**Oncotype DX 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 code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncotype DX Breast Cancer Assay</td>
<td>81519</td>
</tr>
</tbody>
</table>

**What is Oncotype DX for breast cancer prognosis**

**Definition**

Oncotype DX® is a gene expression assay designed to determine the risk of a breast cancer recurrence within 10 years of the original diagnosis.¹

- It is intended for early stage, hormone receptor-positive, lymph node-negative breast cancer.¹⁻⁴
- Oncotype DX should be used with other standard methods of breast cancer assessment such as disease staging, grading, and other tumor markers.¹,²
- Oncotype DX results appear to correlate with chemotherapy benefit,⁵,⁶ which may help with the decision between tamoxifen only and adjuvant chemotherapy. Studies have demonstrated that the addition of Oncotype DX results changed treatment recommendations and decisions in 25% to 44% of patients, with the majority of recommendations changing from chemotherapy plus tamoxifen to tamoxifen only.⁷⁻⁹

**Test information**

- Oncotype DX measures the expression level of 21 genes (16 cancer and 5 reference) from paraffin-embedded breast tumor tissue.¹ These sixteen genes consistently correlated with distant recurrence-free survival in three studies that explored the expression of 250 genes in breast tumor samples.⁵
- The results are provided as a Recurrence Score® (RS, 0-100) with higher scores reflecting higher risk of recurrence. Three risk categories help characterize prognosis:¹,²
  - Low risk (RS<18), ~50% of patients tested
• Least aggressive tumors
  • Metastasis unlikely
  • 7% recurrence by 10 yrs
• Intermediate risk (RS 18-30), ~25% of patients tested
  • More aggressive tumors
  • Metastasis more likely
  • 14% recurrence by 10 yrs
• High risk (RS 31 or higher), ~25% of patients tested
  • Most aggressive tumors
  • Metastasis most likely
  • 31% recurrence by 10 yrs

• Patients with high scores benefit the most from chemotherapy, showing a substantial reduction in 10 year recurrence. Patients with intermediate scores show questionable benefit from chemotherapy, whereas those with low scores benefit the least from chemotherapy.²,⁵,⁶

Guidelines and evidence
• The National Comprehensive Cancer Network (NCCN, 2018) breast cancer treatment guidelines recommend the 21-gene Oncotype DX Breast assay in their treatment algorithm for hormone receptor-positive, HER2-negative breast cancer in both node-negative (category of evidence 1, predictive and prognostic purposes, preferred test status) and node-positive (category of evidence 2A, prognostic purposes only) breast cancer.¹⁰
• The National Institute for Health and Care Excellence (NICE) 2018 stated the following:¹¹
  • “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”
• The Evaluation of Genomic Applications in Practice and Prevention Working Group (EGAPP, 2009 and updated in 2016) found:
  o “Insufficient evidence to make a recommendation for or against the use of tumor gene expression profiles to improve outcomes in defined populations of women with breast cancer. In the updated 2016 publication, “evidence of clinical validity for Oncotype DX was confirmed as adequate. With regard to clinical utility, although there was evidence from prospective retrospective studies that the Oncotype DX test predicts benefit from chemotherapy, and there was adequate evidence that the use of Oncotype DX gene expression profiling in clinical practice changes treatment decisions regarding chemotherapy, no direct evidence was found that the use of Oncotype DX testing leads to improved clinical outcomes. Until definitive evidence for clinical utility is available, clinicians must decide on a case-by-case basis whether to offer the test to patients.” 12,13

• The 14th St Gallen International Breast Cancer Conference (2015) Expert Panel confirmed previously published recommendations:
  o Regarding Oncotype DX, the 2011 recommendations stated: “Several tests are available which define prognosis. These may indicate a prognosis so good that the doctor and patient decide that chemotherapy is not required. A strong majority of the Panel agreed that the 21-gene signature (Oncotype DX) may also be used where available to predict chemotherapy responsiveness in an endocrine responsive cohort where uncertainty remains after consideration of other tests...” 14
  o In 2015, the Panel “considered the role of multiparameter molecular marker assays for prognosis separately in years 1-5 and beyond 5 years and their value in selecting patients who require chemotherapy.” The Panel concluded that “only Oncotype DX commanded a majority in favor of its value in predicting the usefulness of chemotherapy.” 15

• The 2007 evidence-based guidelines from the American Society of Clinical Oncology (ASCO) about breast cancer tumor marker use state:
  o “In newly diagnosed patients with node-negative, estrogen-receptor positive breast cancer, the Oncotype DX assay can be used to predict the risk of recurrence in patients treated with tamoxifen. Oncotype DX may be used to identify patients who are predicted to obtain the most therapeutic benefit from adjuvant tamoxifen and may not require adjuvant chemotherapy. In addition, patients with high recurrence scores appear to achieve relatively more benefit from adjuvant chemotherapy (specifically (C)MF) than from tamoxifen. There are insufficient data at present to comment on whether these conclusions generalize to hormonal therapies other than tamoxifen, or whether this assay applies to other chemotherapy regimens.” 3
  o In 2016, the American Society of Clinical Oncology (ASCO) stated “If a patient has ER/PgR-positive, HER2-negative (node-negative) breast cancer, the
clinician may use the 21-gene recurrence score (RS; Oncotype DX; Genomic Health, Redwood City, CA) to guide decisions on adjuvant systemic chemotherapy. Type: evidence based. Evidence quality: high. Strength of recommendation: Strong.”

- Additional clinical application issues:

  - **Male gender** — No studies specific to the application of Oncotype DX in men with breast cancer have been identified. In general, the NCCN breast cancer treatment guidelines do not differentiate treatment on the basis of gender, which suggests Oncotype DX would not be excluded for males who meet NCCN clinical criteria for considering such testing.

  - **Multiple primary breast tumors** — No studies specific to the application of Oncotype DX in those with multiple breast primary cancers have been identified. Guidelines do not address this issue. A single poster summarized data in a study that used the Oncotype DX test to help assess if synchronous breast cancers were independent neoplastic events or spread of a single tumor. Of 11 patients who met criteria, 5 had different risk scores by Oncotype DX testing (with 3 of these patients having tumors assigned to different risk categories). Of these 5 with significantly different scores, 4 involved bilateral tumors and the other involved tumors in different quadrants. Comparing tumors by histology, 4 of 5 had clearly different histology and 1 had equivocal histology. Of the 6 with similar risk scores, 3 had the same histology, 2 equivocal, and in only 1 case was histology clearly different between the two tumors. This very limited data suggests OncotypeDX may be useful in multiple primaries when tumors independently meet criteria. A study published in 2016 noted that “Among women with synchronous bilateral ER-positive HER2-negative breast cancer, Oncotype DX recurrence scores were concordant in 67% of cases. These data suggest that testing of both tumors should be considered in patients who are candidates for adjuvant chemotherapy.”

  - **Positive lymph nodes** — There is currently insufficient evidence in the peer-reviewed literature regarding the use of Oncotype DX in women with early stage (ER+/HER2-) node-positive breast cancer who are considering adjuvant chemotherapy.

    - Several prospective and retrospective-prospective studies were identified evaluating the use of Oncotype DX in early stage, node-positive breast cancer, and results suggest that use of Oncotype DX allows for prognostic risk stratification. However, without chemotherapy, the risk of recurrence for patients with positive nodes appears to be notably higher than patients with negative nodes, and as such, it is not clear if patients with positive nodes can safely avoid chemotherapy treatment regimens based on Oncotype DX test results.

    - There is at least one clinical trial underway, RxPonder, to evaluate the utility of the Oncotype DX Breast Cancer assay for women with 1-3 positive lymph nodes (ER/PR-positive, HER2-negative). This trial aims to support chance
findings from a retrospective subset analysis of the SWOG-8814 trial data that suggested Oncotype DX high and low risk scores were able to predict chemotherapy benefit regardless of node status. An abstract presented at the European Breast Cancer Conference in 2016 presented the 5-year outcome data from a prospective trial with the conclusion of: WSG PlanB for the first time shows excellent 5-year disease free survival of 94% in a population of high risk node-negative and node-positive (pN1) (41.1% had node-positive disease) early BC patients (HR+ HER2−) who omitted adjuvant CT based on RS ≤11. These 5-year outcome data from a prospective trial incorporating the RS support the incorporation of the assay in combination with nodal status, grade and tumor size for adjuvant treatment decisions in early HR+ HER2− breast cancer.31

- Currently, evidence to support use in node-positive disease remains limited.
  - **Ductal Carcinoma In Situ** — There is currently insufficient evidence in the peer-reviewed literature regarding the use of Oncotype DX in women with ductal carcinoma in situ (DCIS) who are considering radiation therapy.

  - Rakovitch et al. (2015) conducted a population cohort study (n=3320 women with DCIS) with a median follow-up period of 9.6 years.32 Study authors demonstrated that the DCIS Score independently predicted the risk of local recurrence in women with DCIS treated with breast conserving surgery (HR, 2.15; 95% CI, 1.43-3.22). Patients considered low risk via the DCIS Score (62%) had 10-year local recurrence of 13%; intermediate risk (17%) patients had 10-year local recurrence of 33%; and high risk (21%) patients had 10-year local recurrence of 28%. The DCIS Score is intended to provide a quantified risk score for local recurrence to help clinicians guide treatment decisions and potentially reduced the effects of overtreatment with radiotherapy. Study results of this trial and others indicate that despite the ability of Oncotype DX to reclassify patients into different risk groups, it is not clear if the risk estimation is accurate enough to induce changes in treatment strategies or disease management, or if the 10-year local recurrence of approximately 13% is still low enough for patients to successfully avoid radiation therapy and the risk of its associated complications.33

### Criteria

- **Previous Testing:**
  - No repeat Oncotype DX® testing on the same sample when a result was successfully obtained, and
  - No previous gene expression assay (e.g. Prosigna) performed on the same sample when a result was successfully obtained, AND

- **Testing Multiple Samples:**
When more than one breast cancer primary is diagnosed:

- There should be reasonable evidence that the tumors are distinct (e.g., bilateral, 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 Oncotype DX test result (e.g., histopathologic features or previous Oncotype DX 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 outlined below.

• Required Clinical Characteristics:
  
  - Invasive breast cancer meeting all of the following criteria:
    - Tumor size >0.5cm (5mm) in greatest dimension (T1b-T3), and
    - Estrogen receptor positive (ER+), and
    - HER2 negative, and
  
  - Patient has no regional lymph node metastasis or 1-3 positive ipsilateral axillary lymph nodes, and
  
  - Chemotherapy is a treatment option for the patient; results from this Oncotype DX test will be used in making chemotherapy treatment decisions, AND

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

References


