EndoPredict for Breast Cancer Prognosis

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan’s procedure code list for management requirements.

<table>
<thead>
<tr>
<th>Procedure addressed by this guideline</th>
<th>Procedure codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>EndoPredict Breast Cancer Assay</td>
<td>81599</td>
</tr>
<tr>
<td></td>
<td>S3854</td>
</tr>
</tbody>
</table>

What is EndoPredict for breast cancer prognosis

Definition

EndoPredict® is a commercial multigene expression profiling assay designed to assess prognosis in early-stage breast cancer patients.¹

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

Test information

- 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. Each score corresponds to a specific likelihood of breast cancer recurrence within 10 years after the initial diagnosis. Based on the calculated score, the patient is categorized as follows:
  - Low risk: 0 to <5
• High risk: 5 to 15 for distant recurrence under endocrine therapy.¹

• 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 EPclin score assigns patients into low- and high-risk groups. Patients 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

Guidelines and evidence

• The National Comprehensive Cancer Network (NCCN) 2018 Clinical Practice Guidelines for Breast Cancer consider the 12-gene EndoPredict assay suitable for prognostic purposes (with evidence category 2A):²

  o “For patients with T1 and T2 hormone receptor-positive, HER2-negative, and 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, M0.13 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.”

  o These guidelines consider the therapeutic predictive value of this assay as “not determined”.

• The National Institute for Health and Care Excellence (NICE) 2018 stated the following:³

  o “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”.

• St. Gallen International Expert Consensus (updated 2017):⁴

  o “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.”

  o “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 score, the EpClin score, and the Breast Cancer Index. 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.”

- The American Society of Clinical Oncology (ASCO, 2016) published a clinical practice guideline regarding the use of biomarkers to guide clinical decision-making on adjuvant systemic therapy among women with early-stage invasive breast cancer. Based on a review of the peer-reviewed scientific evidence, the following recommendations were published:

  - “If a patient has ER/PgR-positive, HER2-negative (node-negative) breast cancer, the clinician may use the 12-gene risk score (EndoPredict; Sividon Diagnostics, Koln, Germany) to guide decisions on adjuvant systemic chemotherapy. Type: evidence based. Evidence quality: intermediate. Strength of recommendation: moderate.”

  - “If a patient has ER/PgR-positive, HER2-negative (node-positive) breast cancer, the clinician should not use the 12-gene risk score (EndoPredict) to guide decisions on adjuvant systemic chemotherapy. Type: evidence based. Evidence quality: insufficient. Strength of recommendation: moderate.”

  - “If a patient has HER2-positive breast cancer or TN breast cancer, the clinician should not use the 12-gene risk score (EndoPredict) to guide decisions on adjuvant systemic therapy. Type: informal consensus. Evidence quality: insufficient. Strength of recommendation: strong.”

- European Society of Medical Oncology (ESMO) 2015.
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.”

Two clinical validation studies were identified that used archived specimens from previous prospective RCTs (retrospective-prospective study). Of the studies identified, these two prospective-retrospective studies are considered moderate quality evidence (Simon Level I evidence; category B; prospective using archived samples).

Filipits et al. (2011) evaluated two groups of patients derived from two independent RCTs (ABCSG-6 and ABCSG-8) to assess the validity of both the EP and EPclin. ABCSG-6 was a phase 3 RCT comparing tamoxifen alone for 5 years with tamoxifen in combination with aminoglutethimide for the first 2 years of treatment in postmenopausal women. In ABCSG-8, postmenopausal breast cancer patients were randomly assigned to receive tamoxifen for either 5 or 2 years followed by anastrozole for 3 years. Filipits et al. (2011) included women who had participated in the ABCSG-6 trial (n=378; tamoxifen-only arm; mean follow-up, 97.4 months) or the ABCSG-8 trial (n=1324; mean follow-up, 72.3 months). All tumor specimens were collected at the time of surgery before adjuvant therapy. Assessors of samples, qRT-PCR analyses and score calculations were blinded to clinical and outcome data. The primary outcome measure was distant disease recurrence. Study authors reported that qRT-PCR was successfully analyzed in ~96% and ~99% of the two patient groups.

EPclin had significantly greater prognostic power compared with clinical pathology factors alone (c indices: 0.76 vs 0.75; P=0.024 [ABCSG-6]; 0.726 vs 0.70; P=0.003 [ABCSG-8]).

At 10 years, the distant recurrence rates were as follows:
• Low EP and High EP (ABCSG-6): 8% (95% CI, 3-13%) and 22% (95% CI, 15-29%) (P<0.001)
• Low EP and High EP (ABCSG-8): 6% (95% CI, 2-9%) and 15% (95% CI, 11-20%) (P<0.001)
• Low EPClin and High EP (ABCSG-6): 4% (95% CI, 1-8%) and 28% (95% CI, 20-36%) (P<0.001)
• Low EPClin and High EP (ABCSG-8): 4% (95% CI, 2-5%) and 22% (95% CI, 15-29%) (P<0.001)

Buus et al. (2016) conducted a prospective-retrospective study to estimate the risk of distant recurrence in women with early-stage breast cancer (ER+/HER2-) considering adjuvant therapy.\(^8\) Patients were evaluated in the prospective RCT (ATAC) evaluating the safety and efficacy of anastrozole compared with tamoxifen in postmenopausal women. Women with either node-positive or node-negative disease were included (n=928). The majority of the population had node-negative disease (n=680; 73%). (Study results that focused on node-negative disease will be discussed in this section.) Among node-positive patients, 59 had disease recurrence (8.6%). EP and EPClin were predictive of recurrence at 10 years of follow-up in both low- and high-risk groups. At 10 years, the distant recurrence rates based on Kaplan-Meier plots, stratified by pre-specified cut-off points, were as follows:

- Low EP and High EP: 3% (95% CI, 1.5-6%) and 14.6% (95% CI, 11.3-18.8%)
- EP hazard ratio (HR; 95% CI): 5.15 (2.44-10.85) (P<0.001)
- Low EPClin and High EP: 5.9% (95% CI, 4-8.6%) and 20% (95% CI, 14.6-27%)
- EPClin HR (95% CI): 3.90 (2.33-6.52%) (P<0.001)

• A prospective-retrospective study was conducted to evaluate the ability of the EndoPredict assay to identify those patients who would achieve the most benefit from continuing hormonal therapy after 5 years.\(^10\) The study used archived samples from a population of ER-positive/HER2-negative post-menopausal women (node positive and node negative) from the ABCSG-6 (n=378; tamoxifen-only arm) and ABCSG-8 trials (n=1324) described in the earlier Dubsky study.\(^11\) Patients were retrospectively classified to low- and high-risk EP categories based on the incidence of late recurrence. Based on Kaplan-Meier analysis of distant metastasis, assignment to the EP low-risk group was associated with a significantly reduced risk of recurrence between 0 to 5 years (HR 2.80; 95% CI, 1.81-4.34, P<0.001) and greater than 5 years (HR 3.28; 95% CI 1.47-7.24, P=0.002). Values for the EP high-risk group were not reported by study authors. When EndoPredict and clinical parameters were combined, the prediction of late recurrence was improved as evidenced by the improved c-index; the EPClin score had the highest c-index (0.786) in predicting late recurrence.
• In a prospective-retrospective study, Martin et al. (2014) evaluated the EP score in node-positive breast cancer patients (ER+/HER2-) who were treated with adjuvant chemotherapy followed by hormone therapy. The study also evaluated whether EP scores could predict the efficacy of incorporating weekly paclitaxel into anthracycline-based regimens. Patients enrolled in the RCT (n=555; GEICAM 9906) were evaluated for distant metastasis-free survival (MFS). Rates of MFS at 10 years of follow-up were 93% for the EP low-risk group and 70% for the EP high-risk group, with an absolute risk reduction of 23% (HR 4.8; 95% CI 2.5-9.6; P<0.0001). Adding weekly paclitaxel treatment did not have an effect on the risk of relapse. The EPclin score c-index estimate of 0.70 was the highest compared with other risk factors.

• No direct evidence regarding clinical utility of EndoPredict to improve clinical decision making (e.g., predicting recurrence and/or selecting treatment approaches based on test results) and improve patient health outcomes in women with early-stage breast cancer considering adjuvant chemotherapy was identified. Weak indirect evidence from one small study (n=167) that evaluated treatment decisions assessed retrospectively suggests a potential for the test’s clinical utility. When pre- and post-test decisions were compared, a change of therapy was observed in nearly 38%. In addition, 16 patients (~12%) changed to a treatment strategy of additional chemotherapy; 33 patients (~25%) of patients changed to endocrine treatment alone. In addition to limitations of the retrospective study design, it is unclear how these projected and altered treatment recommendations would translate into improved morbidity and mortality outcomes in this patient population.

• There is adequate evidence in the peer-reviewed literature from two retrospective-prospective studies of moderate quality to support testing with EndoPredict in women with early stage (ER+/HER2-) node-negative breast cancer who are considering adjuvant chemotherapy. Moderate quality evidence indicates that use of the EndoPredict test may improve predictions regarding an individual’s long-term prognosis up to 10 years and determine if they can safely avoid adjuvant chemotherapy.

• There is currently insufficient evidence in the peer-reviewed literature regarding the use of EndoPredict in women with early stage (ER+/HER2-) node-positive breast cancer who are considering adjuvant chemotherapy.

• There is currently insufficient evidence in the peer-reviewed literature regarding the use of EndoPredict in women with early stage (ER+/HER2-) node-negative or node-positive breast cancer who are disease-free at 5 years after initial diagnosis, currently receiving adjuvant hormonal therapy, and who are considering continuing hormonal therapy.

• **Ongoing clinical trials:**
  - NCT Number: NCT01805271
  - Title: Safety Study of Adding Everolimus to Adjuvant Hormone Therapy in Women With High Risk of Relapse, ER+ and HER2- Primary Breast Cancer,
Free of Disease After Receiving at Least One Year of Adjuvant Hormone Therapy

Criteria

• Previous Testing:
  o No repeat EndoPredict testing on the same sample when a result was successfully obtained, and
  o No previous gene expression assay (e.g. OncotypeDx Breast) performed on the same sample when a result was successfully obtained, AND

• Required Clinical Characteristics:
  o Primary invasive breast cancer meeting all of the following criteria:
    o Unilateral tumor
      ▪ Tumor size >0.5cm (5mm) in greatest dimension (T1b-T3)
      ▪ Hormone receptor positive (ER+ or PR+), and
      ▪ HER2 negative, and
    o Patient has no regional lymph node metastasis (pN0) or only micrometastases (pN1mi, malignant cells in regional lymph node(s) not greater than 2.0mm), and
    o Adjuvant endocrine systemic chemotherapy is a planned treatment option for the patient 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:
  o 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 with or without knowledge of the EndoPredict test result (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

References


