**Oncotype DX Breast DCIS**

**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>
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<th>Procedure addressed by this guideline</th>
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<td>Oncotype DX Breast DCIS Assay</td>
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**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, which may help with the decision between tamoxifen only and adjuvant chemotherapy.⁵,⁶ 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
- OncotypeDX can be used in individuals with ductal carcinoma in situ (DCIS) in addition to individuals with invasive carcinoma.

**Test information**

- Depending on the risk being calculated (local or distant metastasis), either a DCIS Breast Score® (DCIS or invasive carcinoma) or a Breast Recurrence Score® (invasive carcinoma) is calculated.¹⁰-¹³
- The Oncotype DX DCIS Breast Score® algorithm is intended for use in women with DCIS treated by local excision, with or without tamoxifen treatment. The score result is reported as a number between 0 and 100, with lower scores representing a low chance of recurrence and a higher score representing a high chance of recurrence within 10 years.¹⁰-¹³
• Oncotype DX measures the expression level of 21 genes (16 cancer and 5 reference) from paraffin-embedded breast tumor tissue.\textsuperscript{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.\textsuperscript{5}

• The Oncotype DX DCIS score is calculated using a subset of 12 of the 21 gene Oncotype DX panel, including 7 cancer-related and 5 reference genes. On the patient report, average 10 year rates for any local/same breast recurrence (DCIS and invasive) as well as local invasive rate only are reported for a given DCIS Breast Score. Results of the DCIS Breast Score have the potential to change the treatment decision based on risk of local recurrence.\textsuperscript{10-13}

• The results are provided as a Recurrence Score\textsuperscript{®} (RS, 0-100) with higher scores reflecting higher risk of recurrence. Three risk categories help characterize prognosis:\textsuperscript{1,2}
  
  o Low risk (RS<18), \~50\% of patients tested
    • Least aggressive tumors
    • Metastasis unlikely
    • 7\% recurrence by 10 yrs
  
  o Intermediate risk (RS 18-30), \~25\% of patients tested
    • More aggressive tumors
    • Metastasis more likely
    • 14\% recurrence by 10 yrs
  
  o 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.\textsuperscript{2,5,6}

Guidelines and evidence

National Comprehensive Cancer Network

• The National Comprehensive Cancer Network (NCCN, 2019) 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 1, predictive and prognostic purposes) invasive cancer.\textsuperscript{14}

- Multigene assays are not included in the diagnostic or treatment algorithms for non-invasive cancer, such as DCIS.\textsuperscript{14}

**American Society of Clinical Oncology**

The evidence-based guidelines from the American Society of Clinical Oncology (ASCO) about breast cancer tumor marker use (2007, updated 2016) state:

- “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 regimen.” \textsuperscript{3}

- 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.” \textsuperscript{4}

**Evaluation of Genomic Applications in Practice and Prevention**

The Evaluation of Genomic Applications in Practice and Prevention Working Group (EGAPP, 2009 and updated in 2016) found:

- “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.” \textsuperscript{15,16}

**St. Gallen International Expert Consensus**

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...” 17

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.” 18

European Society of Medical Oncology

The European Society of Medical Oncology (ESMO) in 2015 stated:19

“Gene expression profiles, such as MammaPrint (Agenda, 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.”

Literature Review

The available evidence is insufficient to assess if Oncotype DX DCIS provides a reliable, accurate, and clinically meaningful risk score to estimate local recurrence, facilitate treatment decisions, and potentially reduce the effects of overtreatment with radiotherapy in women with DCIS who have undergone surgical excision. The best available data on OncotypeDx for DCIS is from two clinical validity studies (published in three publications).20-22 They reported that the Oncotype DX Score was significantly associated with the risk of recurrence in women after surgical excision. Some study results also suggested that Oncotype DX DCIS independently predicted risk of recurrence beyond clinicopathologic variables. However, depending on the scope of the recurrence being assessed in the study (ie, local recurrence; invasive carcinoma, DCIS recurrence), these differences were not
statistically significant, and suggested that Oncotype DX DCIS score was not consistently predictive.

- A few studies reported on the degree of association between Oncotype DX DCIS Score and conventional prognostic measures. In general, these studies were small, lacked controls, and conducted at single institutions or centers, and did not provide substantive evidence to the current base of evidence.23-26

- Several observational studies provide surrogate measures of clinical utility, but no direct clinical utility studies were identified that evaluated the impact of the use of Oncotype DX DCIS on survival outcomes relative to conventional prognostic risk assessments.27-30

Criteria

- This test is considered investigational and/or experimental.
  
  o Investigational and experimental (I&E) molecular and genomic (MolGen) tests refer to assays involving chromosomes, DNA, RNA, or gene products that have insufficient data to determine the net health impact, which typically means there is insufficient data to support that a test accurately assesses the outcome of interest (analytical and clinical validity), significantly improves health outcomes (clinical utility), and/or performs better than an existing standard of care medical management option. Such tests are also not generally accepted as standard of care in the evaluation or management of a particular condition.
  
  o In the case of MolGen testing, FDA clearance is not a reliable standard given the number of laboratory developed tests that currently fall outside of FDA oversight and FDA clearance often does not assess clinical utility.

References


