nevertheless, the range of

clinicopathologic features and the pre-assay recommendation for XRT of 73% reported in our study support the representativeness of our cohort, based on current estimates that about 70% of patients with excision receive XRT.

CONCLUSIONS

The current challenge facing patients and physicians with DCIS is how to assess the risk of LR, which will inform treatment decisions regarding XRT. The DCIS Score result is the first clinically validated genomic assay that provides an individualized estimate of the 10-year risk of any LR and invasive LR. The overall change rate of 31.3% (95% CI: 23–40.6%) in XRT recommendation from pre-assay to post-assay in this study is both statistically significant and clinically meaningful. The use of this test by physicians in management of patients with DCIS may aid in making treatment recommendations that reduce both under- and overtreatment with XRT by incorporating information based on patients' individual underlying tumor biology and making the treatment of DCIS truly personalized.

AUTHORS' CONTRIBUTION

Michael Alvarado, Dennis L. Carter, J. Michael Guenther, James Hagans, Rachel Y. Lei, Charles E. Leonard, Jennifer Manders, Amy P. Sing, Michael S. Broder, Dasha Cherepanov, Eunice Chang, Marianne Eagan, Wendy Hsiao, and Michael J. Schultz had substantial contributions to the conception or design of the study; or the acquisition, analysis, or interpretation of data for the study; and drafting of the manuscript or revising it critically for important intellectual content. All 14 co-authors gave their final approval of the manuscript submitted for publication at *JSO*.

DISCLAIMERS

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