Recommendation Report MOAC-4 REQUIRES UPDATING

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Clinical Utility of Multigene Profiling Assays in Invasive Early-Stage Breast Cancer

Members of the Molecular Oncology and Testing Advisory Committee

Recommendation Report MOAC-4 was reviewed in 2018 and the Molecular Oncology and Testing Advisory Committee determined that it REQUIRES UPDATING. (See Section 4: Document Assessment and Review for details)

The reviewed report is comprised of 4 sections. You can access the summary and full report here: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/31766

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Section 1</td>
<td>Recommendations</td>
</tr>
<tr>
<td>Section 2</td>
<td>Recommendation Report Methods Overview</td>
</tr>
<tr>
<td>Section 3</td>
<td>Systematic Review</td>
</tr>
<tr>
<td>Section 4</td>
<td>Document Assessment and Review</td>
</tr>
</tbody>
</table>

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For information about this document, please contact the authors through the PEBC via: Phone: 905-527-4322 ext. 42822 Fax: 905 526-6775 E-mail: ccopgi@mcmaster.ca
### Guideline Report History

<table>
<thead>
<tr>
<th>GUIDELINE VERSION</th>
<th>SYSTEMATIC REVIEW</th>
<th>PUBLICATIONS</th>
<th>NOTES and KEY CHANGES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original version 2016</td>
<td>2002 to Feb 2016</td>
<td>Full Report</td>
<td>Web publication</td>
</tr>
<tr>
<td>Current Version 2 December 2018</td>
<td>2016 to Apr 2018</td>
<td>New data found in Section 4: Document Assessment and Review</td>
<td>Updated web publication</td>
</tr>
</tbody>
</table>
Clinical Utility of Multigene Profiling Assays in Invasive Early-Stage Breast Cancer

Recommendations

The 2016 recommendations REQUIRE UPDATING

This means that the guidance document needs updating to ensure that the recommendations reflect current evidence and practice. The existing recommendations remain relevant and it is still appropriate for this document to be available while the updating process unfolds.

RESEARCH QUESTIONS

1. Given that there are now multiple multigene assays that can predict for recurrence in patients with invasive breast cancer, what is the level of evidence supporting the clinical validity and utility for each of these assays?
   a. Given that Oncotype DX is part of standard practice in Ontario, what is the evidence that other assays can complement or replace Oncotype DX for certain clinical utilities?

TARGET POPULATION

Women diagnosed with invasive early-stage breast cancer for whom further information is needed for treatment decision making.

INTENDED USERS

This Recommendation Report is targeted for use by clinicians, policy makers, and the Ontario Ministry of Health and Long-Term Care.

QUALITY OF EVIDENCE

The tumour marker utility grading system, which was proposed in 1996 [1] and later refined in 2009 [2], provides a framework to evaluate the clinical utility of tumour markers, and was used to grade the levels of evidence of the prognostic and predictive studies that inform the following recommendations. The study categories as defined by this system are summarized in Table 1-1, while Table 1-2 summarizes the level of evidence based on the aggregate quality of the identified studies.

RECOMMENDATIONS, KEY EVIDENCE, AND INTERPRETATION OF EVIDENCE

Recommendation Preamble

Multigene profiling assays are used in combination with clinical-pathological factors in invasive breast cancer patients to ascertain whether a patient’s estrogen receptor (ER)-positive/human epidermal growth factor receptor 2 (HER2)-negative tumour has an intrinsic high-risk or low-risk profile. Oncotype DX, Prosigna, and EndoPredict are examples of assays that are commercially available in Ontario. Although no assay represents a gold standard, Oncotype DX is supported by the widest range of evidence for prognosis and prediction of
chemotherapy benefit, while both Prosigna and EndoPredict have evidence-based validity in providing some of the same or similar clinical information. Figure 1-1 graphically summarizes the included recommendations in a decision tree format for clinical use. At the time of publication, Oncotype DX is the only assay that is publically funded in Ontario.

**Recommendation 1**

Clinicians may offer multigene profile assay testing to potential chemotherapy candidates with invasive breast carcinoma that is ER-positive/HER2-negative (Recommendation Type: Evidence-based; Evidence Quality: Level IB; Recommendation Strength: Moderate).

**Qualifying Statements for Recommendation 1**

- If the patient management plan has been decided based on clinical, pathologic, and/or patient-related factors and is unlikely to change, a multigene profiling assay should not be requested.

**Key Evidence for Recommendation 1**

Multiple clinical trials using retrospective testing on materials made available from a prospective trial (“prospective-retrospective”) have established Level IB evidence [1,2] for the prognostic validity of Oncotype DX [3-8], Prosigna [4,6,9-12], and EndoPredict/EPclin [13,14] scores in invasive breast cancer. Oncotype DX is the most well studied assay with respect to predicting chemotherapy benefit of high-risk tumours, with two category C studies providing Level II evidence for this clinical utility [15,16]. Studies examining physician treatment decisions show that multigene profiling assays may change management in 22% to 52% of cases, depending on the level of confidence of the pre-assay recommendation [17-23].

**Interpretation of Evidence for Recommendation 1**

The main purpose of multigene profiling assays is to determine whether a tumour has a high or low risk for recurrence. As such, all multigene profiling assays evaluate the intrinsic molecular characteristics of a tumour in order to prognosticate behaviour; however, the molecular markers used to ascertain this predicted risk differ between assays. The value in multigene profiling is more evident when an approach to systemic therapy remains difficult for the clinician to make, even after considering all clinical, pathologic, and patient-related factors. Oncotype DX, Prosigna (PAM50) and EndoPredict are all commercially available in Ontario and have Level IB evidence supporting their clinical utility.

**Recommendation 2**

In patients with node-negative ER-positive/HER2-negative disease, clinicians may use a low-risk result from Oncotype DX, Prosigna, or EndoPredict/EPclin assays to support a decision to withhold chemotherapy (Recommendation Type: Evidence-based; Evidence Quality: Level IB; Recommendation Strength: Moderate).

**Qualifying Statements for Recommendation 2**

- A treatment decision should be based on all available clinical and pathological information, rather than depending only on multigene profiling results.

**Key Evidence for Recommendation 2**

Based on the tumour marker utility grading system [1,2], there is Level IB evidence that even in the absence of chemotherapy, patients stratified as low-risk by Oncotype DX [3-7], Prosigna [4,6,9-12], and EndoPredict [13,14] had a low risk of recurrence at five and 10 years post-treatment. The ability of Oncotype DX to identify a very low-risk population (rate of freedom from distant recurrence at 5 years, 99.3%; 95% confidence interval [CI], 98.7% to 99.6%) has been confirmed by an interim analysis from a prospective trial (TAILORx) [8].
Interpretation of Evidence for Recommendation 2

Although Oncotype DX, Prosigna, and EndoPredict assays have all shown that in the absence of chemotherapy treatment, patients stratified as low risk have a low risk of recurrence, there are limited prospective validation data. Nevertheless, a low-risk result from a multigene profiling assay can support the decision to withhold chemotherapy in this subset of patients. Because such a decision is also informed by available clinical and pathological information, not all patients with low-risk tumour features require a multigene profiling assay.

Recommendation 3

In patients with node-negative ER-positive/HER2-negative disease, clinicians may use a high-risk result from Oncotype DX to support a decision to offer chemotherapy. A high-risk Oncotype DX result in this subpopulation has been associated with both poor prognosis without chemotherapy, and a prediction of benefit from giving chemotherapy (Recommendation Type: Evidence-based; Evidence Quality: Level IB-II; Recommendation Strength: Weak).

Qualifying Statements for Recommendation 3

- High-risk stratification by Oncotype DX may support a decision to offer chemotherapy, but treatment decision(s) should be based on all available clinical and pathological information, rather than depending only on Oncotype DX.

Key Evidence for Recommendation 3

Based on the tumour marker utility grading system [1,2], there is Level IB evidence that withholding chemotherapy is associated with a high-risk of recurrence in the high-risk subgroups identified through Oncotype DX [3-7], Prosigna [4,6,9-12], and EndoPredict [13,14]. Although Oncotype DX, Prosigna, and EndoPredict are supported by Level IB evidence for prognosticating high risk of recurrence in a subgroup of patients, only Oncotype DX has been evaluated to determine ability to predict a benefit from chemotherapy. Two studies evaluating the clinical validity of Oncotype DX in predicting chemotherapy benefit in high risk groups [15,16] were not perfectly designed to validate this use, but reported consistent results, resulting in Level II evidence to support the utility.

Interpretation of Evidence for Recommendation 3

Although they are distinct aspects of clinical validity, prognostication for recurrence in the absence of treatment and prediction of benefit from adjuvant chemotherapy, are often addressed together. Oncotype DX has sufficient evidence to address both the prognostic and predictive validity for high-risk tumours simultaneously. However, the two studies that were identified to evaluate the predictive ability of Oncotype DX used chemotherapy regimens that are no longer widely used in Ontario. An ongoing trial (TAILORx) that will provide additional data about the predictive ability of Oncotype DX in the context of more modern adjuvant chemotherapy treatment has not yet reported primary outcome data. Thus, current evidence for the predictive validity of Oncotype DX is of low level (Level II) and supports only a weak recommendation. Based on prognostic ability, other multigene profiling assays likely also have similar predictive utility; however, further validation is needed to support a recommendation for their use.

Recommendation 4

In some patients with ER-positive/HER2-negative tumours and 1-3 nodes involved (N1a disease), clinicians may withhold chemotherapy based on a low-risk Oncotype DX or Prosigna score if the decision is supported by other clinical, pathological, or patient-related factors.
### Qualifying Statements for Recommendation 4

- Node-positive disease is associated with a relatively high risk of recurrence and chemotherapy is frequently recommended.
- Currently, multigene profiling assays are not approved and funded in Ontario for node-positive disease, unless the largest metastatic deposit measures 2 mm or less (micrometastatic disease, pN1mi). The clinical outcome of patients with pN1mi disease is considered more similar to those with node-negative disease; thus, clinicians may offer multigene profiling assay testing for these patients.
- The presence of isolated tumour cells (largest deposit less than 0.2 mm or 200 cells) is considered node-negative disease in this setting.

### Key Evidence for Recommendation 4

Based on the tumour marker utility grading system [1,2], there is Level IB evidence that node-positive low-risk subgroups identified through Oncotype DX [3,15] and Prosigna [11,12] experience lower recurrence rates, even in the absence of adjuvant chemotherapy. However, a low-risk Oncotype DX recurrence score (RS) for a node-positive patient carries a recurrence risk similar in magnitude to an intermediate-to-high RS for a node-negative patient [3,4]. Analysis from the SWOG 8814 trial [15] shows that a high-risk Oncotype DX RS is predictive for chemotherapy benefit, albeit with a wide confidence interval (Level II evidence).

### Interpretation of Evidence for Recommendation 4

Although there is evidence for the prognostic ability of Oncotype DX and Prosigna in node-positive patients, the clinical utility of the multigene profiling assays depends on potential benefit to the patients with node-positive disease. Currently, the routine use of multigene profiling assays for ER-positive/HER2-negative node-positive tumours is not supported by evidence. As such, clinical judgment is needed in considering a role for multigene profiling assays in a subset of patients with low nodal disease burden (e.g. micrometastases only). In current practice, this subset remains a small minority of node-positive cases.

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### Recommendation 5

In patients with ER-positive disease, there is insufficient evidence to recommend the use of multigene profiling assays to inform clinical decision making for late risk of recurrence. A high-risk score using Prosigna or EndoPredict prognosticates for late recurrence; however, evidence is lacking that these tests predict for benefit of extended adjuvant endocrine treatment beyond five years. (Recommendation Type: Consensus-based; Evidence Quality: Lack of evidence; Recommendation Strength: Weak).

### Key Evidence for Recommendation 5

Intervention studies that assess the predictive ability of multigene profiling assays for late recurrence are lacking. The prognostic value of Prosigna [4,12] and EndoPredict [13,14] for late recurrence is based on multivariate statistical analysis performed retrospectively on completed prospective trials (Level II evidence [1,2]). Although a high Oncotype DX RS is also associated with late recurrence, on multivariate analysis the statistical difference between early and late recurrence loses significance [6,15].

### Interpretation of Evidence for Recommendation 5

The ability to predict late recurrence and offer treatment for patients at risk for late recurrence is important; however, the evidence is currently insufficient to support the
clinical utility of multigene profiling assays for this purpose.

FUTURE RESEARCH

Multigene panels are now established tools that have analytic and clinical validity in identifying intrinsically low-risk and high-risk molecular profiles of breast cancer. Among those panels that are commercially available, Oncotype DX has the most established evidence base. Additional prospective studies of the clinical validity and utility of Oncotype DX are pending analysis, mainly TAILORx [24], a prospective randomized trial of hormone therapy versus hormone therapy plus chemotherapy for patients with intermediate Oncotype DX RS; and RxPONDER, a prospective randomized trial to determine benefit of chemotherapy in 1-3 node-positive patients with low-to-intermediate RS. These large studies are well designed to address specific questions of clinical utility of Oncotype DX.

Prosigna, EndoPredict/EPclin, and MammaPrint are other commercially available multigene assays, using the same biological principles as Oncotype DX but comprising different panels of mostly non-overlapping genes. The evidence supports the concept that these tests are at least as informative as Oncotype DX with respect to finding clinically relevant intrinsic molecular profiles [4,6]. Nevertheless, what has been lacking are prospective clinical trials both validating the clinical validity of these assays and designed for relevant clinical utility. An example of one ongoing trial is MINDACT [25], in which patients were randomized to chemotherapy based on both their gene profile (by MammaPrint) and their clinical risk (based on a modified Adjuvant! Online estimate). As additional high-level evidence becomes available, the above recommendations will continue to evolve, possibly including treatment decisions for a wider range of breast carcinoma.

Table 1-1. Summary of Study Categories as Defined by the Tumour Marker Utility Grading System

<table>
<thead>
<tr>
<th>Study Category</th>
<th>Elements of Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>RCT designed with tumour biomarker/assay as the intervention</td>
</tr>
<tr>
<td>B</td>
<td>RCT designed to address a treatment intervention that is not the tumour biomarker/assay. Study prospectively enrolls and follow patients, and collects tumour samples, and then uses archived tumour tissue retrospectively to evaluate the tumour biomarker/assay</td>
</tr>
<tr>
<td>C</td>
<td>Prospective observational registry study that prospectively enrolls patients in a registry and collects, processes, and archives tumour specimens, but treatment and follow-up are standard of care. Archived tumour tissue is used retrospectively to evaluate the tumour biomarker/assay</td>
</tr>
<tr>
<td>D</td>
<td>Retrospective studies</td>
</tr>
</tbody>
</table>

Abbreviation: RCT, randomized controlled trial.

Table 1-2. Levels of Evidence based on the Tumour Marker Utility Grading System

<table>
<thead>
<tr>
<th>Level of Evidence</th>
<th>Number and Types of Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>1 category A study</td>
</tr>
<tr>
<td>IB</td>
<td>At least 2 category B studies with consistent results</td>
</tr>
<tr>
<td>II</td>
<td>1 category B study, OR multiple category B studies with inconsistent results, OR at least 2 category C studies with consistent results</td>
</tr>
<tr>
<td>III</td>
<td>1 category C study OR multiple category C studies with inconsistent results</td>
</tr>
</tbody>
</table>
| IV                | Any number of category D studies. Note that Level IV evidence is not sufficient for
Section 1: Recommendations - June 8, 2016
Figure 1-1. Multigene Profiling Assay Decision Tree

Invasive breast cancer (not microinvasive) that is: ER-positive, HER2-negative

Node Positive?

No

Do not order a multigene profiling assay. Evidence for benefit is Level IV

Yes

Node Negative?

Do the clinical and pathological features of the tumour allow for a well-informed clinical decision to withhold or give chemotherapy?

No

Yes

Are you gathering evidence to support withholding chemotherapy to a node-negative, ER-positive, HER2-negative patient?

Yes

Are you gathering evidence to support offering chemotherapy to a node-negative, ER-positive, HER2-negative patient?

Yes

Oncotype DX, Prosigna, and EndoPredict are all validated and have utility for this indication (Level IB)

Oncotype DX is prognostic for a low-to-high risk result (Level IB) and predictive for a high-risk result (Level II)

No

Yes

Oncotype DX and Prosigna are prognostic within a non-chemotherapy treatment arm (Level IB). Oncotype DX is predictive for chemotherapy benefit in high-risk group (Level II)

Do not order a multigene profiling assay. The treatment decision is valid based on clinical judgement

Do not order a multigene profiling assay. The treatment decision is valid based on clinical judgement

* In practice, this usually applies to micrometastatic (N1mi) disease