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Guideline MOTAC-4 Version 3

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

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

Members of the Multigene Profiling Assays in Early-Stage Invasive Breast Cancer Expert Panel

Report Date: June 2, 2025

Guideline MOTAC-4 Version 2 was reviewed in 2025 and ENDORSED by the Multigene Profiling Assays in Early-Stage Invasive Breast Cancer Expert Panel (See Section 6: Document Assessment and Review for details)

Guideline MOTAC-4 Version 2 is comprised of 6 sections. You can access the summary and full report here:
https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/31766

For information about this document, please contact the PEBC:
Phone: 905-527-4322 ext. 42822 E-mail: ccopgi@mcmaster.ca

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Phone: 905-527-4322 ext. 42822 E-mail: ccopgi@mcmaster.ca

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PUBLICATIONS RELATED TO THIS REPORT

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

Section 1: Recommendations

This section is a quick reference guide and provides the guideline recommendations only. For key evidence associated with each recommendation, the systematic review, and the guideline development process, see the Full Report.

GUIDELINE OBJECTIVES
To update clinical guidance on the use of multigene profiling assays in individuals with early-stage invasive breast cancer.

TARGET POPULATION
Individuals diagnosed with early-stage invasive breast cancer for whom further information is needed for prognosis and treatment decision making. In this guideline, early-stage invasive breast cancer is defined as stage I to III breast cancers that are surgically operable and do not have evidence of inflammatory, locally recurrent or distant metastatic disease with pT1-T3, pN0-N1a based on surgical pathologic staging.

INTENDED USERS
This guideline is targeted for clinicians and policy makers involved in the diagnosis and treatment of breast cancer.

PREAMBLE
The purpose of this guideline is to determine the clinical utility of multigene profiling assays (i.e., Oncotype DX, MammaPrint, Prosigna, EndoPredict, and Breast Cancer Index), not to identify which assay is better. No prospective studies have compared these head-to-head. Given that the assays use different scoring systems and classification systems, please refer to Table 1-1 for a summary of each of the assays. Further, this guideline does not cover the utility of multigene profiling assays in helping to guide clinical treatment decisions regarding the use of either neoadjuvant chemotherapy or radiation.

RECOMMENDATIONS, KEY EVIDENCE, AND JUSTIFICATION

Recommendation 1
In patients with early-stage estrogen receptor (ER)-positive/human epidermal growth factor 2 (HER2)-negative breast cancer, clinicians should consider using multigene profiling assays (i.e., Oncotype DX, MammaPrint, Prosigna, EndoPredict, and Breast Cancer Index) to help guide the use of systemic therapy.
Qualifying Statements for Recommendation 1
• There is currently insufficient evidence to use multigene profiling assays among patients with either HER2-positive or triple negative breast cancers. • Multigene profiling assays are recommended for use in patients with lymph node-negative or lymph node-positive (1-3 lymph nodes) disease who are under consideration for adjuvant chemotherapy if the use is supported by other clinical, pathological, or patient-related factors. Clinical and pathological features include patient age, tumour grade, tumour size and nodal status. • One multigene profiling assay should be requested per patient to guide a specific treatment decision. Requesting multiple tests with different multigene profiling assays

on an individual tumour specimen to guide a single treatment decision is discouraged. Additional testing may be considered for patients with either repeat metachronous breast cancer diagnoses or synchronous breast cancer diagnoses where tumour specimens display varying morphologies, grade or hormone receptor status.
- Multigene profiling assays should be interpreted cautiously in premenopausal patients where a significant benefit from adjuvant chemotherapy may still exist despite a low-risk score.

Recommendation 2

In patients with early-stage node-negative ER-positive/HER2-negative disease, clinicians may use a low-risk result from Oncotype DX, MammaPrint, Prosigna, EndoPredict/EPclin, or Breast Cancer Index assays to support a decision not to use adjuvant chemotherapy.

Qualifying Statements for Recommendation 2

- Patients <50 years of age may still benefit from chemotherapy despite low-risk scores from multigene assay testing. Risk scores should be interpreted with caution and decisions should be made while considering other clinical, pathological, or patient-related factors.
- Treatment decisions should be based on all available clinical and pathological information for each patient, rather than depending entirely on multigene profiling test results.
- In patients with a low-grade tumour (i.e., grade 1) less than 1 cm in size, the Working Group members do not recommend a multigene assay profiling as this is unlikely to inform a treatment decision to use adjuvant chemotherapy.

Added in June 2025:

- Patients in whom surgical axillary staging is omitted, and who are clinically node negative by physical examination and/or axillary ultrasound, should be considered node negative and eligible for molecular profiling for node negative disease. (See Section 6 for details).

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 Oncotype DX recurrence score is capable of predicting adjuvant chemotherapy benefit.

Qualifying Statements for Recommendation 3

- MammaPrint, Prosigna, EndoPredict or EPclin, and Breast Cancer Index do not have sufficient evidence to support a predictive benefit of adjuvant chemotherapy among clinically low-risk patients with breast cancer whose multigene profiling testing indicates a high-risk score.

Recommendation 4

In postmenopausal patients with ER-positive/HER2-negative tumours and one to three nodes involved (N1a disease), clinicians may withhold chemotherapy based on a low-risk Oncotype DX or MammaPrint score if the decision is supported by other clinical, pathological, or patient-related factors.

Qualifying Statements for Recommendation 4

- Premenopausal patients <50 years of age have a significant benefit from chemotherapy despite low-risk scores from multigene assay testing. Risk scores should be interpreted with caution and decisions should be made while considering other clinical, pathological, or patient-related factors.

- It is uncertain whether at least some of the benefit of chemotherapy among premenopausal patients may be due to chemotherapy induced amenorrhea versus the cytotoxic effects of treatment.
- The Prosigna, EndoPredict/EPclin, and Breast Cancer Index assays can identify low-risk node-positive patients whose prognostic outcomes are favourable; however, these assays have not demonstrated predictive evidence to support withholding adjuvant chemotherapy among higher risk, node-positive, ER-positive, HER2-negative breast cancer patients.

Recommendation 5

The evidence to support the use of molecular profiling to select the duration of endocrine therapy is evolving. In patients with ER-positive disease, clinicians may consider using a Breast Cancer Index (BCI) (H/I) high assay result to support a decision to extend adjuvant endocrine therapy if the decision is supported by other clinical, pathological, or patient-related factors.

Qualifying Statements for Recommendation 5

- While a number of studies have demonstrated clinical utility of BCI for extending adjuvant endocrine therapy, the preliminary results of the NSABP B42 trial are negative leading to some uncertainty. Treatment decisions should be based on all available clinical and pathological information for each patient, rather than depending only on multigene profiling tests.
- MammaPrint, Oncotype DX, Prosigna, and EndoPredict currently have insufficient evidence to guide extension of adjuvant endocrine therapy; however, these molecular assays may prognosticate a very low rate of disease recurrence that might not justify an extension of endocrine therapy.

Figure 1-1. Multigene Profiling Assay Decision Tree for Adjuvant Chemotherapy in Node-Negative Patients

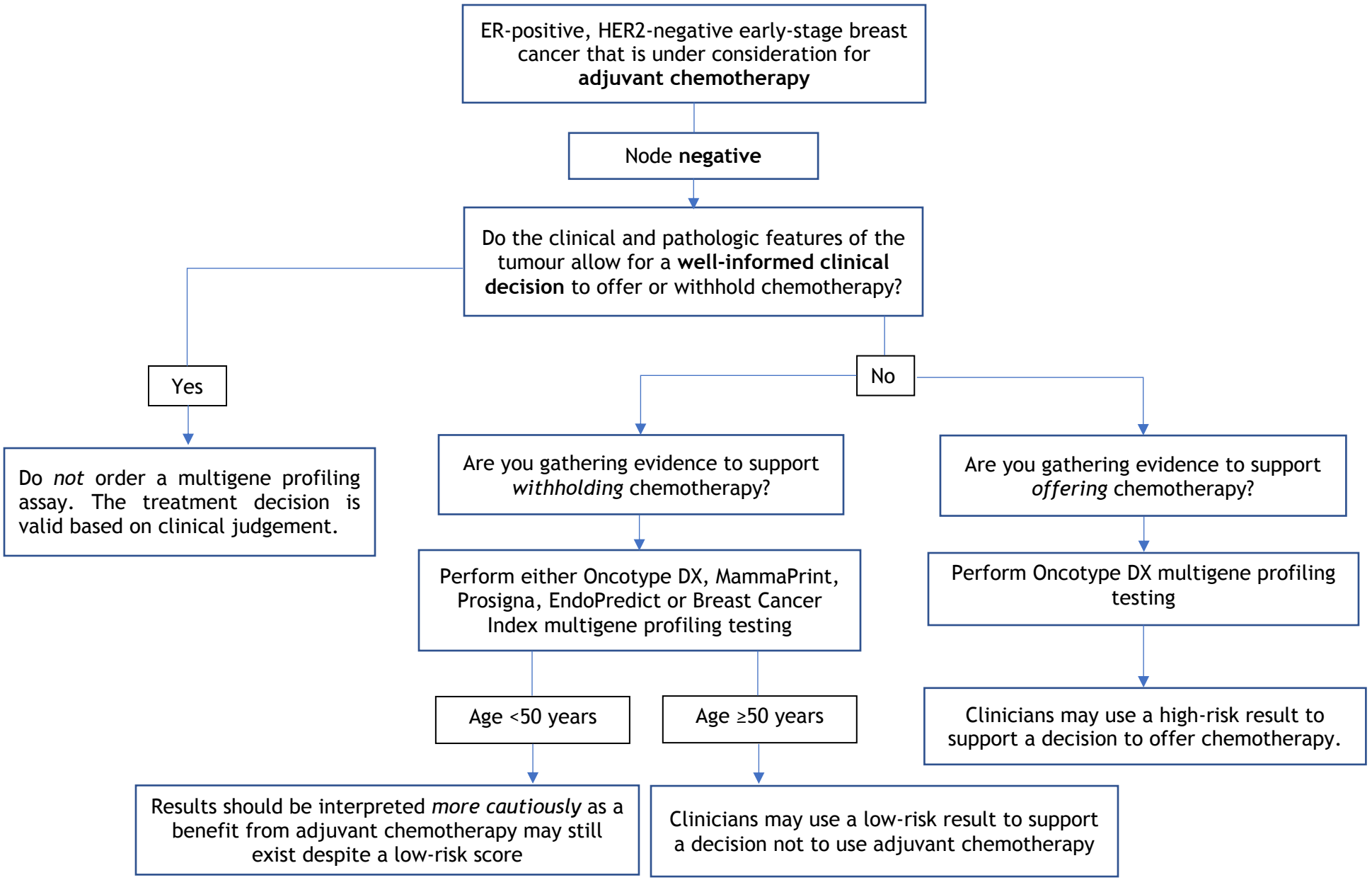

Figure 1-2. Multigene Profiling Assay Decision Tree for Adjuvant Chemotherapy in Node-Positive Patients

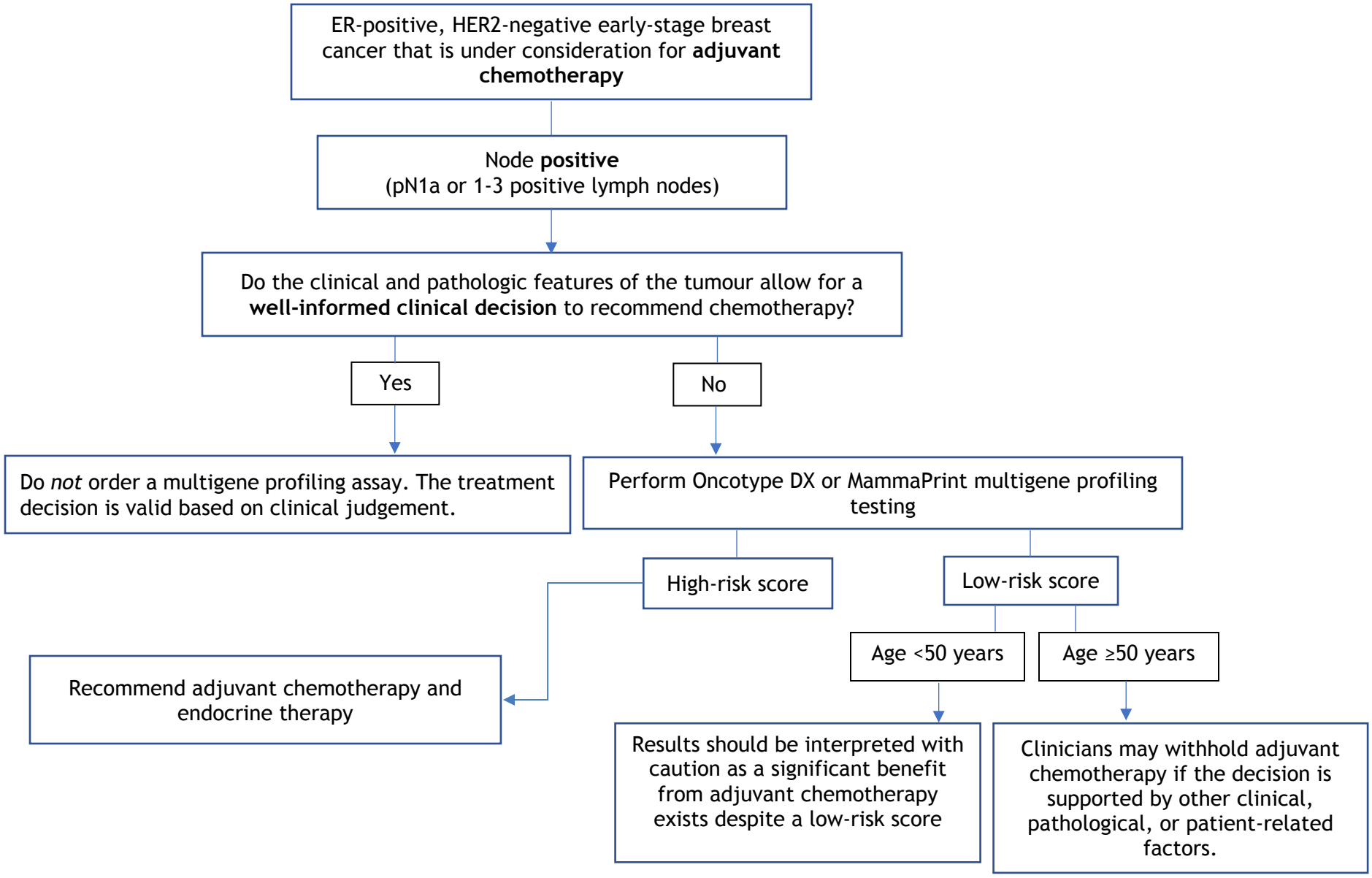

Figure 1-3. Multigene Profiling Assay Decision Tree for Extended Adjuvant Endocrine Therapy

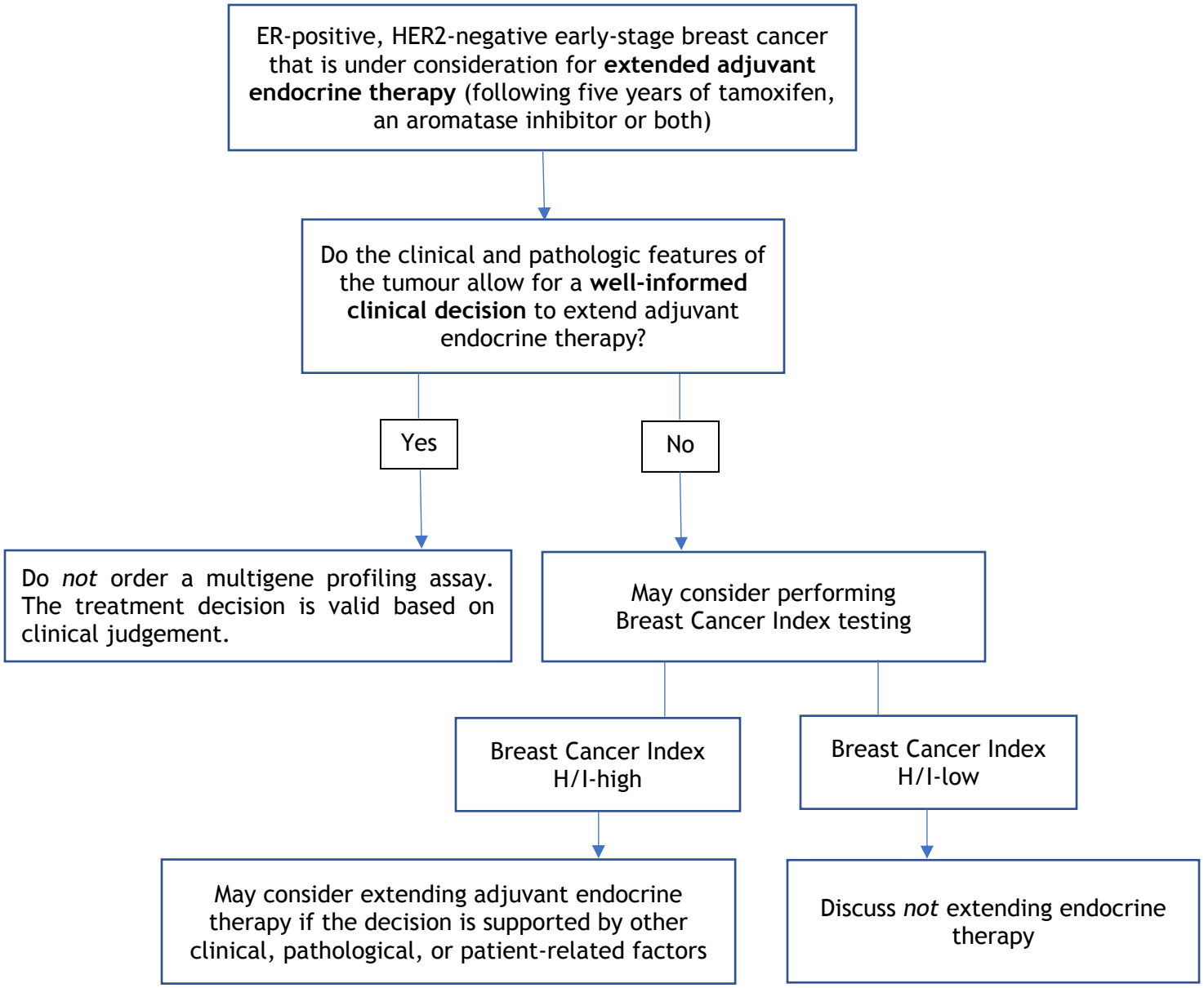

Table 1-1. Summary of assay characteristics.

	Oncotype DX	Prosigna	MammaPrint	EndoPredict	Breast Cancer Index
Tissue Required	FFPE	FFPE	FFPE or fresh tissue	FFPE	FFPE
Technique	qRT-PCR	qRT-PCR and nCounter DX Analysis System	Microarray	qRT-PCR	qRT-PCR
Assay Output	RS (0-100)	Intrinsic subtype and ROR score (0-100)	MammaPrint Index Risk of distant recurrence at 5 years	EPclin score (1-6) Molecular score (1-15)	BCI score (0-10) and BCI (H/I) low and BCI (H/I) high (ratio HoxB13 and interleukin-17B receptor)
Categories for Risk Measurement	*TAILORx categories* Low: ≤15 Intermediate: 16–25 High: 26–100 *Pre-TAILORx categories* Low: <18 Intermediate: 18–30 High: ≥31	*LN-negative* Low: 0–40 Intermediate: 41–60 High: 61–100 *LN-positive (1-3 nodes)* Low: 0–40 High: 41–100	Low: 0 to 1 High: −1 to 0	*EPclin score* Low: <3.3 High: ≥3.3 *Molecular score* Low: <5 High: ≥5	*BCI predictive H/I* Low: <0.06 High: ≥0.06 *BCI prognostic node-negative* Low: <5.0825 Intermediate: 5.0825-6.5025 High: ≥6.5025 *BCI prognostic node-positive* Low: <6.93 High: ≥6.93
Regulatory Approval or Endorsement	Assay conducted in centralized Exact Science's CLIA-certified lab	FDA cleared for decentralized testing (2014)	FDA cleared for Agendia centralized lab testing in FFPE (2015)	CE Mark for decentralized testing (2012)	Assay conducted in centralized CAP/CLIA-certified lab
Manufacturer	Exact Sciences Corp.	Veracyte	Agendia	Myriad Genetics, Inc.	Biotheranostics, Inc.
Testing Location	Central (1 laboratory in US)	Various labs across US, UK	Central (1 laboratory in the Netherlands, 1 in US)	Central laboratory in the US	Central (1 laboratory in US)
Genes, n	21-gene assay	50-gene assay	70-gene assay	12-gene assay EPclin score: 12-gene assay plus tumour size and nodal status	*HOXB13:IL17BR* expression ratio (H/I) and Molecular Grade Index

Abbreviations: BCI (H/I), Breast Cancer Index (HOXB13/IL17BR); CAP: College of American Pathologists; CLIA: Clinical Laboratory Improvement Amendments; EPclin, EndoPredict clinical score; ER, estrogen receptor; FDA, Food and Drug Administration; FDA: Food and Drug Administration; FFPE, formalin-fixed paraffin-embedded; LN, lymph node; qRT-PCR, quantitative reverse-transcription polymerase chain reaction; ROR: risk of recurrence; RS, recurrence score; UK: United Kingdom US, United States.