Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Breast Cancer

Policy # 00731
Original Effective Date: 03/08/2021
Current Effective Date: 03/08/2021

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Genetic Testing for BRCA1 or BRCA2 for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers is addressed separately in medical policy 00047.

Note: Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis in Patients with Breast Cancer is addressed separately in medical policy 00211.

Note: Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies is addressed separately in medical policy 00423.

Note: Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy) is addressed separately in medical policy 00497.

When Services Are Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

PIK3CA Testing

Based on review of available data, the Company may consider *PIK3CA* gene testing to predict treatment response to alpelisib (Piqray) in patients with hormone receptor-positive, HER2 negative advanced or metastatic breast cancer who have progressed on or after an endocrine-based regimen to be **eligible for coverage**** (see Policy Guidelines).

When tumor tissue is available, use of tissue for testing is preferred (see Circulating Tumor DNA Testing below).

***NTRK* Gene Fusion Testing**

Based on review of available data, the Company may consider analysis of *NTRK* gene fusions to predict treatment response to entrectinib (Rozlytrek) or larotrectinib (Vitrakvi) in patients with locally advanced or metastatic breast cancer that has progressed following standard treatment and who have no alternative treatment option to be **eligible for coverage**** (see Policy Guidelines).

PD-L1 Testing

Based on review of available data, the Company may consider PD-L1 (immunohistochemistry) testing to predict treatment response to atezolizumab (Tecentriq) in patients with hormone receptor-negative/HER2-negative (triple negative) metastatic or unresectable breast cancer to be **eligible for coverage**** (see Policy Guidelines).

Based on review of available data, the Company may consider PD-L1 (immunohistochemistry) testing to predict treatment response to pembrolizumab (Keytruda) in patients with hormone receptor-negative/HER2-negative (triple negative) recurrent or metastatic breast cancer to be **eligible for coverage**** (see Policy Guidelines).

MSI-H/dMMR Testing

Based on review of available data, the Company may consider MSI-H/dMMR (immunohistochemistry) testing to predict treatment response to pembrolizumab (Keytruda) in patients with unresectable or metastatic breast cancer that has progressed following standard treatment and who have no alternative treatment option to be **eligible for coverage**** (see Policy Guidelines).

Circulating Tumor DNA Testing (Liquid Biopsy)

Based on review of available data, the Company may consider *PIK3CA* gene testing using therascreen®‡ PIK3CA for analysis of 11 gene variants (utilizing plasma) to predict treatment response to alpelisib (Piqray) in patients with hormone receptor-positive, HER2 negative advanced or metastatic breast cancer who have progressed on or after an endocrine-based regimen to be **eligible for coverage**** when tumor tissue testing was not done before and is not available for PIK3CA gene analysis (see Policy Guidelines).

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When Services Are Considered Not Medically Necessary

Circulating Tumor DNA Testing (Liquid Biopsy)

Based on review of available data, the Company considers circulating tumor DNA testing using FoundationOne Liquid CDx to predict treatment response to alpelisib (Piqray) in patients with hormone receptor-positive, HER2 negative advanced or metastatic breast cancer who have progressed on or after an endocrine-based regimen to be **not medically necessary.****

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

***PIK3CA* Testing**

Based on review of available data, the Company considers *PIK3CA* gene testing of tissue in patients with breast cancer in all other situations to be **investigational.***

***NTRK* Gene Fusion Testing**

Based on review of available data, the Company considers analysis of *NTRK* gene fusions in patients with breast cancer in all other situations to be **investigational.***

PD-L1 Testing

Based on review of available data, the Company considers PD-L1 testing in patients with breast cancer in all other situations to be **investigational.***

MSI-H/dMMR Testing

Based on review of available data, the Company considers MSI-H/dMMR (immunohistochemistry) testing in patients with breast cancer in all other situations to be **investigational.***

Tumor Mutational Burden Testing

Based on review of available data, the Company considers tumor mutational burden testing to predict response to immunotherapy in patients with breast cancer to be **investigational.***

Circulating Tumor DNA Testing (Liquid Biopsy)
Based on review of available data, the Company considers circulating tumor DNA testing in patients with breast cancer in all other situations (except when considered not medically necessary) to be **investigational.***

Circulating Tumor Cell Testing
Based on review of available data, the Company considers analysis of circulating tumor cells to select treatment in patients with breast cancer to be **investigational.***

Policy Guidelines

This policy does not address testing of germline variants (see medical policy 00047).

See U.S. Food and Drug Administration labels, clinical trials, and NCCN guidelines for specific population descriptions. Descriptions varied slightly across sources.

Background/Overview

***PIK3CA* Testing**
Alterations in the protein coding gene *PIK3CA* (Phosphatidylinositol-4, 5-Bisphosphate 3-Kinase Catalytic Subunit Alpha) occur in approximately 40% of patients with HR-positive, HER2-negative breast cancer.

***NTRK* Gene Fusions**
Neurotrophic-tropomyosin receptor kinase *(NTRK)* gene fusions encode tropomyosin receptor kinase fusion proteins that act as oncogenic drivers for solid tumors including lung, salivary gland, thyroid, and sarcoma. *NTRK* gene fusion findings might be more highly associated with rare breast cancer subtypes (eg secretory carcinoma).

Programmed Cell Death Ligand Protein-1
Programmed death ligand-1 (PD-L1) is a transmembrane protein expressed on the surface of multiple tissue types, including many tumor cells. Blocking the PD-L1 protein may prevent cancer cells from inactivating T cells.

Mismatch Repair Deficiency/Microsatellite Instability
Mismatch repair deficiency (dMMR) and high levels of microsatellite instability (MSI-H) describe cells that have alterations in certain genes involved in correcting errors made when DNA is replicated. dMMR tumors are characterized by a high tumor mutational load and potential responsiveness to anti-PD-L1-immunotherapy. MMR deficiency is most common in colorectal cancer, other types of gastrointestinal cancer, and endometrial cancer, but it may also be found in other cancers including breast cancer. Microsatellite instability testing is generally performed using polymerase chain reaction (PCR) for 5 biomarkers, although other biomarker panels and next generation sequencing are sometimes performed. High microsatellite instability is defined as 2 or more of the 5 biomarkers showing instability or more than 30% of the tested biomarkers showing instability depending on what panel is used. Microsatellite instability testing is generally paired with immunohistochemistry (IHC) assessing lack of protein expression from 4 DNA mismatch repair genes thereby reflecting dMMR.

Tumor Mutational Burden
Tumor mutational burden (TMB), a measure of gene mutations within cancer cells, is an emerging biomarker of outcomes with immunotherapy in multiple tumor types. Initially, assessments of TMB involved whole exome sequencing (WES). More recently, targeted next generation sequencing (NGS) panels are being adapted to estimate TMB. Currently FoundationOne CDx is the only U.S. Food and Drug Administration (FDA) approved panel for estimating TMB, but others are in development.

Circulating Tumor DNA
Normal and tumor cells release small fragments of DNA into the blood, which is referred to as cell-free DNA. Cell-free DNA from nonmalignant cells is released by apoptosis or programmed cell death. Most cell-free tumor DNA is derived from apoptotic and/or necrotic tumor cells, either from the primary tumor, metastases, or circulating tumor cells (CTCs). Unlike apoptosis, necrosis is considered a pathologic process and generates larger DNA fragments due to incomplete and random digestion of genomic DNA. The length or integrity of the circulating DNA can potentially distinguish between apoptotic and necrotic origin. Circulating tumor DNA can be used for genomic characterization of the tumor.

Circulating Tumor Cells
Intact CTCs are released from a primary tumor and/or a metastatic site into the bloodstream. The half-life of a CTC in the bloodstream is short (1-2 hours), and CTCs are cleared through extravasation into secondary organs. Most assays detect CTCs through the use of surface epithelial markers such as EpCAM and cytokeratins. The primary reason for in detecting CTCs is prognostic, through quantification of circulating levels.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of these tests.

Table 1 summarizes available targeted treatments with FDA approval for recurrent or metastatic breast cancer (including immunotherapy) and the FDA approved companion diagnostic tests associated with each.

Table 1. Targeted Treatments for Metastatic Breast Cancer and FDA Approved Companion Diagnostic Tests

Treatment	Class	Indications in Breast Cancer	Companion Diagnostic
ado-trastuzumab emtansine (Kadcyla)	HER2-targeted antibody and microtubule inhibitor conjugate	As a single agent, for: • Treatment of patients with HER2-positive, metastatic breast cancer who previously received trastuzumab and a taxane, separately or in	FoundationOne CDx HER2 FISH pharmDx Kit HercepTest INFORM HER2 Dual ISH DNA

		combination. Patients should have either: ○ received prior therapy for metastatic disease, or ○ developed disease recurrence during or within 6 months of completing adjuvant therapy. • Adjuvant treatment of patients with HER2-positive early breast cancer who have residual invasive disease after neoadjuvant taxane and trastuzumab-based treatment.	Probe Cocktail PATHWAY anti-Her2/neu (4B5) Rabbit Monoclonal Primary Antibody
Alpelisib (Piqray)	Kinase inhibitor	In combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA-mutated, advanced or metastatic breast cancer as detected by an FDA approved test following progression on or after an endocrine-based regimen	FoundationOne CDx FoundationOne Liquid CDx therascreen PIK3CA RGQ PCR Kit
Atezolizumab (Tecentri)	PD-L1 blocking antibody	In combination with paclitaxel protein-bound for the treatment of adult patients with unresectable locally advanced or metastatic TNBC	VENTANA PD-L1(SP142) Assay

		whose tumors express PD-L1, as determined by an FDA approved test.	
Entrectinib (Rozlytrek)	Kinase inhibitor	Adult and pediatric patients 12 years of age and older with solid tumors that: • have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion without a known acquired resistance mutation, • are metastatic or where surgical resection is likely to result in severe morbidity, and • have progressed following treatment or have no satisfactory alternative therapy	No FDA approved companion diagnostic test
Larotrectinib (Vitrakvi)	Kinase inhibitor	Adult and pediatric patients 12 years of age and older with solid tumors that: • have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion without a known acquired resistance mutation, • are metastatic or where surgical resection is likely to result in severe morbidity, and • have progressed following treatment or have no satisfactory alternative therapy	FoundationOne CDx

Olaparib (Lynparza)	PARP inhibitor	Adult patients with deleterious or suspected deleterious germline BRCA mutated, HER2-negative metastatic breast cancer who have been treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting. Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine therapy. Select patients for therapy based on an FDA approved companion diagnostic for Lynparza.	BRACAnalysis CDx
Pembrolizumab (Keytruda)	PD-L1-blocking antibody	• in combination with chemotherapy, for the treatment of patients with locally recurrent unresectable or metastatic TNBC whose tumors express PD-L1 as determined by an FDA approved test	PD-L1 IHC 22C3 pharmDx
		• Adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and who have	No FDA approved companion diagnostic test

		no satisfactory alternative treatment options	
		• Unresectable or metastatic tumor mutational burden-high (≥10 mutations/megabase) solid tumors, as determined by an FDA approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options.	FoundationOne CDx (Solid tumors TMB ≥ 10 mutations per megabase)
Pertuzumab (Perjeta)	HER2/neu receptor antagonist	• Use in combination with trastuzumab and docetaxel for treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease. • Use in combination with trastuzumab and chemotherapy as o neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater	HER2 FISH pharmDx Kit HercepTest FoundationOne CDx

		than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer. ○ adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence	
Talzenna (Talazoparib)	PARP inhibitor	Adult patients with deleterious or suspected deleterious germline BRCA-mutated HER2-negative locally advanced or metastatic breast cancer.	BRACAnalysis CDx
Trastuzumab (Herceptin)	HER2/neu receptor antagonist	The treatment of HER2-overexpressing breast cancer	Bond Oracle HER2 IHC System FoundationOne CDx HER2 CISH pharmDx Kit HER2 FISH pharmDx Kit HercepTest INFORM HER-2/neu INFORM HER2 Dual ISH DNA Probe Cocktail InSite Her-2/neu

			KITPathVysion HER-2 DNA Probe Kit PATHWAY anti-Her2/neu (4B5) Rabbit Monoclonal Primary Antibody SPOT-LIGHT HER2 CISH KitVENTANA HER2 Dual ISH DNA Probe Cocktail

dMMR: mismatch repair deficient; FDA: U.S. Food & Drug Administration; HER2: human epidermal growth factor receptor 2; MSI-H: microsatellite instability-high; NTRK: neurotrophic-tropomyosin receptor kinase; PD-L1: programmed death-ligand 1 ; PIK3CA: phosphatidylinositol 3-kinase catalytic alpha polypeptide; TNBC: triple-negative breast cancer

Rationale/Source

Description

Multiple biomarkers are being evaluated to predict response to targeted treatments and immunotherapy for patients with advanced breast cancer. These include tissue-based testing as well as circulating tumor DNA and circulating tumor cell testing (known as liquid biopsy).

The objective of this evidence review is to examine whether biomarker testing for *PIK3CA*, *NTRK gene fusions*, PD-L1, MSI-H/dMMR, TMB, circulating tumor DNA, or circulating tumor cells improves the net health outcome in patients with recurrent, metastatic, or unresectable breast cancer.

Summary of Evidence

For individuals with hormone receptor-positive, HER2 negative advanced or metastatic breast cancer who receive *PIK3CA* gene testing to select targeted treatment, the evidence includes a randomized, placebo-controlled trial of alpelisib compared to placebo in men and postmenopausal

women with advanced breast cancer who had previously received endocrine therapy. Relevant outcomes include overall survival, disease-specific survival, test validity, quality of life, and treatment-related morbidity. Among patients with *PIK3C*A-positive tumors who received targeted therapy, PFS was 11.0 months (95% CI, 7.5 to 14.5), compared to 5.7 months (95% CI, 3.7 to 7.4) in *PIK3CA*-positive patients who received standard care. In contrast, the hazard ratio for PFS in the cohort without PIK3CA-mutatied cancer was not significantly different for the active vs placebo groups. The overall response rate was higher in patients with *PIK3CA*-positive tumors compared to the rate in the standard care group (26.6% [95% CI [20.1- 34.0] vs 12.8% [8.2-18.7%]). The evidence is sufficient to determine that the technology results in an improvement in the net health outcomes.

For individuals with locally advanced or metastatic breast cancer being considered for immunotherapy who receive *NTRK* gene fusion testing, the evidence includes integrated analyses of nonrandomized trials of larotrectinib and entrectinib in patients with *NTRK*-fusion positive solid tumors. Relevant outcomes are OS, disease-specific survival, test validity, QOL, and treatment-related morbidity. In an analysis of 159 patients with *NTRK*-fusion positive solid tumors who received larotrectinib, including 5 patients with breast tumors, the overall response rate was 79% (95% CI 72 to 85). The median PFS was 28·3 months (95% CI 22.1 to not estimable), and 67% of patients were progression-free at 12 months (95% CI 58–76). In an integrated analysis of 3 phase 1-2 trials in 54 patients with *NTRK*-positive solid tumors who received entrectinib, 6 of whom had breast cancer, the overall response rate was 57% (95% CI 43.2–70.8). At data cutoff, 16 (30%) of 54 patients had died, and the estimated median overall survival was 21 months (95% CI 14.9 to not estimable. Responses were observed regardless of tumor type or age of the patient. The evidence is sufficient to determine that the technology results in an improvement in the net health outcomes.

For individuals with recurrent, metastatic, or unresectable hormone receptor-negative, HER2 negative (triple negative) breast cancer being considered for immunotherapy who receive PD-L1 testing, the evidence includes a RCT of atezolizumab and nonrandomized trials of pembrolizumab. Relevant outcomes include overall survival, disease-specific survival, test validity, quality of life, and treatment-related morbidity. In a placebo controlled trial of atezolizumab in combination with nab-paclitaxel for patients with PD-L1 positive TNBC, median PFS (HR 0.62; 95% CI, 0.49 to 0.78) and OS 0.62 (95% CI, 0.45–0.86) were longer among patients who received the targeted immunotherapy. In 2 nonrandomized trials of pembrolizumab for patients with PD-L1 positive TNBC, the objective response rate was 21.4% (95% CI, 13.9 to 31.4) and 18.5% (95% CI, 6.3 to

38.1). The evidence is sufficient to determine that the technology results in an improvement in the net health outcomes.

For individuals with unresectable or metastatic breast cancer who are being considered for immunotherapy who receive MSI-H/dMMR testing, the evidence includes nonrandomized trials of pembrolizumab in patients with solid tumors. Relevant outcomes include overall survival, disease-specific survival, test validity, quality of life, and treatment-related morbidity. In a phase 2 trial of pembrolizumab in 233 previously treated patients with MSI-H solid tumors, the overall response rate was 34.3% (95% CI, 28.3% to 40.8%). Median PFS was 4.1 months (95% CI, 2.4 to 4.9 months) and median OS was 23.5 months (95% CI, 13.5 months to not reached). Treatment-related adverse events occurred in 151 patients (64.8%). The evidence is sufficient to determine that the technology results in an improvement in the net health outcomes.

For individuals with unresectable or metastatic breast cancer who are being considered for immunotherapy who receive tumor mutational burden (TMB) testing, the evidence includes prospective and retrospective subgroup analyses of nonrandomized trials. Relevant outcomes include overall survival, disease-specific survival, test validity, quality of life, and treatment-related morbidity. In a prespecified subgroup analysis of a nonrandomized trial of pembrolizumab in patients with various solid tumors, objective responses were observed in 24 (35%; 95% CI 24–48) of 68 participants who had both tTMB-high status and PD-L1-positive tumors and in 6 (21%; 8–40) of 29 participants who had tTMB-high status and PD-L1-negative tumors. In exploratory analyses, retrospective observational studies have reported an association between higher TMB and longer PFS and OS in patients receiving immunotherapy. These results need to be confirmed in additional, well-designed prospective studies. The evidence is insufficient to determine that the technology results in an improvement in the net health outcomes.

For individuals with hormone receptor-positive, HER2 negative advanced or metastatic breast cancer who receive circulating tumor DNA testing to select targeted treatment, the evidence includes a randomized, placebo-controlled trial of alpelisib compared to placebo in men and postmenopausal women with advanced breast cancer who had previously received endocrine therapy. Relevant outcomes include overall survival, disease-specific survival, test validity, quality of life, and treatment-related morbidity. Clinical validity of the FoundationOne Liquid CDx test was demonstrated through retrospective testing of plasma samples of patients enrolled in the SOLAR-1

trial. The positive predictive agreement and negative predictive agreement between FoundationOne Liquid CDx and the tissue-based assay were 71.7% (95% CI 65.4%, 77.5%) and 100% (97.2%, 100%), respectively. Among the circulating tumor DNA-positive population, there was an estimated 54% risk reduction in disease progression or death in the alpelisib plus fulvestrant arm compared to the placebo plus fulvestrant arm (HR = 0.46, 95% CI: 0.30, 0.70). The evidence is sufficient to determine that the technology results in an improvement in the net health outcomes. Targeted liquid biopsy PIK3CA gene testing is available and is also FDA approved companion diagnostic test (therascreen PIK3CA). The evidence is insufficient to determine that the technology (FoundationOne Liquid CDx) results in an improvement in the net health outcomes as compared to more targeted testing.

For individuals with metastatic breast cancer who receive CTC testing to guide treatment decisions, the evidence includes randomized controlled trials, observational studies, and systematic reviews. Relevant outcomes include overall survival, disease-specific survival, test validity, quality of life, and treatment-related morbidity. Systematic reviews and meta-analyses have described an association between CTCs and poor prognosis in metastatic breast cancer, but evidence that CTC-driven treatment improves health outcomes is lacking. One RCT found no improvement in OS or PFS with CTC-driven treatment (early switching to a different chemotherapy regimen) compared to continuing initial therapy. A second RCT found that CTC-driven first-line therapy was noninferior to clinician-driven therapy in previously untreated patients with metastatic breast cancer (hazard ratio for PFS 0.94; 95% CI 0.81 to 1.09).The evidence is insufficient to determine that the technology results in an improvement in the net health outcomes.

Supplemental Information

Professional Society Guidelines

National Comprehensive Cancer Network

Table 2 summarizes National Comprehensive Cancer Network guidelines (v.6.2020) on biomarker testing for the biomarkers included in this policy. The guidelines state that the use of circulating tumor cells or circulating tumor DNA in metastatic breast cancer is not yet included in algorithms for disease assessment and monitoring. For patients being considered for treatment with alpelisib,

testing for PIK3CA with either tissue or liquid biopsy is recommended (category of evidence 2A). The guidelines do not address TMB testing.

Table 2. National Comprehensive Cancer Network Guidelines on Biomarker Testing for Targeted Treatment of Breast Cancer

Biomarker	Breast Cancer Subtype	FDA Approved Agents	Testing Recommendation	Targeted Therapy Category of Evidence	Targeted Therapy Category of Preference
PIK3CA	HR-positive/HER2-negative	Alpelisib + fulvestrant	For HR-positive/HER2-negative breast cancer, assess for PIK3CA mutations with tumor or liquid biopsy to identify candidates for alpelisib plus fulvestrant.PIK3CA mutation testing can be done on tumor tissue or ctDNA in peripheral blood (liquid biopsy). If liquid biopsy is negative, tumor tissue testing is recommended.	1	Preferred second-line therapy

PD-L1 expression (≥1% on tumor-infiltrating immune cells)	HR-negative/HER2-negative	Atezolizumab + albumin-bound paclitaxel	For triple-negative breast cancer, assess PD-L1 expression biomarker status on tumor-infiltrating immune cells to identify patients most likely to benefit from candidates for atezolizumab plus albumin-bound paclitaxel	2A	Preferred
NTRK fusion	Any	Larotrectinib Entrectinib	No specific testing recommendation. If a patient with recurrent/stage IV breast cancer presents with a tumor with an NTRK fusion, treatment with an NTRK inhibitor is an option if no satisfactory alternative treatments exist or that have progressed following treatment, treatment with an NTRK inhibitor is an option	2A	Useful in certain circumstances

MSI-H/dMMR	Any	Pembrolizumab	No specific testing recommendation. If a patient with recurrent/stage IV breast cancer has a tumor with a MSI-H/dMMR mutation, whose disease has progressed following prior treatments and no satisfactory alternative treatments exist, treatment with pembrolizumab is an option	2A	Useful in certain circumstances

Source: Adapted from National Comprehensive Cancer Network guidelines on Breast Cancer (v.6.2020)

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 3.

Table 3. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02889978[a]	The Circulating Cell-free Genome Atlas Study	15000	Mar 2024
NCT02568267[a]	An Open-Label, Multicenter, Global Phase 2 Basket Study of Entrectinib for the Treatment of Patients With Locally Advanced or Metastatic	500	Dec 2024

	Solid Tumors That Harbor NTRK1/2/3, ROS1, or ALK Gene Rearrangements		
NCT04098640	Molecular Profiling Using FoundationOne CDx in Young (<50 Years of Age) Patients With Metastatic Breast Cancer (ML41263)	200	Jul 2021
NCT04591431	The Rome Trial From Histology to Target: the Road to Personalize Target Therapy and Immunotherapy	384	Aug 2024

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

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Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2020 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	
CPT	0155U, 0177U, 81191, 81192, 81193, 81194, 81301, 81309, 81445, 86152, 86153
HCPCS	No codes
ICD-10 Diagnosis	C50.11-C50.929, C79.81

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or

diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company

recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.