Test Specific Guidelines

EndoPredict for Breast Cancer Prognosis

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Introduction

The EndoPredict assay for breast cancer prognosis is addressed by this guideline.

Procedures Addressed

The inclusion of any procedure code in this table is provided for informational purposes and is not a guarantee of coverage nor an indication that prior authorization is required.

Procedure addressed by this guideline	Procedure codes
EndoPredict Breast Cancer Assay	81522

What Is EndoPredict for Breast Cancer Prognosis?

Definition

EndoPredict® is a commercial multigene expression profiling assay designed to assess prognosis in individuals with early-stage breast cancer.[1-4]

The assay combined with results of the tumor size and nodal status is intended to predict the likelihood of women with early stage, node-negative, hormone receptor positive, and HER2 negative breast cancer of developing metastasis within 10 years of initial diagnosis.[1-4]

This test identifies 12 genes related to tumor proliferation and hormone receptor activity, but does not assess ER or HER2 status.[1-4]

Test results of the 12-gene risk score are designed to guide decisions regarding adjuvant systemic chemotherapy in women with early-stage invasive breast cancer with known hormone receptor and human epidermal growth factor receptor 2 (HER2) status following surgical management of breast cancer.[1-4]

Test Information

Introduction

The EndoPredict assay analyzes the gene expression level of 8 breast-cancer related genes and 4 reference genes (12 genes in total) within a breast tumor to determine an EndoPredict score (EP), ranging from 0 to 15.[1-4]

Each score corresponds to a specific likelihood of breast cancer recurrence within 10 years after the initial diagnosis. Based on the calculated score, the individual is categorized as follows:

Low risk: 0 to <5

High risk: 5 to 15 for distant recurrence under endocrine therapy.[1-4]

When combining the score with clinical risk factors, such as tumor size and node status, a combined molecular and clinical risk score, EPclin, is established. The integrated EPclin Risk score, estimating the 10-year likelihood of distant recurrence, ranges from 1 to 3.5 for low risk and >3.5 to 6.0 for high risk. Individuals placed in the high-risk group may be recommended to have chemotherapy, but those in the low-risk group may be able to forego chemotherapy and be spared its associated complications.[1-4]

Guidelines and Evidence

Introduction

This section includes relevant guidelines and evidence pertaining to EndoPredict testing.

American Society of Clinical Oncology

The most recent evidence-based guideline from the American Society of Clinical Oncology (ASCO, 2022) stated:[5]

"If a patient is postmenopausal and has breast cancer that is node-negative or node-positive with 1-3 positive nodes, the clinician may use the EndoPredict test to guide decisions for adjuvant endocrine and chemotherapy (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate)."

"If a patient is premenopausal and has breast cancer that is node-negative or node-positive with 1-3 positive nodes, the clinician should not use the EndoPredict test to guide decisions for adjuvant endocrine and chemotherapy (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: moderate)."

"If a patient has breast cancer with 4 or more positive nodes, evidence on the clinical utility of routine use of the EndoPredict test to guide decisions for

adjuvant endocrine and chemotherapy is insufficient (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate)."

"If a patient has node-negative breast cancer and has had 5 years of endocrine therapy without evidence of recurrence, there is insufficient evidence to use Oncotype DX, EndoPredict, Prosigna, Ki67, or IHC4 scores to guide decisions about extended endocrine therapy (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate)."

"If a patient has HER2-positive breast cancer or TNBC [triple negative breast cancer], the clinician should not use multiparameter gene expression or protein assays (Oncotype DX, EndoPredict, MammaPrint, BCI, Prosigna, Ki67, or IHC4) to guide decisions for adjuvant endocrine and chemotherapy (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: strong)."

European Society of Medical Oncology

The European Society of Medical Oncology (ESMO, 2015) stated the following regarding gene expression profiles:[6]

“Gene expression profiles, such as MammaPrint (Agendia, Amsterdam, the Netherlands), Oncotype DX Recurrence Score (Genomic Health, Redwood City, CA), Prosigna (Nanostring Technologies, Seattle, WA) and EndoPredict (Myriad Genetics), may be used to gain additional prognostic and/or predictive information to complement pathology assessment and to predict the benefit of adjuvant chemotherapy. The three latter tests are designed for patients with ER-positive early breast cancer only.”

“In cases of uncertainty regarding indications for adjuvant chemotherapy (after consideration of other tests), gene expression assays, such as MammaPrint, Oncotype DX, Prosigna and Endopredict, may be used, where available.”

“In cases when decisions might be challenging, such as luminal B HER2-negative and node-negative breast cancer, commercially available molecular signatures for ER-positive breast cancer, such Oncotype DX, EndoPredict, Prosigna, and for all types of breast cancer (pN0–1), such as MammaPrint and Genomic Grade Index, may be used in conjunction with all clinicopathological factors, to help in treatment decision making.”

In 2019, ESMO stated: “Validated gene expression profiles may be used to gain additional prognostic and/or predictive information to complement pathology assessment and help in adjuvant ChT [chemotherapy] decision making."[7]

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN, 2022) Clinical Practice Guidelines for Breast Cancer considered the 12-gene EndoPredict assay suitable for prognostic purposes (with evidence category 2A):[8]

"For patients with T1 and T2 HR [hormone receptor]-positive, HER2-negative, and pN0 [lymph node-negative] tumors, a 12-gene low- risk score, regardless of T size, places the tumor into the same prognostic category as T1a–T1b, N0, M0. In ABCSG 6/8, patients in the low risk group has risk of distant recurrence of 4% at 10 years and in the TransATAC study, patients with 1-3 positive nodes in the low-risk group had a 5.6% risk of distant recurrence at 10 years."

These guidelines consider the therapeutic predictive value of this assay as "not determined".

National Institute for Health and Care Excellence

The National Institute for Health and Care Excellence (NICE, 2018) stated:[9]

"EndoPredict (EPClin score), Oncotype DX Breast Recurrence Score and Prosigna are recommended as options for guiding adjuvant chemotherapy decisions for people with oestrogen receptor (RE)-positive, human epidermal growth factor receptor 2 (HER2)-negative and lymph node (LN)-negative (including micrometastatic disease; see section 5.4) early breast cancer, only if:"

"they have intermediate risk of distant recurrence using a validated tool such as PREDICT or the Nottingham Prognostic index"

"information provided by the test would help them choose, with their clinician, whether or not to have adjuvant chemotherapy taking into account their preference".

Ontario Health (Cancer Care Ontario) Program in Evidence-Based Care

The Ontario Health (Cancer Care Ontario) Program in Evidence-Based Care (PEBC, 2022) conducted a systematic review of the literature to serve as the basis of their clinical practice guideline. The clinical practice guideline for the clinical utility of multigene profiling assays in early-stage invasive breast cancer stated the following regarding EndoPredict:[10]

"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 the Breast Cancer Index) to help guide the use of systemic therapy.

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."

St. Gallen International Expert Consensus

The St. Gallen International Expert Consensus (2017) stated:[11]

"The panel agreed that there was no role in clinical low risk cases [such as pT1a/b, grade 1 (G1), ER high, N0] and similar settings where chemotherapy would not be indicated under any circumstances."

"The Panel agreed that a number of gene expression signatures served as prognostic markers in the setting of adjuvant endocrine therapy in node-negative breast cancers, including the 21 gene recurrence score, the 70 gene signature, the PAM50 ROR scoreV R, the EpClin score V R, and the Breast Cancer Index V R. The Panel endorsed all of these assays for guiding the decision on adjuvant chemotherapy in node-negative tumors as they all identify node-negative cases at low risk, with an excellent prognosis that would not warrant chemotherapy."

"The Panel agreed that gene expression signatures offered information that can refine the prognosis for node-positive breast cancers. However, the Panel did not uniformly endorse the use of gene expression signatures for making treatment decisions regarding adjuvant chemotherapy in node positive cases."

"The Panel did not recommend the use of gene expression signatures for choosing whether to recommend extended adjuvant endocrine treatment, as no prospective data exist and the retrospective data were not considered sufficient to justify the routine use of genomic assays in this setting."

"In patients who are not candidates for adjuvant chemotherapy owing to comorbid health conditions or tumor stage/risk, or in patients who 'obviously' need adjuvant chemotherapy, typically including stage III breast cancer, there is no routine need for genomic tests."

"In general, the zone 'in between' is where genomic assays may be most valuable. These would often be patients with tumors between 1 and 3 cm, with zero to two or three positive lymph nodes, and intermediate proliferative fraction. Multigene assay should not be the only factor considered in making a decision to proceed or to avoid chemotherapy."

In 2019, the panel stated they "believed strongly that genomic assays are valuable for determining whether or not to recommend adjuvant chemotherapy in T1/T2 N0 ER-positive breast cancers, and recognized the value of such tests in patients with ER-positive tumors and limited nodal involvement".[12]

Selected Relevant Publications

There is adequate evidence in the peer-reviewed literature to support testing with EndoPredict in women with early stage (ER+/HER2-) node-negative breast cancer who are considering adjuvant chemotherapy. However, there is insufficient evidence in the peer-reviewed literature regarding the prognostic or predictive use of EndoPredict in women with early stage (ER+/HER2-), node-positive, invasive breast cancer who are either considering adjuvant chemotherapy or who are disease-free at 5 years after initial diagnosis, currently receiving adjuvant hormonal therapy, and who are considering continuing hormonal therapy.[13-34]

Additional prospective-retrospective studies evaluating EndoPredict/EPClin scores and the magnitude of association with distant recurrence or survival outcomes at 10 years with consistently narrow precision estimates are necessary to support the expanded use of the test to identify women who could safely forego adjuvant chemotherapy, spared associated complications, without increasing the risk for disease recurrence and metastatic disease. No direct clinical utility studies were identified that demonstrate EndoPredict can guide clinical decision making in a manner that results in improved health outcomes. Several decision impact studies showed that EndoPredict results increased physician confidence and changed treatment recommendations for some individuals however, these studies did not report the outcomes associated with these changes in treatment.

Clinical trials may be ongoing. Additional information can be found at https://clinicaltrials.gov.

Criteria

Introduction

Requests for EndoPredict testing are reviewed using these criteria.

Previous Testing:

No repeat EndoPredict testing on the same tumor when a result was successfully obtained, and

No previous gene expression assay (e.g. OncotypeDx Breast) performed on the same tumor when a result was successfully obtained, AND

Required Clinical Characteristics:

Primary invasive breast cancer meeting all of the following criteria:

Unilateral tumor

Tumor size >0.5cm (5mm) in greatest dimension (T1b-T3)

Hormone receptor positive (ER+ or PR+), and

HER2 negative, and

The individual has no regional lymph node metastasis (pN0) or only micrometastases (pN1mi, malignant cells in regional lymph node(s) not greater than 2.0mm), and

Adjuvant endocrine systemic chemotherapy is a planned treatment option for the individual or results from this EndoPredict test will be used in making adjuvant chemotherapy treatment decisions, AND

Rendering laboratory is a qualified provider of service per the Health Plan policy.

Other Considerations

Testing Multiple Samples:

When more than one ipsilateral breast cancer primary is diagnosed, testing should be performed on the tumor with the most aggressive histologic characteristics. If an exception is requested, the following criteria will apply:

There should be reasonable evidence that the tumors are distinct (e.g., different quadrants, different histopathologic features, etc.), AND

There should be no evidence from either tumor that chemotherapy is indicated (e.g., histopathologic features or previous EndoPredict result of one tumor suggest chemotherapy is indicated), AND

If both tumors are to be tested, both tumors must independently meet the required clinical characteristics

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