Ann Surg Oncol (2019) 26:3282–3288
https://doi.org/10.1245/s10434-019-07537-y

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

Check for updates

ORIGINAL ARTICLE – BREAST ONCOLOGY

Comparison of Local Recurrence Risk Estimates After Breast-Conserving Surgery for DCIS: DCIS Nomogram Versus Refined Oncotype DX Breast DCIS Score

Kimberly J. Van Zee, MS, MD[1], Emily C. Zabor, DrPH[2], Rosemarie Di Donato, MD[3], Bryan Harmon, MD[3], Jana Fox, MD[4], Monica Morrow, MD[1], Hiram S. Cody III, MD[1], and Susan A. Fineberg, MD[3]

[1]Breast Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY; [2]Biostatistics Service, Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY; [3]Department of Pathology, Montefiore Medical Center, Bronx, NY; [4]Department of Radiation Oncology, Montefiore Medical Center, Bronx, NY

ABSTRACT

Background. A ductal carcinoma in situ (DCIS) Nomogram integrating 10 clinicopathologic/treatment factors and a Refined DCIS Score (RDS) that incorporates a genomic assay and three clinicopathologic factors (Oncotype DX DCIS Score) are available to estimate DCIS 10-year local recurrence risk (LRR). This study compared these estimates.

Methods. Patients 50 years of age or older with DCIS size 2.5 cm or smaller and a genomic assay available were identified. An RDS within 1–2% of the range of Nomogram LRR estimates obtained by assuming use and non-use of endocrine therapy (Nomogram ± ET) was defined as concordant. Assuming a 10-year risk threshold of 10% for recommending radiation, Nomogram ± ET and RDS estimates were compared, and threshold concordance was determined.

Results. For 54 (92%) of 59 patients, the RDS and Nomogram ± ET LRR estimates were concordant. For the remaining 5 (8%) of the 59 patients, the RDS LRR estimates were lower than the Nomogram + ET estimates, with an absolute difference of 3–8%, and thus were discordant. For these five patients, the RDS estimates of 10-year LRR were lower than 10% (range 5–8%) and the Nomogram + ET estimates were 10% or higher (range 11–14%). These five patients with both discordant and threshold-discordant estimates all had close margins (≤ 2 mm).

Conclusions. Among 92% of women 50 years of age or older with DCIS size 2.5 cm or smaller, free-of-charge online Nomogram 10-year LRR estimates were concordant with those obtained using the commercially available RDS (> $4600). Among the 8% with discordant risk estimates, the RDS appeared to underestimate the LRR and may lead to inappropriate omission of radiotherapy. Unless other data show a clinically significant advantage of the RDS (Oncotype DX DCIS Score), the study data suggest that for women 50 years of age or older with DCIS size 2.5 cm or smaller, its use is not warranted.

Ductal carcinoma in situ (DCIS) accounts for 20% of all newly diagnosed breast cancers.[1] Most patients with DCIS will be treated with breast-conserving surgery (BCS) and radiation[2] due to the proven benefit of radiation in reducing the local recurrence risk (LRR) by about half.[3] The meta-analysis of the four mature randomized trials of radiation after BCS for DCIS, accrued in the 1980s and 1990s, showed that the 10-year local recurrence rate of 28.1% after BCS alone was reduced to 12.9% with the addition of radiation, but that it did not lessen the 10-year breast cancer mortality rate.[3]

© Society of Surgical Oncology 2019

First Received: 2 January 2019;
Published Online: 24 July 2019

K. J. Van Zee, MS, MD
e-mail: vanzeek@mskcc.org

Efforts have been made to identify a subset of patients with low-risk DCIS who derive no benefit from radiation, especially because local recurrence rates have decreased in the decades since the four randomized trials.[4] However, to date, such a subset has not been established.

In a randomized trial of patients with low-risk DCIS, defined as low- or intermediate-grade DCIS size 2.5 cm or smaller with margins greater than 3 mm, the addition of radiation resulted in significantly reduced 12-year local failure rates (2.8% with radiation vs 11.4% without radiation).[5,6] Yet, given the lack of improvement in survival and the rare but potentially serious morbidity of radiation,[7] there are continuing efforts to develop tools for accurate estimation of recurrence risk so that patients and clinicians can weigh the advantages and disadvantages of various treatment options.

The Memorial Sloan Kettering DCIS Nomogram (Nomogram), available online at www.nomograms.org, and the Oncotype DX Breast DCIS Score (Genomic Health, Redwood City, CA, USA), currently reported as a "refined" DCIS Score (RDS) incorporating a genomic assay and three clinicopathologic factors, are two clinically available tools designed to estimate LRR for patients who have DCIS treated with BCS.[8,9]

This study compared LRR estimates for women with lower-risk DCIS (age, $\geq$ 50 years; DCIS size, $\leq$ 2.5 cm) who underwent BCS without radiation. The estimates were obtained by using the Nomogram and the RDS, as reported by Genomic Health since late 2017 (adjusted for age, size, and diagnosis year). Furthermore, assuming that radiation would be recommended if the 10-year LRR met a threshold of 10% or higher, we sought to determine how often these two assays would yield similar or discordant radiation recommendation results.

METHODS

After institutional review board approval, the pathology database at Montefiore Medical Center was searched to identify all patients 50 years of age or older with DCIS size 2.5 cm or smaller, without positive margins, treated with BCS, and for whom a DCIS Score was obtained. Clinicopathologic information was obtained by chart review including age, family history of breast cancer in a first- or second-degree relative, screen-detected or clinical presentation of DCIS, nuclear grade, necrosis, estrogen receptor status, number of surgical excisions, DCIS size, surgical margin status (negative if $>$ 2 mm; close if $>$ 0 and $\leq$ 2 mm), and year of surgery.

Nomogram 10-year LRR estimates were calculated using the online tool available at http://nomograms.mskcc.org/breast/DuctalCarcinomaInSituRecurrencePage.aspx. These estimates were calculated without radiation or endocrine therapy (Nomogram – ET) and also without radiation but with endocrine therapy (Nomogram + ET). These two values defined the Nomogram $\pm$ ET estimate range.

The Oncotype DX Breast DCIS Score reports were reviewed, and the numeric score was recorded. Until late 2017, the Genomic Health report showed a 10-year LRR estimate corresponding to the DCIS Score that was defined by a single curve for all patients. Since late 2017, there have been four different curves that are adjusted for diagnosis year ($\geq$ 2000), and that depend on age category (age $<$ 50 vs $\geq$ 50 years) and tumor size ($\leq$ 1.0 vs $>$ 1.0 to $\leq$ 2.5 cm). In this report, we use the term RDS to designate the 10-year LRR estimate currently reported and calculated according to diagnosis year, age, and tumor size.[10] In this study, tumor size was determined in accordance with College of American Pathologists guidelines.[11]

For DCIS Scores reported before November 2017, we calculated RDS risk by using the Genomic Health curves (reported after November 2017) for the appropriate age and size stratum. We used DigitizeIt software (DigitizeIt, Braunschweig, Germany) to apply individual patient DCIS Scores to the appropriate current curves to obtain the RDS estimate.[12] For two patients with scores higher than 70, we used the maximum DCIS Score of 70, which is the approach used for such patients in Genomic Health RDS reports.

The 10-year LRR estimates obtained from Nomogram and RDS were compared. The RDS is reported with a 95% confidence interval of at least 5% for a tumor size of 1 cm or smaller, and of at least 8% for a tumor size $>$ 1.0–2.5 cm. The RDS was designed to be unaltered by use of ET. Therefore, RDS LRR estimates within 1–2% of the Nomogram $\pm$ ET estimate range were defined to be "concordant."

We assessed the number of women with risk estimates $\geq$ 10% and $\geq$ 15%. Assuming a threshold for recommending radiation of 10%, 10-year LRR Nomogram $\pm$ ET and RDS estimates were compared and defined to be "threshold concordant" if the estimates were concordant, or if the discordant estimates were on the same side of the 10% threshold (i.e., either both did or both did not estimate risk $\geq$ 10%).

All statistical analyses were conducted in R version 3.4.4 (R Core Development Team, Vienna, Austria).

RESULTS

The study identified 59 women 50 years of age or older who underwent BCS without positive margins for DCIS size 2.5 cm or smaller, and for whom a DCIS Score was

TABLE 1 Clinicopathologic characteristics of 59 patients with ductal carcinoma in situ (DCIS)

Characteristic		*n* (%)
Median age at surgery: years (range)		67 (50–81)
Median DCIS size: cm (range)		0.6 (0.2–2.5)
Presentation	Radiologic	55 (93)
	Clinical	4 (6.8)
Family history of breast cancer	Yes	12 (20)
	No	47 (80)
Nuclear grade	1	10 (17)
	2	34 (58)
	3	15 (25)
Necrosis present	Yes	35 (59)
	No	24 (41)
Size category (cm)	≤ 1	42 (71)
	> 1 and ≤ 2.5	17 (29)
No. of excisions	1	55 (93)
	2	4 (6.8)
Margin width (mm)	> 0 and ≤ 2	12 (20)
	> 2	47 (80)
Estrogen receptor	Positive	58 (98)
	Negative	1 (1.7)

available. All the patients underwent BCS between November 2011 and December 2017. Table 1 presents their clinicopathologic characteristics.

The median Nomogram – ET 10-year LRR was 14% (range 9–27%), with 56 (95%) of the patients having a risk of 10% or higher, and 24 (41%) of the patients having a risk of 15% or higher. The median Nomogram + ET 10-year LRR was 7% (range 4–14%), with 12 (20%) of the patients having a risk of 10% or higher and none having a risk of 15% or higher (Table 2).

Comparison of the reported LRR estimates from DCIS Scores before late 2017 (based solely on the DCIS Score) with the RDS LRR estimates reported since late 2017 (adjusted for diagnosis year, age, and size) showed that for every patient in our cohort (age, $\geq$ 50 years; tumor size, $\leq$ 2.5 cm), the RDS estimate was lower. The median RDS 10-year LRR estimate was 8% (range 5–17%), with 24 patients (41%) having a risk of 10% or higher, and with 4 patients (7%) having a risk of 15% or higher (Table 2).

Comparison of Nomogram and RDS Local Recurrence Risk Estimates

Overall, the Nomogram ± ET and RDS risk estimates were concordant in 54 (92%) of the 59 cases and discordant in 5 (8%) of the 59 cases (Figs. 1 and 2). Only two women (ages 76 and 78 years) had a higher RDS than the Nomogram – ET LRR estimate. The estimates differed by 1% and 2%, respectively, and were therefore concordant (RDS vs Nomogram – ET: 13% vs 12%; 13% vs 11%) (Fig. 1). Both women had risk estimates meeting the 10% radiation threshold by both methods and were therefore threshold concordant.

Compared with the Nomogram + ET, the RDS LRR estimates were lower for 16 of the 59 patients. For 11 of these patients, the absolute difference in risk estimates was only 1–2%, and the estimates were therefore concordant. For 5 (8%) of the 59 patients, the RDS risk estimates were more than 1–2% lower than the Nomogram + ET estimates (absolute difference, 3–8%) and therefore discordant. For these five patients, the RDS 10-year LRR estimates were lower than 10% (range 5–8%) compared with the Nomogram + ET estimates of 10% or higher (range 11–14%) and therefore deemed threshold-discordant. These five patients (8%) with both discordant and threshold-discordant estimates all had close margins ($\leq$ 2 mm) (Figs. 1 and 2).

Overall, 12 patients (20%) had margins of 2 mm or smaller. The RDS LRR estimate was below the 10% radiation recommendation threshold for 7 (58%) of 12 patients. In contrast, 11 (92%) of the 12 patients met the radiation threshold of 10% or higher based on the Nomogram + ET, and all 12 patients (100%) reached it based on the Nomogram – ET LRR estimate (Fig. 3).

TABLE 2 Number and proportion of women (n = 59) with local recurrence risk estimates in each risk category[a]

Method of risk estimation	10-year local recurrence risk estimate		
	$< 10\%$ *n* (%)	$\geq 10\%$ *n* (%)	$\geq 15\%$ *n* (%)
Nomogram, with endocrine therapy	47 (80)	12 (20)	0 (0)
Nomogram, without endocrine therapy	3 (5)	56 (95)	24 (41)
Refined DCIS Score	35 (59)	24 (41)	4 (7)

DCIS ductal carcinoma in situ

[a]Risk was estimated by Nomogram, with/without endocrine therapy, and by Refined Oncotype DX DCIS Score (genomic assay adjusted for year of diagnosis, age, and size)

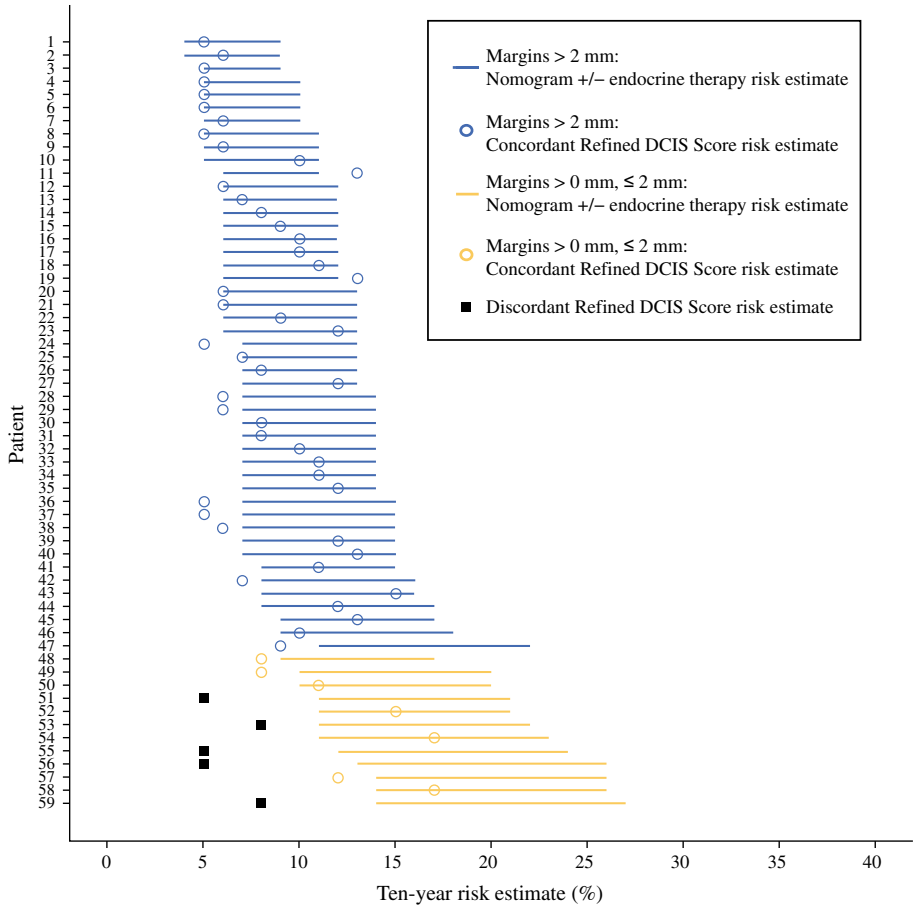

FIG. 1 Refined Oncotype DX Breast DCIS Score (RDS) and Nomogram with/without endocrine therapy risk estimates for each patient. The estimates were deemed concordant if the RDS was within 1–2% of the Nomogram with/without the endocrine therapy range (open circles, concordant estimates; black solid squares, discordant estimates). *DCIS* ductal carcinoma in situ

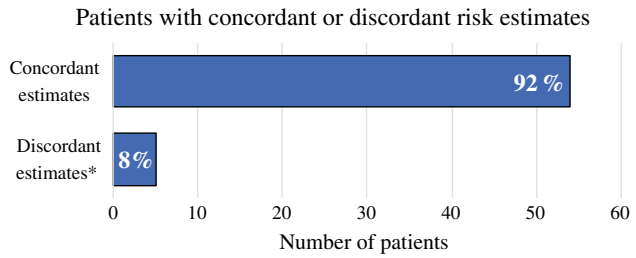

FIG. 2 Concordance of 10-year local recurrence risk estimates as estimated by the Refined Oncotype DX Breast DCIS Score compared with the Nomogram with/without endocrine therapy. *All five discordant estimates were for patients with close (> 0 mm, ≤ 2 mm) margins. *DCIS* ductal carcinoma in situ

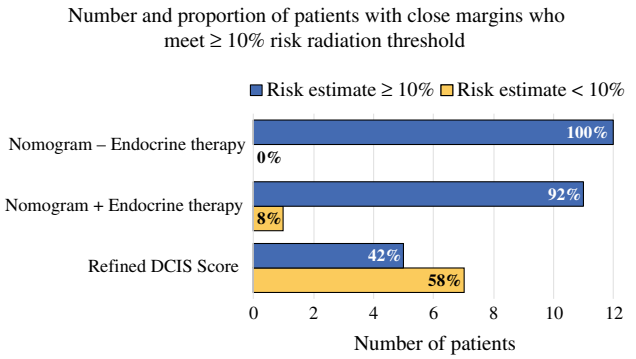

FIG. 3 Among 12 ductal carcinoma in situ (DCIS) patients with close margins (≤ 2 mm), the proportion of patients with risk estimates reaching the ≥ 10% 10-year local recurrence risk threshold using the Nomogram without endocrine therapy, the Nomogram with endocrine therapy, and the Refined Oncotype DX Breast DCIS Score. *DCIS* ductal carcinoma in situ

DISCUSSION

This study found a remarkable concordance between the Nomogram and RDS 10-year LRR estimates among 59 women 50 years of age or older with DCIS size 2.5 cm or smaller. The Nomogram was developed with a population of 1681 women who had DCIS treated with BCS from 1991 to 2006.[8] Age, family history, clinical presentation, margin width, nuclear grade, necrosis, number of excisions necessary (included as a surrogate for size), year of surgery, and use of radiotherapy and ET were included. Each factor is associated with LRR.

Studies have shown that age heavily influences LRR for women who receive radiation and for those who do not.[3,13] Cronin et al.[13] performed a multivariable LRR analysis by

decade of age, stratifying by receipt of radiation and adjusting for seven other clinicopathologic variables. Among women who underwent BCS without radiation, the youngest cohort (age < 40 years) had a 4.2-fold higher 10-year LRR than the oldest group (age ≥ 80 years).

The meta-analysis of the four prospective randomized studies investigating radiation for women with DCIS who underwent BCS showed that among women with DCIS who underwent BCS alone, larger DCIS size was associated with a greater 10-year LRR.[3] Notably, however, pathologic size was missing for most of the women in these trials due to difficulties determining the microscopic extent of disease.[3] Although the College of American Pathologists has issued guidelines for determining DCIS size,[11] any DCIS size measurement must be considered as an estimate[14] because it is highly dependent on specimen sampling completeness, with optimal sampling requiring the entire specimen to be serially submitted.

In a 2018 survey of more than 800 pathology departments, only 29% reported routine submission of the entire DCIS specimen.[15] Furthermore, several methods exist for reporting DCIS size, and although the College of American Pathologists recommends use of the method that yields the largest size, only 32% of institutions follow the recommendation. Recipients of the RDS report may not realize that the RDS estimate is highly dependent on the size provided. Recognizing the difficulty of determining DCIS size, the Nomogram does not use pathologic size, but instead includes number of excisions, which is a correlate of extent of disease, especially radiographically occult disease.

Treatment period also has been shown to have a large impact on LRR. Subhedar et al.[4] examined almost 3000 women with DCIS who underwent BCS from 1978 to 2010 and examined outcomes based on treatment year. They found that among the women who underwent BCS alone, the 10-year LRR fell over time, and even after adjustment for nine clinicopathologic/treatment factors, a 38% reduction in risk was observed for women treated in later versus earlier years. Surgery year is included in the Nomogram, and it is one of the factors that currently refines the DCIS Score estimates.

The original DCIS Score was a poor predictor of LRR, as shown in a multivariable analysis of 571 women from the Ontario cohort.[16] Although the DCIS Score was associated with LRR ($p = 0.02$) after adjustment for age, size, grade, necrosis, multifocality, and architectural growth pattern,[16] each of these clinicopathologic variables had a larger effect on LRR than did the DCIS Score. It also was applied to a subset (49%) of 327 women from the Eastern Cooperative Oncology Group (ECOG) 5194 study and found to be associated with LRR ($p = 0.02$) after adjustment for menopausal status and size.[9] However in both populations, the LRR associated with an "intermediate" DCIS Score was higher than for a "high" DCIS Score. Importantly, to our knowledge, no measure of the predictive accuracy (either discrimination or calibration) of the DCIS Score has been provided in any publication for either the Ontario or the original ECOG population subset in which it was "validated."[9,16–18]

In contrast, the Nomogram's accuracy has been validated with at least five independent populations, constituting a total of 2594 patients.[19–23] Measures of discrimination (area under the receiver operator curve or c-index) range from 0.65 to 0.92, consistent with a good-to-excellent model, and calibration (correlation between observed and predicted values) has been very good to excellent in these populations.[19–23]

In keeping with their previous finding that several clinicopathologic factors had a greater predictive value than the DCIS Score, Rakovitch et al.[16] recently created predictive models with age, size, multifocality, grade, necrosis, margin status, margin width, and radiation, both with and without the DCIS Score. They found that discrimination increased only from 0.68 to 0.70 with the addition of the DCIS Score, proving that most of the model's predictive ability was from the clinicopathologic and treatment variables rather than the DCIS Score.[17]

Presumably because of these findings, "refined estimates" of LRR by DCIS Score, adjusted for age, size, and diagnosis year, were derived from a combination of subsets of the ECOG 5194 and Ontario populations ($n = 773$).[18] Currently, they are provided when the DCIS Score is performed and reported (which we have referenced in the current study as the RDS). Examination of these LRR estimates shows that the estimates vary more due to patient age and DCIS size than from a change in DCIS Score from low to high, again demonstrating that age and size contribute more to LRR estimation than does the DCIS Score.[18]

Given the evidence provided by Rakovitch et al.[16–18] showing that the contribution of clinicopathologic features to risk estimation is greater than the DCIS Score, and that the currently reported RDS incorporates three important clinicopathologic factors (age, size, diagnosis year), it should not be surprising that we found no clinically significant discordance between the Nomogram and RDS risk estimates in 92% of our cases. The RDS estimates were substantially lower than the Nomogram + ET estimates for only five women, all of whom had close margins.

Margins 2 mm in size or smaller have been clearly associated with a higher LRR for women receiving radiation[24,25] and appear to be even more important for those not receiving radiation.[26] The Nomogram incorporates margin width, whereas the RDS does not, suggesting that the Nomogram provides a more realistic LRR estimate,

whereas the RDS underestimates the risk for those with close margins. Such underestimation could lead to inappropriate omission of radiation.

To our knowledge, the current study is the first to directly compare the Nomogram and RDS. It highlights another important difference between them, which is that the DCIS Score was designed to be unaltered by ET use,[9] although ET has been shown in randomized trials to reduce LRR substantially,[27–29] and although ET was received by about half of the patients (48.9%) with a diagnosis in the year 2000 or later, in whom the RDS was derived.[18] This design renders the RDS insensitive to a treatment that clearly reduces LRR and thereby lessens the precision of the RDS (i.e., the RDS is not altered by ET use, so LRR should be lower than the RDS estimate if the patient takes ET, and should be higher if she does not). Because the Nomogram incorporates ET use, the appropriate comparison is between the RDS and the range of estimates defined by the Nomogram ± ET. In the current series, the risk estimates derived from the Nomogram identified more women (without ET) at the highest risk (≥ 15%; 41% vs 7% with RDS) and more women (with ET) at low risk (< 10%; 80% vs 59% with RDS), which suggests better risk separation.[18]

An important limitation of our work was that actual local recurrence outcomes were not available for these recently treated patients. The best assessment of any prediction tool is obtained by comparing predicted with observed outcomes, and assessing measures of discrimination and calibration. Whereas discrimination and calibration in independent populations have been published for Nomogram predictions,[19–23] they have not been published for either the original DCIS Score or the RDS estimates.

Another limitation of our work was the number of patients. The DCIS Score was available only if ordered at the discretion of clinicians and patients after discussion and shared decision making.

CONCLUSIONS

This study showed that for 92% of patients 50 years of age or older with DCIS size 2.5 cm or smaller, a readily available, free-of-charge online Nomogram provided 10-year LRR estimates concordant with an RDS incorporating a genomic assay and three clinicopathologic variables, and costing $4620. The 8% of women with discordant estimates all had close margins, which is incorporated into the Nomogram but not the RDS LRR estimates, thereby suggesting that the RDS likely underestimates their risk. Unless and until further data demonstrate a clinically significant advantage of the costly genomic assay, our data suggest that for women 50 years of age or older with DCIS size 2.5 cm or smaller, use of the RDS for LRR estimation is not warranted.

ACKNOWLEDGMENT The preparation of this manuscript was funded in part by NIH/NCI Cancer Center Support Grant No. P30 CA008748 to Memorial Sloan Kettering Cancer Center.

DISCLOSURES Dr. Kimberly J. Van Zee and Dr. Susan Fineberg, have served on the Advisory Board of Genomic Health (Redwood City, CA), and Dr. Jana Fox serves as a consultant to Genomic Health. Dr. Monica Morrow has received speaking honoraria from Genomic Health and Roche.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin.* 2016;66:7–30.
2. Worni M, Akushevich I, Greenup R, et al. Trends in treatment patterns and outcomes for ductal carcinoma in situ. *J Natl Cancer Inst*. 2015;107:djv263.
3. Correa C, McGale P, et al. Overview of the randomized trials of radiotherapy in ductal carcinoma in situ of the breast. *J Natl Cancer Inst Monogr.* 2010;41:162–77.
4. Subhedar P, Olcese C, Patil S, Morrow M, Van Zee KJ. Decreasing recurrence rates for ductal carcinoma in situ: analysis of 2996 women treated with breast-conserving surgery over 30 years. *Ann Surg Oncol*. 2015;22:3273–81.
5. McCormick B, Winter K, Hudis C, et al. RTOG 9804: a prospective randomized trial for good-risk ductal carcinoma in situ comparing radiotherapy with observation. *J Clin Oncol.* 2015;33:709–15.
6. McCormick B. Randomized trial evaluating radiation following surgical excision for "good risk" DCIS: 12-year report from NRG/RTOG 9804. 2018 ASTRO annual meeting. Abstract no. LBA1 Presented 21 October 2018.
7. Henson KE, McGale P, Taylor C, Darby SC. Radiation-related mortality from heart disease and lung cancer more than 20 years after radiotherapy for breast cancer. *Br J Cancer.* 2013;108:179–82.
8. Rudloff U, Jacks LM, Goldberg JI, et al. Nomogram for predicting the risk of local recurrence after breast-conserving surgery for ductal carcinoma in situ. *J Clin Oncol.* 2010;28:3762–9.
9. Solin LJ, Gray R, Baehner FL, et al. A multigene expression assay to predict local recurrence risk for ductal carcinoma in situ of the breast. *J Natl Cancer Inst.* 2013;105:701–10.
10. Oncotype DX Breast DCIS Score: Clinical evidence. Genomic Health, Redwood City, CA. Retrieved 15 October 2018 https://www.oncotypeiq.com/en-US/breast-cancer/healthcare-professionals/oncotype-dx-breast-dcis-score/clinical-evidence.
11. Fitzgibbons PL, Bose S, Chen YY, et al. Protocol for the examination of specimens from patients with ductal carcinoma in situ (DCIS) of the breast. College of American Pathologists 2018. Retrieved 26 December 2018 http://www.cap.org/cancerprotocols.
12. Satagopan JM, Iasonos A, Kanik JG. A reconstructed melanoma data set for evaluating differential treatment benefit according to biomarker subgroups. *Data Brief.* 2017;12:667–75.
13. Cronin PA, Olcese C, Patil S, Morrow M, Van Zee KJ. Impact of age on risk of recurrence of ductal carcinoma in situ: outcomes of 2996 women treated with breast-conserving surgery over 30 years. *Ann Surg Oncol.* 2016;23:2816–24.

14. Saqi A, Osborne MP, Rosenblatt R, Shin SJ, Hoda SA. Quantifying mammary duct carcinoma in situ: a wild-goose chase? *Am J Clin Pathol.* 2000;113(Suppl 1):S30–7.
15. Guidi AJ, Tworek JA, Mais DD, Souers RJ, Blond BJ, Brown RW. Breast specimen processing and reporting with an emphasis on margin evaluation: a College of American Pathologists survey of 866 laboratories. *Arch Pathol Lab Med.* 2018;142:496–506.
16. Rakovitch E, Nofech-Mozes S, Hanna W, et al. A population-based validation study of the DCIS Score predicting recurrence risk in individuals treated by breast-conserving surgery alone. *Breast Cancer Res Treat.* 2015;152:389–98.
17. Paszat L, Sutradhar R, Zhou L, Nofech-Mozes S, Rakovitch E. Including the ductal carcinoma in situ (DCIS) Score in the development of a multivariable prediction model for recurrence after excision of DCIS. *Clin Breast Cancer.* 2018; 19:35–46
18. Rakovitch E, Gray R, Baehner FL, et al. Refined estimates of local recurrence risks by DCIS score adjusting for clinicopathological features: a combined analysis of ECOG-ACRIN E5194 and Ontario DCIS cohort studies. *Breast Cancer Res Treat.* 2018;169:359–69.
19. Collins LC, Achacoso N, Haque R, et al. Risk prediction for local breast cancer recurrence among women with DCIS treated in a community practice: a nested, case-control study. *Ann Surg Oncol.* 2015;22(Suppl 3):S502–8.
20. Sedloev T, Vasileva M, Kundurzhiev T, Hadjieva T. Validation of the Memorial Sloan-Kettering Cancer Center nomogram in the prediction of local recurrence risks after conserving surgery for Bulgarian women with DCIS of the breast. Conference Paper presented at the 2nd world congress on controversies in breast cancer (CoBrCa), Barcelona, Spain, September 2016. Retrieved 22 March 2017 https://www.researchgate.net/publication/312232507_Validation_of_the_Memorial_Sloan-Kettering_Cancer_Center_nomogram_in_the_prediction_of_local_recurrence_risks_after_conserving_surgery_for_Bulgarian_women_with_DCIS_of_the_breast.
21. Sweldens C, Peeters S, van Limbergen E, et al. Local relapse after breast-conserving therapy for ductal carcinoma in situ: a European single-center experience and external validation of the Memorial Sloan-Kettering Cancer Center DCIS nomogram. *Cancer J.* 2014;20:1–7.
22. Wang F, Li H, Tan PH, et al. Validation of a nomogram in the prediction of local recurrence risks after conserving surgery for Asian women with ductal carcinoma in situ of the breast. *Clin Oncol R Coll Radiol.* 2014;26:684–91.
23. Yi M, Meric-Bernstam F, Kuerer HM, et al. Evaluation of a breast cancer nomogram for predicting risk of ipsilateral breast tumor recurrences in patients with ductal carcinoma in situ after local excision. *J Clin Oncol.* 2012;30:600–7.
24. Marinovich ML, Azizi L, Macaskill P, et al. The association of surgical margins and local recurrence in women with ductal carcinoma in situ treated with breast-conserving therapy: a meta-analysis. *Ann Surg Oncol.* 2016;23(12):3811–21.
25. Morrow M, Van Zee KJ, Solin LJ, et al. Society of Surgical Oncology–American Society for Radiation Oncology–American Society of Clinical Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in ductal carcinoma in situ. *Ann Surg Oncol.* 2016;23:3801–10.
26. Van Zee KJ, Subhedar P, Olcese C, Patil S, Morrow M. Relationship between margin width and recurrence of ductal carcinoma in situ: analysis of 2996 women treated with breast-conserving surgery for 30 years. *Ann Surg.* 2015;262:623–31.
27. Wapnir IL, Dignam JJ, Fisher B, et al. Long-term outcomes of invasive ipsilateral breast tumor recurrences after lumpectomy in NSABP B-17 and B-24 randomized clinical trials for DCIS. *J Natl Cancer Inst.* 2011;103:478–88.
28. Cuzick J, Sestak I, Pinder SE, et al. Effect of tamoxifen and radiotherapy in women with locally excised ductal carcinoma in situ: long-term results from the UK/ANZ DCIS trial. *Lancet Oncol.* 2011;12:21–9.
29. Allred DC, Anderson SJ, Paik S, et al. Adjuvant tamoxifen reduces subsequent breast cancer in women with estrogen receptor-positive ductal carcinoma in situ: a study based on NSABP protocol B-24. *J Clin Oncol.* 2012;30:1268–73.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.