Medical Policy
Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis in Patients with Breast Cancer

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Policy Number: 055
BCBSA Reference Number: 2.04.36
NCD/LCD:
- Local Coverage Determination (LCD): MolDX: Breast Cancer Index Genetic Assay (L35631)
- Local Coverage Determination (LCD): MolDX - Oncotype DX Breast Cancer for DCIS (Genomic Health (L36912)

Related Policies
None

Policy
Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity

The use of the 21-gene reverse transcriptase-polymerase chain reaction (RT-PCR) assay (ie, Oncotype DX®) to determine recurrence risk for deciding whether to undergo adjuvant chemotherapy may be considered MEDICALLY NECESSARY in women with primary, invasive breast cancer meeting all of the following characteristics:

- Unilateral tumor
- Hormone receptor-positive (ie, estrogen receptor-positive or progesterone receptor-positive)
- Human epidermal growth factor receptor 2-negative
- Tumor size 0.6-1.0 cm with moderate or poor differentiation or unfavorable features OR tumor size larger than 1 cm
- Node negative (lymph nodes with micrometastases [<2 mm in size] are considered node negative for this policy statement)
- Who will be treated with adjuvant endocrine therapy (eg, tamoxifen, aromatase inhibitors)
- When the test result will aid the patient in making the decision regarding chemotherapy (ie, when chemotherapy is a therapeutic option). AND
- When ordered within 6 months after diagnosis, because 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 (ie, 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 when the test result will aid 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 histologic characteristics should be submitted for testing. It is not necessary to conduct testing on each tumor; treatment is based on the most aggressive lesion.

Use of EndoPredict, the Breast Cancer Index℠, and Prosigna to determine recurrence risk for deciding whether to undergo adjuvant chemotherapy may be considered MEDICALLY NECESSARY in women with primary, invasive breast cancer with the same characteristics as considered MEDICALLY NECESSARY for Oncotype DX®.

All other indications for the 21-gene RT-PCR assay (ie, Oncotype DX®, EndoPredict, the Breast Cancer Index℠, and Prosigna, including determination of recurrence risk in invasive breast cancer patients with positive lymph-nodes, patients with bilateral disease, or to consider length of treatment with tamoxifen are 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 (ie, Oncotype DX® Breast DCIS Score) to inform treatment planning after excisional surgery is INVESTIGATIONAL.

The use of 70-gene signature (MammaPrint®) and the Breast Cancer Index℠ for any indication is considered INVESTIGATIONAL.

The use of BluePrint in conjunction with MammaPrint® or alone is considered INVESTIGATIONAL.

The use of gene expression assays in men with breast cancer is considered INVESTIGATIONAL.

Medicare HMO Blue℠ and Medicare PPO Blue℠ Members

Medical necessity criteria and coding guidance for Medicare Advantage members living in Massachusetts can be found through the links below.

Local Coverage Determination (LCD): MolDX: Breast Cancer Index℠ Genetic Assay (L35631)

Local Coverage Determination (LCD): MolDX - Oncotype DX® Breast Cancer for DCIS (Genomic Health ™) (L36912)

Local Coverage Determination (LCD): MolDX: Breast Cancer Assay: Prosigna (L36125)

For medical necessity criteria and coding guidance for Medicare Advantage members living outside of Massachusetts, please see the Centers for Medicare and Medicaid Services website for information regarding your specific jurisdiction at https://www.cms.gov.

Prior Authorization Information

Inpatient
- For services described in this policy, precertification/preauthorization IS REQUIRED for all products if the procedure is performed inpatient.

Outpatient
- For services described in this policy, see below for products where prior authorization might be required if the procedure is performed outpatient.
Outpatient Commercial Managed Care (HMO and POS) Prior authorization is not required.
Commercial PPO and Indemnity Prior authorization is not required.
Medicare HMO BlueSM Prior authorization is not required.
Medicare PPO BlueSM Prior authorization is not required.

CPT Codes / HCPCS Codes / ICD Codes
Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The above medical necessity criteria MUST be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

CPT Codes

<table>
<thead>
<tr>
<th>CPT codes:</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>81519</td>
<td>Oncology (breast), mRNA, gene expression profiling by real-time RT-PCR of 21 genes, utilizing formalin-fixed paraffin embedded tissue, algorithm reported as recurrence score</td>
</tr>
<tr>
<td>81520</td>
<td>Oncology (breast), mRNA gene expression profiling by hybrid capture of 58 genes (50 content and 8 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a recurrence risk score</td>
</tr>
<tr>
<td>0008M</td>
<td>Oncology (breast), mRNA analysis of 58 genes using hybrid capture, on formalin-fixed paraffin-embedded (FFPE) tissue, prognostic algorithm reported as a risk score</td>
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</table>

The following ICD Diagnosis Codes are considered medically necessary when submitted with the CPT and/or HCPCS codes above if medical necessity criteria are met:

ICD-10 Diagnosis Codes

<table>
<thead>
<tr>
<th>ICD-10-CM Diagnosis codes:</th>
<th>Code Description</th>
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<tbody>
<tr>
<td>C50.011</td>
<td>Malignant neoplasm of nipple and areola, right female breast</td>
</tr>
<tr>
<td>C50.012</td>
<td>Malignant neoplasm of nipple and areola, left female breast</td>
</tr>
<tr>
<td>C50.019</td>
<td>Malignant neoplasm of nipple and areola, unspecified female breast</td>
</tr>
<tr>
<td>C50.111</td>
<td>Malignant neoplasm of central portion of right female breast</td>
</tr>
<tr>
<td>C50.112</td>
<td>Malignant neoplasm of central portion of left female breast</td>
</tr>
<tr>
<td>C50.119</td>
<td>Malignant neoplasm of central portion of unspecified female breast</td>
</tr>
<tr>
<td>C50.211</td>
<td>Malignant neoplasm of upper-inner quadrant of right female breast</td>
</tr>
<tr>
<td>C50.212</td>
<td>Malignant neoplasm of upper-inner quadrant of left female breast</td>
</tr>
<tr>
<td>C50.219</td>
<td>Malignant neoplasm of upper-inner quadrant of unspecified female breast</td>
</tr>
<tr>
<td>C50.311</td>
<td>Malignant neoplasm of lower-inner quadrant of right female breast</td>
</tr>
<tr>
<td>C50.312</td>
<td>Malignant neoplasm of lower-inner quadrant of left female breast</td>
</tr>
<tr>
<td>C50.319</td>
<td>Malignant neoplasm of lower-inner quadrant of unspecified female breast</td>
</tr>
<tr>
<td>C50.411</td>
<td>Malignant neoplasm of upper-outer quadrant of right female breast</td>
</tr>
<tr>
<td>C50.412</td>
<td>Malignant neoplasm of upper-outer quadrant of left female breast</td>
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</tbody>
</table>
The following CPT and HCPCS code are considered investigational for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

### CPT Codes

<table>
<thead>
<tr>
<th>CPT codes:</th>
<th>Code Description</th>
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<tbody>
<tr>
<td>0045U</td>
<td>Oncology (breast ductal carcinoma in situ), mRNA, gene expression profiling by real-time RT-PCR of 12 genes (7 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence score</td>
</tr>
<tr>
<td>81521</td>
<td>Oncology (breast), mRNA, microarray gene expression profiling of 70 content genes and 465 housekeeping genes, utilizing fresh frozen or formalin-fixed paraffin-embedded tissue, algorithm reported as index related to risk of distant metastasis</td>
</tr>
</tbody>
</table>

### HCPCS Codes

<table>
<thead>
<tr>
<th>HCPCS codes:</th>
<th>Code Description</th>
</tr>
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<tbody>
<tr>
<td>S3854</td>
<td>Gene expression profiling panel for use in the management of breast cancer treatment</td>
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</table>

**Description**

An important part of treatment planning for women with breast cancer involves determining which patients could benefit from adjuvant treatments. For example, for women with early-stage, invasive breast cancer (i.e., cancer extending beyond the basement membrane of the mammary ducts into adjacent tissue), adjuvant cytotoxic chemotherapy consistently provides approximately a 30% relative risk reduction in 10-year breast cancer mortality regardless of prognosis. However, the absolute benefit of chemotherapy depends on the baseline risk of recurrence. Women with the best prognosis have small tumors, are estrogen receptor–positive, and are 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 (eg, Adjuvant! Online) estimate recurrence risk by considering criteria such as tumor size, type, grade, and histologic characteristics; hormone receptor status; and lymph node status. Consensus guidelines for defining receptor status exist. However, no single classifier is considered a criterion 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’s decision making, some who may prefer to avoid chemotherapy if assured that their risk is low.

In other clinical scenarios involving breast cancer, accurate assessment of prognosis may affect the decision to offer certain treatments. 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, radiotherapy, and endocrine therapy (for hormone receptor–positive tumors). Several gene expression tests commercially available in the United States are listed in Table 1. If these panels are more accurate risk predictors than current conventional classifiers, they could be used to aid decision making on adjuvant treatments without greatly affecting disease-free survival and overall survival (OS). This review focuses on gene expression profiling (GEP) panels that have prognostic or predictive ability in individuals with early-stage, invasive breast cancer with known estrogen receptor and progesterone receptor and human epidermal growth factor receptor \( (HER2) \) status. The proposed clinical utility of these tests varies depending on the clinical context; these specific indications are discussed in this review:

1. Prognosis and/or prediction of treatment response in patients with node-negative, early-stage, \( HER2 \)-negative invasive breast cancer who will receive adjuvant hormonal therapy for the purpose of determining whether patients can avoid adjuvant cytotoxic chemotherapy.

2. Prognosis and/or prediction of treatment response in patients with node-positive (1-3 nodes), early-stage, \( HER2 \)-negative invasive breast cancer who will receive adjuvant hormonal therapy for the purpose of determining whether patients can avoid adjuvant cytotoxic chemotherapy.

3. Prognosis and/or prediction of treatment response in patients with ductal carcinoma in situ (DCIS) for the purpose of determining whether patients can avoid radiation therapy.

4. Prognosis and/or prediction of treatment response in patients with node-negative, early-stage, \( HER2 \)-negative invasive breast cancer, receiving adjuvant hormonal therapy, who have survived without progression to 5 years postdiagnosis, for the purpose of determining whether patients should continue adjuvant hormonal therapy.

For each of these clinical indications, clinical trials have shown that there is some clinical benefit to receiving the additional therapy under consideration. However, each of the additional treatments has potential adverse effects. If a patient subgroup can be defined that has an extremely low risk of distant recurrence, or a subgroup can be defined that does not respond to the treatment, then the additional treatment can be forgone with little effect on cancer outcome due to the low risk of poor outcome or lack of response to treatment.

**Table 1. Gene Expression Tests Reporting Recurrence Risk for Breast Cancer Considered Herein**

<table>
<thead>
<tr>
<th>Test</th>
<th>Manufacturer</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>Oncotype DX</td>
<td>Genomic Health (Redwood City, CA)</td>
<td>21-gene RT-PCR</td>
</tr>
<tr>
<td>EndoPredict</td>
<td>Sividon Diagnostics (acquired by Myriad [Salt Lake City, UT] in 2016)</td>
<td>12-gene real-time RT-PCR</td>
</tr>
<tr>
<td>Breast Cancer Index</td>
<td>bioTheranostics (San Diego, CA)</td>
<td>Combines MGI and the HOXB13:IL17BR Index using RT-PCR</td>
</tr>
<tr>
<td>MammaPrint</td>
<td>Agendia (Amsterdam, The Netherlands)</td>
<td>70-gene DNA microarray</td>
</tr>
<tr>
<td>Prosigna</td>
<td>NanoString Technologies (Seattle, WA)</td>
<td>nCounter® digital analysis system based on PAM50 breast cancer intrinsic subtype classifier</td>
</tr>
</tbody>
</table>

MGI: Molecular Grade Index; PAM50: prediction analysis of microarray 50 gene set; RT-PCR: reverse transcriptase polymerase chain reaction.
Additional commercially available tests may provide some prognostic or predictive information for breast cancer. Tests intended to assess estrogen receptor, progesterone receptor, and HER2 status, such as TargetPrint® (Agendia; via quantitative microarray), are outside the scope of this review. In addition, tests that do not provide a specific recurrence risk are outside the scope of this review.

Other commercially available biomarkers are designed to provide information about tumors’ molecular subtypes (ie, luminal A, luminal B, HER2 type, and basal type). Prosigna was initially offered a molecular subtype test. The BluePrint 80-gene molecular subtyping assay (Agendia) is offered in combination with MammaPrint to augment predictive data about response to chemotherapy.

Many studies have investigated individual biomarkers or combinations of biomarkers that are associated with breast cancer outcomes. Determining which studies constitute sufficient evidence that the test or biomarker is likely to be clinically useful depends on attributes of the test such as its performance and the quality of the study generating the results. Simon et al has described a framework to evaluate prognostic biomarker evidence.² Study designs such as prospective clinical trials or previously conducted clinical trials with archived tumor samples constitute stronger evidence than studies with less planned and systematic patient recruitment and data collection. Randomized trials allow determination of treatment-biomarker interactions that may be clinically important. In some clinical scenarios, demonstration of a treatment-biomarker interaction is not critical, because the decision to withhold chemotherapy in a low-risk group (to avoid chemotherapy-related morbidity) does not require the presence of a biomarker-treatment interaction. The study must generate an absolute estimate of outcome in the patient group of interest that would result in a change in management (eg, withholding of chemotherapy), and the study must have sufficient precision (narrow confidence intervals). Results of the same test across studies should show consistency of results and more than 1 study demonstrating the desired result should be available. Simon has proposed that at least 2 Simon category B studies showing results consistent with clinical utility are necessary to demonstrate adequate evidence of a biomarker.²

The main outcome of interest to this review is 10-year distant recurrence-free survival. Distant recurrence is a hallmark of advanced breast cancer and thus more informative of OS than disease-free survival. Disease-free survival also includes local recurrence, which has a much better treatment prognosis distant disease. For one of the indications in this review, the main outcome of interest is 10-year distant recurrence-free survival conditional on recurrence-free survival for 5 years. There is no definitive threshold for an acceptable trade-off of distant recurrence risk for avoidance of treatment toxicity and inconvenience that is derived from empirical evidence on patient preferences. While some studies have shown that patients are willing to accept intensive chemotherapy for even a small chance of benefit,³-⁶ individual patients will vary in their preferences and tolerance for adverse effects.

**Summary**

Laboratory tests have been developed that detect the expression, via messenger RNA 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 postsurgical management of breast cancer or to alter treatment in patients with ductal carcinoma in situ (DCIS). This report summarizes the evidence of 5 tests for 4 indications and is organized by indication.

For all tests and all indications, relevant outcomes include disease-specific survival and changes in disease status.

**Early-Stage Node-Negative Invasive Breast Cancer**

Only studies presenting 10-year distant recurrence rates in node-negative women not receiving adjuvant chemotherapy were included in this part of the evidence review. In addition to negative nodes, the type of patient considered for this indication have positive hormone receptors and are human epidermal growth factor receptor 2 (HER2) negative.
21-Gene Assay (Oncotype DX)
For individuals who have early-stage node-negative invasive breast cancer considering adjuvant chemotherapy who receive gene expression profiling with the 21-gene assay (Oncotype DX), the evidence includes multiple prospective clinical trials and prospective-retrospective studies. Patients classified as low risk with Oncotype DX have a low risk of recurrence in which avoidance of adjuvant chemotherapy is reasonable (average risk at 10 years, 7%-9%; upper bound of the 95% confidence intervals, 11% to 15%). These results have been demonstrated with stronger study designs for evaluating biomarkers. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

EndoPredict
For individuals who have early-stage node-negative invasive breast cancer considering adjuvant chemotherapy who receive gene expression profiling with EndoPredict, the evidence includes 3 prospective-retrospective studies and observational studies. The studies showed that a low score was associated with a low absolute risk of 10-year distant recurrence. Over half of patients in the studies were classified at low risk. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Breast Cancer Index
For individuals who have early-stage node-negative invasive breast cancer considering adjuvant chemotherapy who receive gene expression profiling with the Breast Cancer Index (BCI), the evidence includes findings from 2 prospective-retrospective studies and 1 registry-based observational study. The findings from the 2 prospective-retrospective studies showed that a low-risk BCI score is associated with low 10-year distant recurrence rates. The findings from the registry-based observational study also showed low 10-year distant recurrence rates. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

70-Gene Signature (MammaPrint)
For individuals who have early-stage node-negative invasive breast cancer considering adjuvant chemotherapy who receive gene expression profiling with the 70-gene signature (MammaPrint), the evidence includes 1 study with outcomes in node-negative patients. Although the study showed a low risk of 10-year distant recurrence, it did not derive from high-quality data sources. A recently reported study of clinical utility only reported 5-year results and may not identify a group with sufficiently low risk. The evidence is insufficient to determine the effects of the technology on health outcomes.

Prosigna
For individuals who have early-stage node-negative invasive breast cancer considering adjuvant chemotherapy who receive gene expression profiling with Prosigna, the evidence includes 2 prospective-retrospective studies evaluating the prognostic ability of Prosigna. Both studies showed a low absolute risk of distant recurrence in patients with low risk scores. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Early-Stage Node-Positive Invasive Breast Cancer
For this indication, Oncotype DX and MammaPrint have been evaluated.

21-Gene Assay (Oncotype DX)
For individuals who have early-stage node-positive invasive breast cancer considering adjuvant chemotherapy who receive gene expression profiling with the 21-gene assay (Oncotype DX), the evidence includes clinical trials and prospective-retrospective studies. Although studies showed that Oncotype DX stratifies node-positive patients into high and low risks, it is still uncertain that the risk of disease recurrence is sufficiently low to avoid chemotherapy. Studies have suggested that treatment benefit in chemotherapy is restricted to high-risk patients. The evidence supporting this treatment interaction should be more robust to consider avoiding otherwise currently recommended treatment in patients not at low risk of recurrence. The evidence is insufficient to determine the effects of the technology on health outcomes.
**70-Gene Signature (MammaPrint)**
For individuals who have early-stage node-positive invasive breast cancer considering adjuvant chemotherapy who receive gene expression profiling with the 70-gene signature (MammaPrint), the evidence includes prospective-retrospective studies. Existing studies have not reported 10-year distant recurrence outcomes in the patients of interest. The studies are confounded by various factors (eg, receipt of treatment) or do not report the outcome of interest. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Ductal Carcinoma In Situ**
The Oncotype DX Breast DCIS Score is the only assay investigated for patients with DCIS.

For individuals who have DCIS considering radiotherapy who receive gene expression profiling with the Oncotype DX Breast DCIS assay, the evidence includes prospective-retrospective studies and prospective trials. Although studies have shown that the test stratifies patients into high- and low-risk groups, they have not yet demonstrated with sufficient precision that the risk of disease recurrence in patients identified with Oncotype DX Breast DCIS Score is low enough to consider changing the management of DCIS. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Continuation of Tamoxifen Therapy Beyond 5 Years**
For this indication, EndoPredict, BCI, and Prosigna have been evaluated.

**EndoPredict**
For individuals who have early-stage node-negative invasive breast cancer free of distant recurrence at 5 years considering extending tamoxifen treatment who receive gene expression profiling with EndoPredict, the evidence includes 1 study of archived tissue samples from a previously conducted clinical trial. The study showed low distant recurrence rates in patients classified at low risk with the test. Further studies are necessary to reinforce this finding. It is unclear what an appropriate risk threshold is to consider avoidance of extending tamoxifen treatment. The evidence is insufficient to determine the effect of the technology on health outcomes.

**Breast Cancer Index**
For individuals who have early-stage node-negative invasive breast cancer free of distant recurrence at 5 years considering extending tamoxifen treatment who receive gene expression profiling with BCI, the evidence includes 1 study of archived tissue samples from a previously conducted clinical trial. The study showed low distant recurrence rates in patients classified at low risk with the test. Further studies are necessary to reinforce this finding. It is unclear what an appropriate risk threshold is to consider avoidance of extending tamoxifen treatment. The evidence is insufficient to determine the effect of the technology on health outcomes.

**Prosigna**
For individuals who have early-stage node-negative invasive breast cancer free of distant recurrence at 5 years considering extending tamoxifen treatment who receive gene expression profiling with the Prosigna, the evidence includes 2 studies from previously conducted clinical trials. The studies showed low distant recurrence rates in patients classified at low risk with the test. Further studies are necessary to reinforce this finding. It is unclear what an appropriate risk threshold is to consider avoidance of extending tamoxifen treatment. The evidence is insufficient to determine the effect of the technology on health outcomes.

**Policy History**

<table>
<thead>
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<th>Date</th>
<th>Action</th>
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<tr>
<td>7/2018</td>
<td>Clarified coding information.</td>
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<tr>
<td>1/2018</td>
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<td>1/2018</td>
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Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:
- Medical Policy Terms of Use
- Managed Care Guidelines
- Indemnity/PPO Guidelines
- Clinical Exception Process
- Medical Technology Assessment Guidelines

References


