A subset of patients with ductal carcinoma in situ (DCIS) of the breast develop ipsilateral invasive breast cancer after breast-conserving surgery with or without adjuvant radiotherapy. Risk assessment and prediction of adverse outcomes for individual patients based on traditional clinical and pathological parameters are limited. The Oncotype DCIS Score is a commercially available multigene assay that has been independently validated in a prospective clinical trial and a population-based cohort. The score helps to identify a subset of women >50 years old with unifocal disease that carries <10% risk of any local recurrence after breast-conserving surgery alone. In this population, individual patients and physicians may consider omitting adjuvant radiotherapy. In this article, we review the literature and summarize the evidence regarding the role of the Oncotype DCIS Score in estimating the risk of ipsilateral local recurrence and ipsilateral invasive breast cancer recurrence. The available data on clinical utility and cost-effective analysis for optimizing decisions on adjuvant treatments are discussed.

clinical outcome and sets of invasive breast carcinoma with clinical outcome. The development was based in part on evidence that the 21 gene Oncotype DX Recurrence Score for early invasive breast cancer may provide information on the risk of recurrence in DCIS. The initial studies found that the assay yielded a wide range of Recurrence Scores in DCIS samples. The 21-gene algorithm was then modified, and a panel of 12 genes was selected for the initial clinical validation study in a retrospective analysis of Eastern Cooperative Oncology Group—American College of Radiology Imaging Network (ECOG-ACRIN) E5194 prospective clinical trial. The final DCIS panel was selected based on genes known to predict distant recurrence and breast cancer mortality in tamoxifen-treated and untreated invasive cancer. The assay includes proliferation gene group, progestosterone receptor (PGR), and GSTM1. GSTM1 gene is a member of glutathione S-transferases superfamily of ubiquitous, multifunctional enzymes, which play a key role in cellular detoxification, protecting macromolecules from attack by reactive electrophiles.\textsuperscript{2} Notably, the ER and ERBB2/HER2/neu genes that were included in the 21-gene assay were removed from the DCIS panel. The cutoff points and scales for the algorithm were primarily based on the distribution of the scores in the DCIS developmental sets.

The final 12-gene panel for the Oncotype DX Breast DCIS Score includes seven cancer-related (Ki-67, AURKA/STK15, BIRC5/survivin, CCNB1, MYBL2, PGR, and GSTM1) and five reference genes (ACTB, GAPDH, RPLPO, GUS, and TFR). The DCIS Score is scaled numerically from zero to 100 and classified into three risk prespecified categories: i) low risk (Oncotype DCIS Score <39); ii) intermediate risk (Oncotype DCIS DX Score = 39 to 54); and iii) high risk (Oncotype DCIS Score ≥55). The Oncotype DCIS DX Score was designed to quantify the 10-year risk of any ipsilateral breast event (local or invasive recurrence) after BCS for pure DCIS after BCS for pure DCIS without radiotherapy.\textsuperscript{1}

**Clinical Validation**

There are limited resources of cohorts for discovery and validation of putative prognostic assays in patients with pure DCIS and available annotated tissue as well as confirmed treatments and outcomes worldwide. The Oncotype DX Breast DCIS Score was primarily validated in two independent cohorts. The first clinical validation used archival formalin-fixed, paraffin-embedded blocks from the ECOG-ACRIN E5194 study, a prospective, cohort study with two groups of patients with DCIS treated with BCS alone between 1997 and 2002.\textsuperscript{1} The first group consisted of low- or intermediate-grade DCIS (tumor size <25 mm), and the second group consisted of high-grade DCIS (tumor size ≤10 mm). Treatment for all patients included surgical excision (BCS) with a minimum negative margin width of 3 mm or no tumor on reexcision. Adjuvant tamoxifen was offered to patients from May 2000. The ECOG-ACRIN E5194 study population largely included clinically low-risk cases: 579 patients with low- or intermediate-grade tumors and 101 patients with high-grade tumors, with a median size of 6 and 7 mm, respectively, and mostly wide clear margins (≥5 mm). Tamoxifen treatment was planned in 31% of the participants. Sufficient tissue was available for molecular analysis in 49% of the cases enrolled in the clinical trial. LR developed in 46 patients (n = 26 DCIS only and n = 20 invasive carcinoma). The Oncotype DCIS Score (based on the 12-gene assay) was used for the three prespecified risk groups. The 10-year rates for developing an ipsilateral breast event were 10.6%, 26.7%, and 25.9% for the low-, intermediate-, and high-risk groups, respectively (log rank P = 0.006). The corresponding 10-year rates for developing an invasive ipsilateral breast event were 3.7%, 12.3%, and 19.2%, respectively (log rank P = 0.003). In contrast, the Recurrence Score (based on the 21-gene assay) was not significantly associated with developing an ipsilateral breast event. In multivariable analyses, factors statistically significantly associated with developing any LR were Oncotype DCIS Score, tumor size, and menopausal status (all P ≤ 0.02).

The Oncotype DCIS Score was independently validated in a subset of 3303 patients from the Canadian population—based (Ontario) cohort diagnosed with pure DCIS between 1994 and 2003.\textsuperscript{3} The cohort is well characterized, with covariate information extracted from medical record review, comprehensive centralized pathology review, and 10-year outcome measures. Slides and blocks were available for 80% of the cohort, which is the largest in the world. The primary analysis was for patients treated with BCS with negative margins who did not receive adjuvant radiotherapy. In this subset of the cohort, negative margins were defined as no ink on tumor, and tissue was available for analysis in 50% of the cohort, all these had complete centralized pathology review. In the prespecified primary analysis, the Oncotype DCIS Score was significantly associated with risk of ipsilateral breast event both in patients with ER-positive DCIS [hazard ratio (HR) = 2.3; 95% CI, 1.41–3.59; P < 0.001] and irrespective of ER status (HR = 2.2; 95% CI, 1.43–3.22; P < 0.001), although close to 95% of the tumors were ER positive. Most patients by BCS alone had a low-risk category Oncotype DCIS Score and a 10-year rate of LR of 12.7%, whereas the risk was 33% for intermediate- and 27.8% for high-risk categories. The corresponding 10-year rates of invasive LR were 8.0%, 20.9%, and 15.5%, respectively. For a secondary analysis without restrictions on margin status (N = 718), there were 147 patients with positive or unknown margins. Adjusting for margin status, the HR for the Oncotype DCIS Score was 2.11 (95% CI, 1.43–3.09; P < 0.001).\textsuperscript{4}

A follow-up analysis of the Oncotype DCIS Score included 571 and 689 patients treated with BCS or BCS and radiotherapy, respectively, from the Ontario DCIS cohort.\textsuperscript{5} With a median follow-up of 9.4 years, there were 100 LRs [57 invasive, 44 DCIS (one invasive developed after
DCIS]) among patients treated with BCS alone, and 86 LRs among those treated with radiotherapy (55 invasive, 32 DCIS). As expected in this population-based, non-randomized cohort, the group of patients who received radiotherapy had more adverse features than those treated with BCS alone. Among patients treated with BCS and radiotherapy, the 10-year risks of LR were 20.5% (95% CI, 15.1% to 27.5%) for those with a high-risk score, 13.6% (95% CI, 8.6% to 21.2%) for those with an intermediate-risk score, and 7.5% (95% CI, 4.9% to 11.2%) for those with a low-risk score (P < 0.001). On multivariable analysis of the two groups (with and without radiotherapy), using a propensity score—adjusted model, factors associated with LR included radiotherapy, age at diagnosis, tumor size, and multifocality. In this study, multifocality was defined as four of DCIS separated by at least 5 mm of benign breast tissue. Adjusting for these factors, the Oncotype DCIS Score risk group was statistically significantly associated with LR risk (HR for the high- and intermediate-risk group = 1.75; 95% CI, 1.28–2.41; P < 0.001). However; the Oncotype DCIS Score did not significantly predict benefit from radiotherapy (no significant interaction). Although patients across the Oncotype DCIS Scores benefited from radiotherapy, the magnitude of risk reduction differed. Individuals with a high-risk Oncotype DCIS Score experienced higher risks of LR and invasive LR and had a greater absolute benefit with radiotherapy compared with those with a low-risk score.

A recent analysis combined data from the two Oncotype DCIS Score validation cohorts, namely, the ECOC-ACRIN E5194 (with extended 12-year follow up) and the Ontario DCIS cohort. Only patients treated with BCS without radiotherapy who had negative margins and unifocal disease were included in the Ontario cohort. The combined population for patient-specific meta-analysis included 773 patients. Significant independent prognostic factors were the Oncotype DCIS Score, age at diagnosis, tumor size, and year of diagnosis. The HRs from the ECOC-ACRIN E5194 and Ontario DCIS cohorts were similar for the Oncotype DCIS Score (2.48 and 1.95 per 50 units, respectively), tumor size <1 versus >1 to 2.5 cm (1.45 and 1.47, respectively), age ≥50 versus <50 years (0.61 and 0.84, respectively), and year ≥2000 (0.67 and 0.49, respectively).

Use of the Oncotype DCIS Score combined with tumor size and age at diagnosis identified 25.9% of patients with an estimated 10-year risk LR <8% compared to 17.7% of cases based on the Oncotype DCIS Score alone. Moreover, no patients with LR <8% were identified using tumor size and age. In addition, the model integrating the effects of tumor size and age at diagnosis with the Oncotype DCIS Score also identified more women (21.1%) with a predicted high risk of LR (defined as 10-year LR risk >15%) compared with 18.4% in models based on the Oncotype DCIS Score alone or 10.9% using tumor size and age alone. The combined analysis highlighted that integration of clinicopathologic features with the Oncotype DCIS Score improved risk estimates and identified a larger group of patients with minimal risk of recurrence. Table 1 summarizes the risk estimates in the validation cohorts.

Oncotype DCIS Score and Histopathologic Features

A few studies on the correlation between the Oncotype DCIS Score and traditional histopathologic prognosticators were recently published. A single-institution study of 46 cases of pure DCIS and available Oncotype DCIS Score looked specifically at the correlation among PGR expression by immunohistochemistry, mitotic count, and periductal lymphocytic infiltrate. These markers were selected because the Oncotype DCIS Score relies heavily on five proliferation-related genes and PGR. Only the slide from the block used for Oncotype DCIS Score testing was evaluated. Dense lymphocytic infiltrate was defined as at least three cell layers of inflammatory infiltrate approximately ≥75% of the circumference. A low Oncotype DCIS Score was significantly associated with low nuclear grade, ER and PGR expression ≥90%, mitotic count ≤1, and absence of dense periductal inflammation. They found a significant association between high ER and PGR expression, low mitotic rate, and low Oncotype DCIS Score, as well as absence of dense periductal chronic inflammation. In this limited sample, all 13 cases with PR expression ≥90%, ≤1 mitotic figure, and absence of dense chronic inflammation around DCIS had a low score. Moreover, a low score was not observed in any case with at least two of the following: negative PGR expression, >1 mitotic figure, and/or presence of dense chronic inflammation. In contrast with ECOC-ACRIN E5194 and the Ontario DCIS cohort analyses, nuclear grade was associated with the Oncotype DCIS Score in this audit. This is an interesting hypothesis-generating observation; however, the significance to clinical practice has to be explored further because the cases included in this study were selected by the mere availability of the Oncotype DCIS Score and lack any outcome data.

Another single-institution study examined the association between Oncotype DCIS Score and traditional histopathologic features and to what extent the assay affects management decision. The study included 37 patients with DCIS and available Oncotype DCIS Score (based in patients or physician request); low Oncotype DCIS Score was associated with low nuclear grade, absence of necrosis, high ER and PGR expression by immunohistochemistry, and a lower rate of adjuvant radiotherapy (P < 0.008). In this study, patient age, mitoses, DCIS size, final margin, DCIS cellularity, dense inflammation, and calcification were not significantly different between the low, intermediate, and high Oncotype DCIS Score groups. However, in approximately one-fifth of cases, Oncotype the DCIS Score was considered unexpected in relation to the histopathologic findings (ie, high nuclear grade with comedo necrosis and a low Oncotype DCIS Score) or hormone receptor
discrepancies. In this study, five of the 15 patients made the decision to forgo radiotherapy and two opted for completion mastectomy based on the Oncotype DCIS Score results. This is in line with the analysis of both ECOG-ACRIN E5194 and the Ontario cohort analysis, which found that 10% to 15% of cases with low-risk clinicopathological features had an intermediate- to high-risk Oncotype DCIS Score and a higher risk of LR, indicating that the Oncotype DCIS Score assay can identity a subset of women with low-risk features but high-risk molecular features that have a higher risk of LR after BCS alone.

Clinical Utility

Given the relatively short period since the Oncotype DCIS assay became commercially available and limited accessibility to cost coverage, there is limited experience with regard to the clinical utility of the Oncotype DCIS Score. Shumway et al\(^9\) evaluated patient experiences with decisions regarding radiotherapy for DCIS and assessed clinician views on the role of radiotherapy with favorable features in the United States. The proportion of patients receiving radiotherapy after BCS varied by geographic regions. In general, omitting radiotherapy was associated with age (trend), tumor grade, ER status, and endocrine therapy. Clinicians were presented with the hypothetical case of a 65-year-old woman with ER-positive DCIS who had a lumpectomy with negative margins (>10 mm) and agreed to undergo adjuvant tamoxifen therapy. Among the 539 clinicians who responded to the survey, approximately one-third would have personally ordered the Oncotype DCIS assay.

A prospective, observational study evaluated the influence of the Oncotype DCIS assay in 115 patients from 10 centers in the United States.\(^\) Prospective data collected included clinicopathologic factors, Oncotype DCIS Score, and treatment recommendation before and after the assay.

Table 1  Summary of Validation Cohorts by Treatments and Estimates for Any and Invasive LR at 10 Years

<table>
<thead>
<tr>
<th>Cohort and treatment</th>
<th>Margins</th>
<th>Patients with available score, n (Low-risk DCIS Score)</th>
<th>10-Year risk estimates of LR, % (95% CI)</th>
<th>Intermediate-risk DCIS Score</th>
<th>High-risk DCIS Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG-ACRIN E5194</td>
<td>BCS</td>
<td>327</td>
<td>Any LR: 10.6 (6.9–16.2)</td>
<td>26.7 (16.2–41.9)</td>
<td>25.9 (14.8–43.1)</td>
</tr>
<tr>
<td></td>
<td>BCS</td>
<td>571</td>
<td>Intermediate-risk LR: 16.0 (12.2–20.9)</td>
<td>32.7 (25.9–40.6)</td>
<td>9.4 (7.0–12.5)</td>
</tr>
<tr>
<td></td>
<td>BCS and RT</td>
<td>689</td>
<td>High-risk LR: 20.0 (7.4–12.5)</td>
<td>11.9 (4.7–9.7)</td>
<td>6.8 (15.9–24.9)</td>
</tr>
<tr>
<td>Population-based Ontario DCIS cohort</td>
<td>Negative (no tumor on ink)</td>
<td>773</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

*ECOG-ACRIN E5194 and population-based Ontario DCIS cohorts, with BCS excluding cases with positive margins and multifocality. BCS, breast-conserving surgery; DCIS, ductal carcinoma in situ; ECOG-ACRIN, Eastern Cooperative Oncology Group—American College of Radiology Imaging Network; LR, local recurrence; NA, not available; RT, radiotherapy.

Table 2  Clinical Pathologic Characteristics in Patients Tested with the Oncotype DCIS Assay

<table>
<thead>
<tr>
<th>Reference</th>
<th>Mean age, years (range)</th>
<th>Mean size, mm (range)</th>
<th>Association</th>
<th>Patients by DCIS Score, n (low, intermediate, high)</th>
<th>RT DCIS Score (low, intermediate, high)</th>
<th>Change in management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knopfelmacher et al,(^7) 2015</td>
<td>64 (41–84)</td>
<td>9 (2–70)</td>
<td>Age, PGR/ER, mitoses, periductal inflammation, nuclear grade</td>
<td>46 (33, 8, 4)</td>
<td>14 (6, 4, 3)</td>
<td></td>
</tr>
<tr>
<td>Farrugia et al,(^8) 2017</td>
<td>57.7 (34–82)</td>
<td>15 (3–50)</td>
<td>Necrosis, PGR/ER, VNPI, biopsy site, nuclear grade</td>
<td>37 (25, 7, 5)</td>
<td>20 (9, 6, 5)</td>
<td>5/15 no RT</td>
</tr>
<tr>
<td>Alvarado et al,(^10) 2015</td>
<td>60.1 (36–83)</td>
<td>13.6 (1–115)</td>
<td>NA</td>
<td>115 (72, 24, 19)</td>
<td>68 (25, 24, 19)</td>
<td>26/84 no RT, 10/31 add RT</td>
</tr>
</tbody>
</table>

NA, not applicable; RT, radiotherapy; VNPI, Van Nuys Prognostic Index.
result was known. Patients receiving active treatment were included if they had pure DCIS and were treated by BCS before the results of the assay became available. The Oncotype DCIS Score led to a change in the treatment recommendation in 36 patients (31.3%); 26 of 84 patients (22%) who were initially considered for radiotherapy changed to no radiotherapy, and 10 of 31 patients (8.7%) who were considered for no radiotherapy had radiotherapy added after the Oncotype DCIS assay. Exploratory analyses revealed there was a range of Oncotype DCIS Score results within the categories of clinicopathologic factors (eg, age, margin, size, and nuclear grade). Table 2 summarizes the clinical pathological characteristics of patients with Oncotype DCIS Scores in recent studies.

Another prospective, nonrandomized trial is open for enrollment in Canada and is designed to assess the effect of the Oncotype DCIS Score on clinical practice, in particular, the ability of the Oncotype DCIS Score to change physician recommendations for radiotherapy and the effect on patient radiotherapy treatment preference in low- or intermediate-risk pure DCIS. In this study, patients are excluded if radiotherapy was recommended or omitted regardless of the score (Clinical Trials Identifier: NCT02766881).

A real-life cost-effectiveness analysis for the Oncotype DCIS ASSAY in not yet available. However, considering the relatively high cost of the assay ($3416 USD), it is crucial to assess whether the refined risk stratification offered by the assay is economically justified and whether health care professionals can establish testing strategies for selecting patients for whom the assay is most cost-effective. This is of great value for any health care professionals, especially in jurisdictions with limited resources. A cost-effectiveness analysis based on a Markov model simulating 10-year outcomes for women 60 years old who were eligible for the ECOG-ACRIN E5194 study was conducted. The study compared five different treatment strategies with the reference strategy (surgical excision with no radiotherapy and no Oncotype DCIS Score testing); two of the strategies incorporated Oncotype DCIS Score testing for all patients or selected patients with intermediate- and high-grade DCIS and recommended radiotherapy for patients with intermediate or high Oncotype DCIS Scores. The strategies using the Oncotype DCIS Score lowered the proportion of women undergoing radiotherapy per ipsilateral breast event prevented. However, no strategy incorporating the Oncotype DCIS Score was cost-effective. It has been suggested that a recommendation to use the Oncotype DCIS Score could be made by multidisciplinary teams in the context of a tumor board or direct communication.

The Oncotype DCIS assay is a prognostic test that assists in estimating an individual’s risk of any LR (in situ or invasive), in particular in combination with other clinical pathological features, such as age, size, margins status, and multifocality. The risk estimates provide information about an individual’s risk of developing any LR and their risk of developing an ipsilateral invasive LR. The assay was not designed to predict response to radiotherapy or endocrine therapy, and available data failed to identify a subset of patients who do not benefit from radiotherapy. The role of the assay in BRCA1/2 is currently unknown. On the basis of current data, the assay may assist in the decision-making process for clinicians and patients, especially when it yields a low enough baseline score to waive a minute absolute benefit of radiotherapy for achieving local control.

Consideration for Block Selection

The Oncotype DCIS Score is performed on tissue fixed in neutral-buffered formalin and embedded in paraffin. The optimal block for testing should represent the highest nuclear grade of DCIS, preferably with the greatest dimension on a single slide. In our experience, ≥2 mm of contiguous linear lesional tissue, at least in one dimension, is required. Foci with extensive comedo necrosis, leading to diminished cellularity, should also be avoided. Hemorrhage and adipose tissue do not need to be minimized because they contain little RNA and thus do not significantly affect the assay. In some cases, the core biopsy specimen may be more suitable for testing than the excisional specimen, particularly when a relatively small lesion was assessed by vacuum-assisted biopsy and the resection has minimal residual DCIS scattered around the biopsy site reaction. Special attention should be paid to Oncotype DCIS assay requests for lesions of debatable classification, such as encysted papillary carcinoma and solid papillary carcinoma without conventional invasion. The World Health Organization categorizes these lesions as low-risk lesions that in the absence of conventional invasion and recommends they be treated similarly to DCIS (World Health Organization classification of tumors of the breast). Clinicians should be made aware that the prognostic role of the Oncotype DCIS Score in these specific lesions has not been clinically validated. Another special consideration is related to the appropriate assay for DCIS with microinvasion. Currently, the Oncotype DCIS Score has not been clinically validated for cases with one or more foci of microinvasion, and performing the assay for invasive carcinoma is not technically feasible.

References


