The following Protocol contains medical necessity criteria that apply for this service. It is applicable to Medicare Advantage products unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Preauthorization is required. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient’s contract at the time the services are rendered.

Description

Laboratory tests have been developed that detect the expression, via messenger RNA (mRNA) or protein, of many different genes in breast tumor tissue and combine the results into a prediction of distant recurrence risk for women with early stage breast cancer. Test results may help providers and patients decide whether to include adjuvant chemotherapy in post-surgical management.

Background

For women with early-stage breast cancer, adjuvant chemotherapy provides the same proportional benefit regardless of prognosis. However, the absolute benefit of chemotherapy depends on the baseline risk of recurrence. For example, women with the best prognosis have small tumors, are estrogen-receptor-positive, and lymph node negative. These women have an approximately 15% baseline risk of recurrence; approximately 85% of these patients would be disease free at 10 years with tamoxifen treatment alone and could avoid the toxicity of chemotherapy, if they could be accurately identified. Conventional risk classifiers estimate recurrence risk by considering criteria such as tumor size, type, grade, and histologic characteristics; hormone receptor status; and lymph node status. However, no single classifier is considered a gold standard, and several common criteria have qualitative or subjective components that add variability to risk estimates. As a result, more patients are treated with chemotherapy than can benefit. Better predictors of baseline risk could help women, who prefer to avoid chemotherapy if assured that their risk is low, make better treatment decisions in consultation with their physicians.

Recently, several groups have identified panels of gene expression markers (“signatures”) that appear to predict the baseline risk of invasive breast cancer recurrence after surgery, radiation therapy, and endocrine therapy (for hormone-receptor-positive tumors). Five gene expression tests are commercially available in the U.S.: Oncotype DX™ (a 21-gene reverse transcriptase-polymerase chain reaction [RT-PCR] assay; Genomic Health), the 70-gene signature MammaPrint® (Agenda), Mammastrat® Breast Cancer Test (Clariant Diagnostic Services), the Breast Cancer IndexSM, a combination of the Molecular Grade Index (MGI) and the HOXB13:IL17BR Index (bioTheranostics), the BreastOncPx™ (Breast Cancer Prognosis Gene Expression Assay; LabCorp), NexCourse® Breast IHC4 (Geneoptix), and the PAM50 Breast Cancer Intrinsic Classifier (ARUP National Reference Laboratory). If these panels are more accurate than current conventional classifiers, they could be used to aid chemotherapy decision making, when current guidelines do not strongly advocate its use, without negatively affecting disease-free and overall survival (OS) outcomes.

Oncotype DX, using a slightly different algorithm to calculate results, is also marketed for patients with noninvasive, ductal carcinoma in situ (DCIS) to predict the 10-year risk of local recurrence (DCIS or invasive
cancer). The stated purpose is to help guide treatment decision making in women with DCIS treated by local excision, with or without adjuvant tamoxifen therapy.

**Regulatory Status**

All tests except MammaPrint are provided as laboratory-developed tests (LDTs) in Clinical Laboratory Improvement Act (CLIA)-licensed laboratories operated by each company. These LDTs have not been cleared by the U.S. Food and Drug Administration (FDA); to date, FDA clearance is not required.

MammaPrint has received 510(k) clearance for marketing by the FDA. All U.S. tests are performed at the CLIA-licensed Agendia clinical laboratory.

**Corporate Medical Guideline**

The use of the 21-gene reverse transcriptase-polymerase chain reaction (RT-PCR) assay (i.e., Oncotype DX™) to determine recurrence risk for deciding whether or not to undergo adjuvant chemotherapy may be considered medically necessary in women with primary breast cancer meeting the following characteristics:

- unilateral, non-fixed tumor;
- hormone receptor positive (that is estrogen-receptor [ER]-positive or progesterone receptor [PR]-positive);
- human epidermal growth factor receptor 2 (HER2) negative*;
- tumor size 0.6–1 cm with moderate/poor differentiation or unfavorable features OR tumor size larger than 1 cm;
- node negative (lymph nodes with micrometastases [less than 2 mm in size] are considered node negative for this policy statement);
- who will be treated with adjuvant endocrine therapy, e.g., tamoxifen or aromatase inhibitors;
- when the test result will aid the patient in making the decision regarding chemotherapy (i.e., when chemotherapy is a therapeutic option); AND
- when ordered within six months following diagnosis, since the value of the test for making decisions regarding delayed chemotherapy is unknown.

The 21-gene RT-PCR assay Oncotype DX™ should only be ordered on a tissue specimen obtained during surgical removal of the tumor and after subsequent pathology examination of the tumor has been completed and determined to meet the above criteria (i.e., the test should not be ordered on a preliminary core biopsy). The test should be ordered in the context of a physician-patient discussion regarding risk preferences and when the test result will aid the patient in making decisions regarding chemotherapy.

For patients who otherwise meet the above characteristics but who have multiple ipsilateral primary tumors, a specimen from the tumor with the most aggressive histological characteristics should be submitted for testing. It is not necessary to conduct testing on each tumor; treatment is based on the most aggressive lesion.

All other indications for the 21-gene RT-PCR assay (i.e., Oncotype DX™) including determination of recurrence risk in breast cancer patients with positive lymph nodes or patients with bilateral disease, are considered investigational.

Use of a subset of genes from the 21-gene RT-PCR assay for predicting recurrence risk in patients with noninvasive ductal carcinoma in situ (i.e., Oncotype DX DCIS) to inform treatment planning following excisional surgery is considered investigational.

The use of other gene expression assays (e.g., MammaPrint 70-gene signature, Mammomat Breast Cancer Test, the Breast Cancer Index, the BreastOncPx, NexCourse Breast IHC4, or PAM20 Breast Cancer Intrinsic Classifier)
for any indication is considered investigational.

Policy Guideline

Unfavorable features that may prompt testing in tumors from 0.6 to 1 cm in size include the following: angiolymphatic invasion, high histologic grade, or high nuclear grade.

The 21-gene RT-PCR assay Oncotype DX™ should not be ordered as a substitute for standard estrogen receptor, progesterone receptor testing, or human epidermal growth factor receptor 2 (HER2) testing.

According to the American Society of Clinical Oncology-College of American Pathologists Guideline Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer, “a positive HER2 result is IHC [immunohistochemistry] staining of 3+ (uniform, intense membrane staining of > 30% of invasive tumor cells), a fluorescent in situ hybridization (FISH) result of more than six HER2 gene copies per nucleus or a FISH ratio (HER2 gene signals to chromosome 17 signals) of more than 2.2; a negative result is an IHC staining of 0 or 1+, a FISH result of less than 4.0 HER2 gene copies per nucleus, or FISH ratio of less than 1.8. Equivocal results require additional action for final determination.” (1)

Benefit Application

*For all business, labs performing HER2 testing are required to be enrolled in and have satisfactory performance in a HER2 proficiency testing program. In cases of HER2 determination of 2+ by immunohistochemistry (IHC) the HER2 status determined by in situ hybridization (ISH) is also required. Documentation on file with the treating physician should indicate that results of the Oncotype DX test are expected to play a significant role in management of the patient. For example, a patient with a large, high grade carcinoma who, in agreement with the oncologist and patient, has decided to have adjuvant chemotherapy regardless of the results of the test would not be an appropriate candidate for this test.

Medicare Advantage

For Medicare Advantage members the above medical necessity criteria would apply for Oncotype DX™ and MammaPrint®.

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. Some of this Protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.

References

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.


81. Noridian Administrative Services, LLC Local Coverage Determination (LCD): Molecular Diagnostic Tests (MDT) (L33541), Primary Geographic Jurisdiction-Northern, California, Revision Effective Date For services performed on or after 09/16/2013.