Clinical Utility of the 12-gene DCIS Score™ Result: Impact on Treatment Recommendations

Alvarado M,[1] Carter D,[2] Guenther JM,[3] Hagans J,[4] Lei R,[2] Leonard C,[5] Manders J,[6] Sing AP,[7] Broder MS,[8] Chang E,[8] Cherepanov D,[8] Hsiao W,[9] Schultz M,[10] On behalf of the patients participating in the study

[1]University of California, San Francisco, CA; [2]Rocky Mountain Cancer Centers, Aurora, CO; [3]St. Elizabeth Healthcare, Edgewood, KY; [4]The Surgical Clinic of Central Arkansas, Little Rock, AR; [5]Rocky Mountain Cancer Centers, Littleton, CO; [6]The Christ Hospital, Cincinnati, OH; [7]Genomic Health, Inc., Redwood City, CA; [8]Partnership for Health Analytic Research, LLC , Beverly Hills, CA; [9]University of Southern California, Los Angeles, CA; [10]University of Maryland St. Joseph Medical Center, Towson, MD

Background

- The incidence of ductal carcinoma *in situ* has dramatically increased over the past 30 years with the advent of routine mammography starting at age 40 years for most women.[1]
- The rate of invasive disease and breast cancer related death, however, has been relatively stable and not increasing in incidence over the same time period.[1]
- DCIS now accounts for approximately 20% of all breast cancers in the US.[2]
- Local recurrence (LR) rates with surgery alone range from 15–60%; about 50% of which are invasive.[3]
- Radiation therapy (XRT) reduces LR by 50% but has not been shown to impact overall or disease-free survival.[4]
  - None of the studies have been able to identify a patient group that did not derive benefit (i.e. risk reduction) with XRT.
- Clinicians and patients must decide between multiple treatment options including breast conserving surgery, mastectomy, partial or whole breast XRT, and hormonal manipulation.[2]
- The decision around recommending XRT is dependent on an assessment of LR risk with an assumption that around half of those recurrences will be invasive disease.
- Additionally, while reduction of LR, particularly invasive LR, is important, there are other goals of therapy that are taken into consideration, such as the cosmetic outcomes and the side effects from XRT.
- Currently, LR risk is estimated based on clinicopathologic factors and provides an average risk derived from population studies.
  - For example, younger patients or patients with higher grade DCIS are considered higher risk and are generally treated more aggressively.
- The *Oncotype* DX® assay for DCIS is the first molecular assay that gives additional independent and individualized estimates of 10-year risk of any LR and invasive LR.[5]
- The DCIS Score result was clinically validated in a cohort of patients from the ECOG 5194 study who were selected for observation (no XRT) after surgical excision based on characteristics conferring a low risk of LR.
- The DCIS Score results showed that in this group of patients, there was a range of scores and patients who could be categorized at low, intermediate, or high risk of LR based on the biology of the disease as measured by the expression of 12 of the 21 genes in the *Oncotype* DX invasive assay (7 cancer related genes and 5 reference genes).[5]
- While age and 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 the measures, indicating that these measures were unable to "predict" what the score result would be.

Figure 1. The DCIS Score Genes

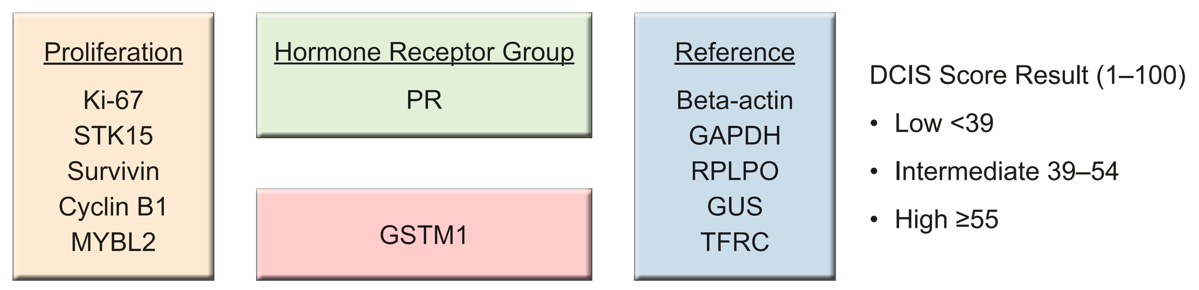
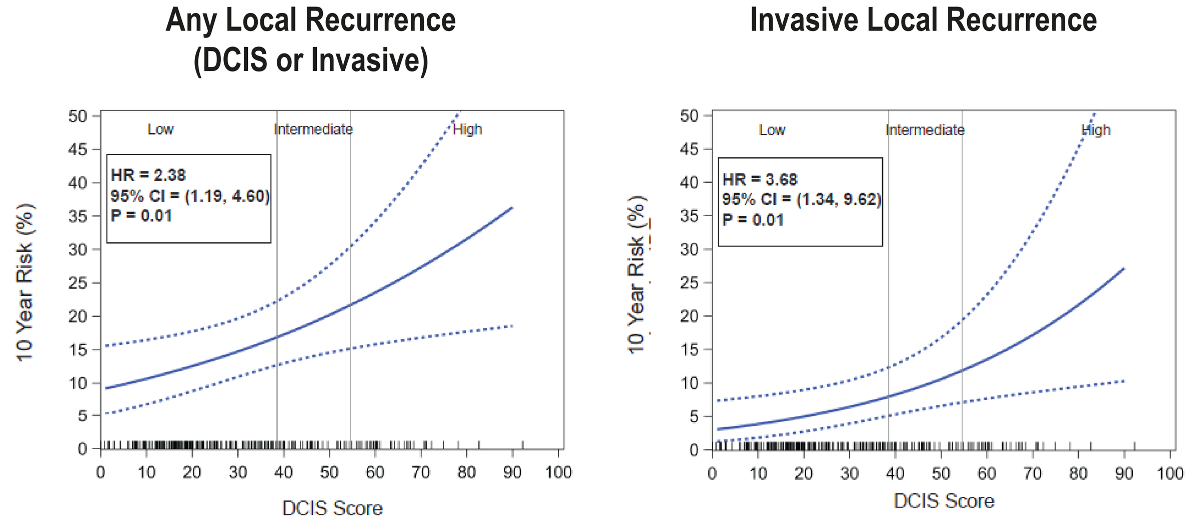


Figure 2. The DCIS Score 10-year Risk of LR



- In addition, the DCIS Score result was significantly associated with the risk of an invasive LR, separate from the overall LR risk.
- Demonstrating clinical utility is of paramount importance once an assay has been clinically validated.
- The first study to address clinical utility was initiated shortly after the assay became available for clinical use.
- The study was designed to assess the impact of the DCIS Score result on the treatment recommendation for XRT in patients that had surgical excision of their tumor.

Objectives

Primary

- To estimate the proportion of patients for whom obtaining the DCIS Score result lead to a change in the recommendation for XRT

Exploratory

- To determine whether the proportion of patients for whom physicians recommended XRT changed from pre- to post-DCIS Score result
- To characterize the clinical features of those patients who received the DCIS Score result
- To characterize the factors influencing the physician's post-assay treatment recommendation

Methods

Study Design

- Prospectively enrolled observational study of newly diagnosed patients with histologically proven pure DCIS
- Physicians filled out standardized questionnaires prior to and after the DCIS Score results were known
- Patient and tumor characteristics were abstracted from the medical record
- The study was approved by Institutional Review Boards at each study site

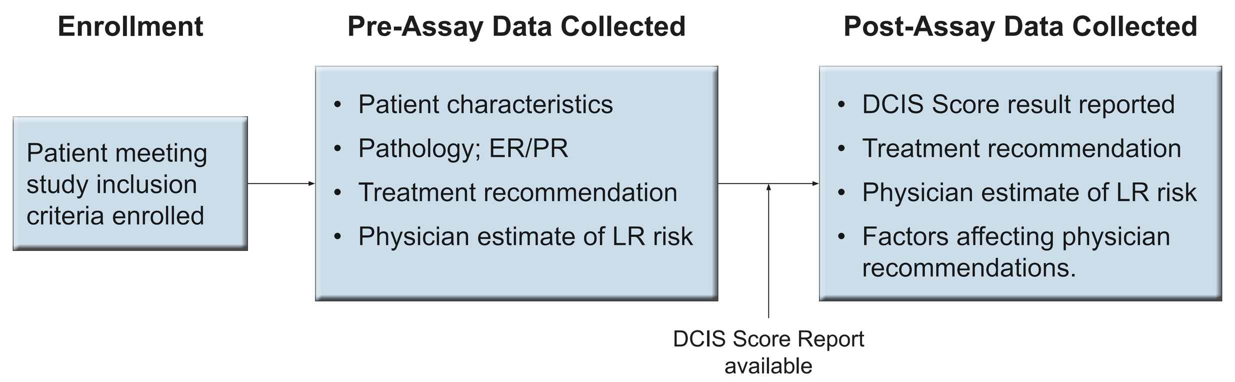
Patient Population

- Each participating center was responsible for identifying eligible patients from among actively treated patients at the site using the following criteria:
  - **Inclusion Criteria:** ≥18 years old, female, histologically proven DCIS, eligible for breast conserving therapy, **s**urgical excision pathology report available, DCIS Score result ordered but result not yet available
  - **Exclusion Criteria:** LCIS without DCIS, invasive carcinoma, mastectomy planned

Data Collection

- Trained data coordinators at each site reviewed patient records and prospectively collected data using a secure electronic data capture form before (pre-assay) and after (post-assay) the DCIS Score results were known to the treating physician

Figure 3. Data Collection Process



Statistical Considerations

- All analyses were descriptive unless otherwise specified
  - Clinical and pathological data are presented as mean (SD), median (range) for continuous variables and N (%) 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
- Hypothesis testing was performed using SAS® version 9.2 (SAS Institute, Cary, NC)
  - McNemar's test was used to determine if a significant proportion of patients had a change in XRT recommendation after receiving the DCIS Score result
  - P < 0.05 was considered significant

Limitations

- Physicians in this study were early adopters of the assay

Results

Patients

- 122 patients were enrolled at 10 centers (RMCC 5 sites) throughout the US from September 2012 to February 2014
- 115 pts were evaluable for the primary analysis. Excluded patients: no DCIS Score result (N=4), mastectomy planned (N=1), declined *Oncotype* DX testing (N=1), no DCIS on final pathology (N=1)
- The 115 evaluable pts were enrolled by 5 radiation oncologists (48 patients; 41.7%) and 5 surgeons (67 patients; 58.3%)
- Enrollment:
  - RMCC, Denver CO - 48 pts, SCCA, Little Rock, AR - 28 pts, TCH, Cincinnati, OH - 15 pts, UCSF, San Francisco, CA - 9 pts, UMSJMC, Towson MD - 9 pts, SEH, Edgewood, KY - 6 pts

Table 1. Patient/Tumor Characteristics (N=115)

Characteristic	N (%)
Patient Age	Mean 60.1 yr (SD:10.2)
<50	18 (15.7)
50–59	38 (33.0)
60–69	41 (35.7)
≥70	18 (15.7)
Postmenopausal	86 (74.8)
DCIS Size (mm)	
Mean (SD)	13.6 (15.7)
≤5	42 (36.5)
6–10	27 (23.5)
11–20	23 (20.0)
>20	23 (20.0)
Nuclear Grade	
I	23 (20.0)
II	53 (46.1)
III	39 (33.9)

Characteristic	N (%)
Distance from Margin (mm)	
Mean (SD)	4.2 (4.2)
Median (range)	3 (0–20)
Missing	2 (1.7)
<1	11 (9.6)
1–1.9	27 (23.5)
2–2.9	14 (12.2)
3–4.9	21 (18.3)
5–9.9	20 (17.4)
≥10	20 (17.4)
Necrosis	
Not identified	25 (21.7)
Not reported	16 (13.9)
Central	41 (35.7)
Focal	33 (28.7)

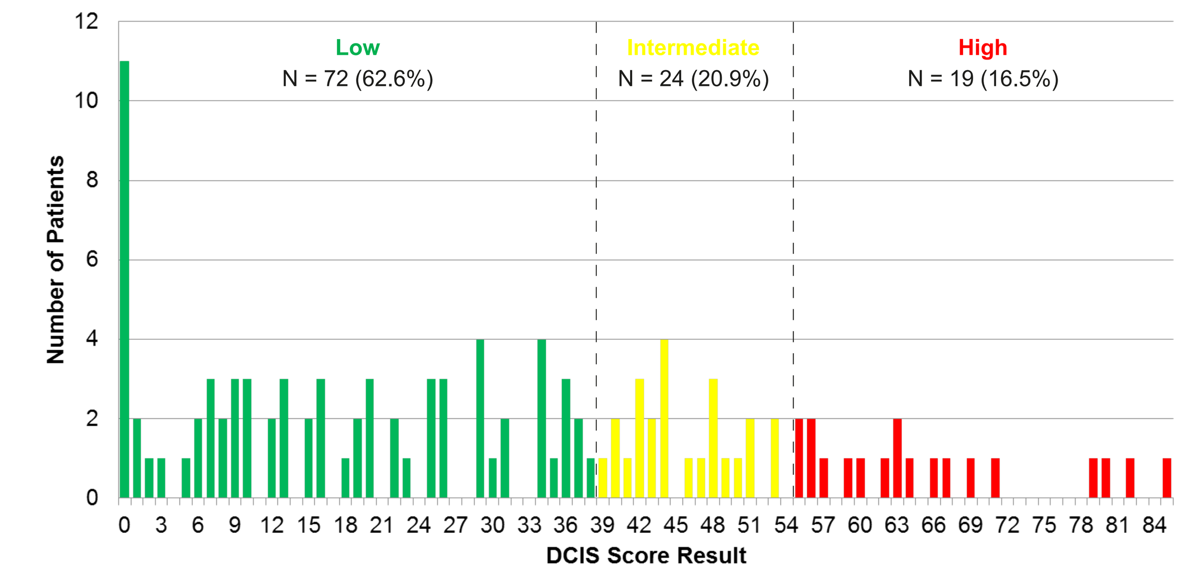
Characteristic	N (%)
ER (IHC)[a]	
Negative	8 (7.0)
Positive	99 (86.1)
PR (IHC)[a]	
Negative	16 (13.9)
Positive	91 (79.1)
ER (RT-PCR)	
Negative	13 (11.3)
Positive	102 (88.7)
PR (RT-PCR)	
Negative	22 (19.1)
Positive	93 (80.9)

[a] for N=1 (0.9%) result was uninterpretable; N=7 (6.1%) were missing.

Race:[b] Caucasian - 77.4%, Black - 8.7%, Asian - 6.1%, Hispanic/Latino - 4.3% and Other/unknown - 7.8%

[b] Pts could select more than one ethnicity (e.g. Caucasian and Asian)

Figure 4. Range of *Oncotype* DX DCIS Score Results



- Mean DCIS Score result was 30.7 (SD: 22.1) and median was 29 (range: 0-85)

Table 2. Pre- to Post-Assay Change in XRT Recommendations

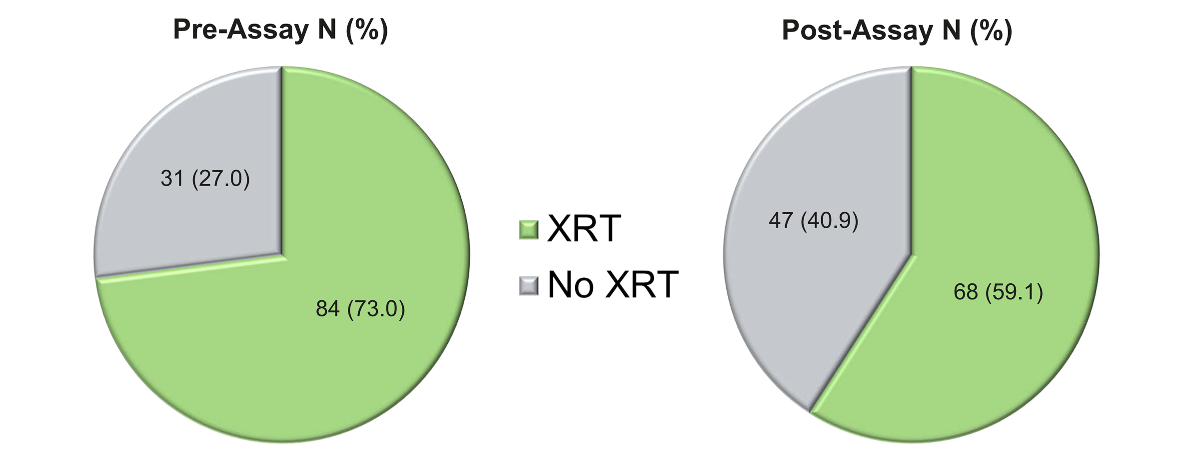
	N	Percent	95% CI[b]	Change Rate
Pre-assay XRT recommendation	84	73.0%	64.0%–80.9%	–
Change to Post-assay No XRT recommendation	26	22.6%	15.3%–31.3%	**30.9%**
Pre-assay No XRT recommendation	31	27.0%	19.1%–36.0%	–
Change to Post-assay XRT recommendation	10	8.7%	4.2%–15.4%	**32.2%**
Total patients with change in recommendation from pre-assay to post-assay	36		23.0%–40.6%	**31.3%**

[b] Clopper-Pearson Exact confidence interval.

- **31.3%** (95% CI: 23.0–40.6%) of patients had a change in recommendation for XRT from pre- to post-assay:
  - 26 patients changed from a pre-score XRT recommendation to No-XRT post-score.
  - 10 patients changed from pre-score No-XRT recommendation to XRT post-score.
  - All of the patients with a high DCIS Score result had a recommendation for XRT post assay.

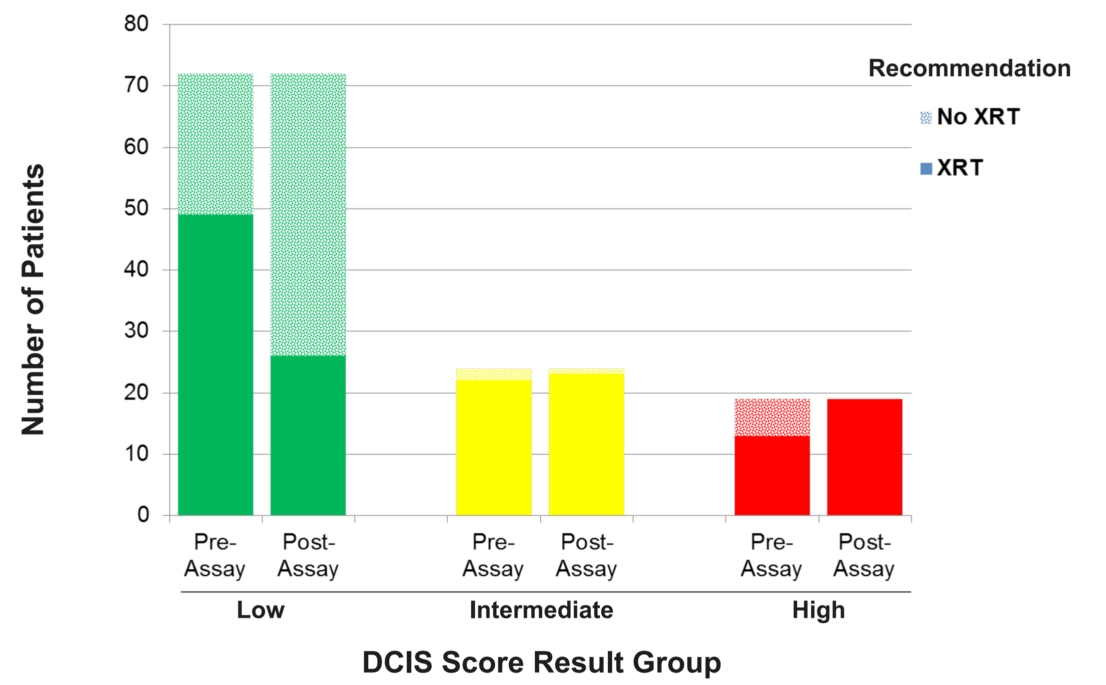
Results (cont.)

Figure 5. Recommendations for XRT



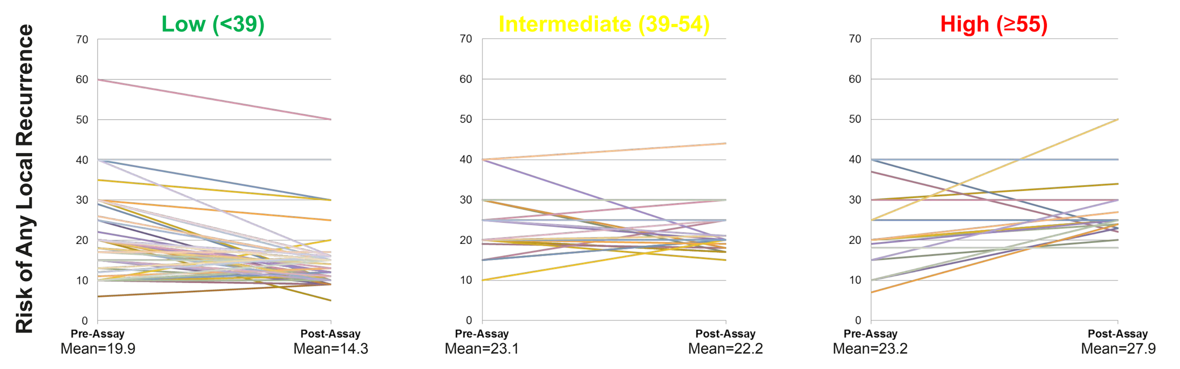
- There was a significant change in the proportion of pts receiving recommendations for XRT pre- to post-DCIS Score result (P=0.008; McNemar's test).
- 73% of the patients had a pre-assay recommendation for XRT.
- The post-assay XRT recommendation rate dropped to 59% showing the impact of the DCIS Score result on treatment recommendations.

Figure 6. Changes in Recommendation for XRT based on DCIS Score Result Group



- The shift in XRT recommendation by DCIS Score result was most pronounced in the low risk group.
- There was an associated shift in XRT recommendation in the high risk group towards XRT, consistent with the overall risk assessment.

Figure 7. Individual Patient 10-year LR Risk Assessments (Pre- and Post-DCIS Score result)

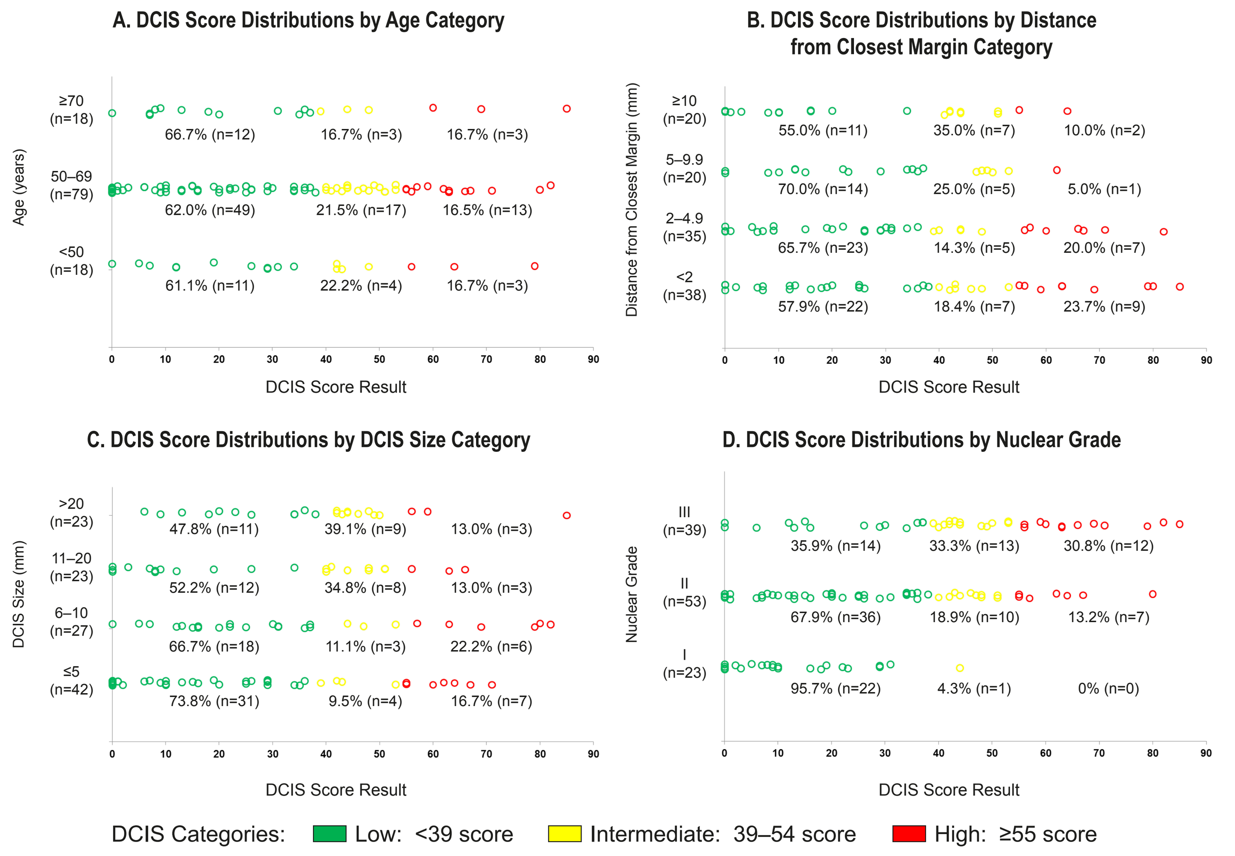


- LR risk, defined as any DCIS or invasive recurrence, was assessed for each patient by the physician
  - Pre-assay assessments were based on clinical and pathologic (CP) factors
  - Post assay assessments included but were not limited to the DCIS Score result
- Mean 10-year LR risk assessments decreased from pre-assay to post-assay:
  - Any LR from 21.1% (range: 6–60%) pre-assay to 18.2% (5–50%) post-assay
  - Invasive LR from 10.9% (range: 3–25%) pre-assay to 8.7% (2–25%) post-assay
- Average risk decreased in the low DCIS Score result group from 10.1% to 6.2%
- Average risk increased in the high DCIS Score result group from 13.1% to 15.2%

Results (cont.)

Figure 8. Distribution of the DCIS Score Result by Clinical and Pathologic (CP) Factors

- There was a range of DCIS Score results across the CP characteristics within each group - e.g. age >70y, 50–70y and <50y.



Conclusions

- The *Oncotype* DX Breast Cancer assay for DCIS is the first genomic test that provides an individualized assessment of the likelihood of local recurrence for patients diagnosed with DCIS and differentiates patients with a lower LR risk from those with higher risk.
- The DCIS Score result was clinically validated in a cohort of patients from the ECOG 5194 study and showed a strong and independent association with LR for any recurrence or an invasive recurrence.
- The results of the first clinical utility study demonstrate that:
  - Integration of the DCIS score result changes treatment recommendations for XRT 31.3% of the time: pre-assay 73% of the patients had a recommendation for XRT vs 59% post-assay.
  - Mean pre-assay LR risk assessment based on traditional CP features alone was 21% vs 18% post assay and was indicative of the impact of the score result on risk estimates.
    - There was a decrease in risk in the patients with low score results and an increase in risk assessment in patients with high score results.
  - There was a range of DCIS Score results across the CP characteristics including age, grade, size and margin width, indicating that the CP factors alone are insufficient to fully assess LR risk.
- Changes in recommendation were concentrated in patients with low and high DCIS Score results:
  - 25 of 27 changes in patients with low scores eliminated previously recommended XRT.
  - 6 out of 6 changes in patients with high scores added XRT, where none had been previously recommended.
- These results support the clinical utility of the DCIS Score result as an important tool for assessing risk of LR in patients with DCIS after surgical excision.
  - The DCIS Score result reflects the individual patient's underlying tumor biology beyond the traditional CP factors.
  - The score result provides a quantitative estimate of the risk of any (DCIS or invasive) LR or an invasive LR; other estimates based on the traditional CP factors can only provide group estimates of any LR and no specific information on the risk of an invasive LR.
- Better definition of underlying LR risk is critically important for improving treatment decisions, improving overall patient outcomes, and addressing the issue of overtreatment with XRT in patients with DCIS.

References

1. Siegel et al. *CA Cancer J Clin*. 2014.
2. Ernster et al. *J Natl Cancer Inst*. 2002.
3. NCCN Guidelines™. Breast Cancer. v2.2014.
4. Hughes et al. *J Clin Oncol*. 2009.
5. Solin et al. *J Natl Cancer Inst*. 2013.

The authors thank Kevin Chew, Emily Burke, Megan Rothney, and Melissa Stoppler for their contributions.