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

Policy # 00731
Original Effective Date: 03/08/2021
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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.*

BRCA1 and BRCA2 Testing

Based on review of available data, the Company may consider genetic testing for *BRCA1* or *BRCA2* germline variants to predict treatment response to FDA-approved treatment (i.e., PARP inhibitors such as olaparib [Lynparza] and talazoparib [Talzenna]) in all individuals with triple-negative breast cancer, recurrent or metastatic breast cancer and in individuals with human epidermal receptor 2 negative (HER2-negative) early stage high-risk breast cancer to be **eligible for coverage**** (see Policy Guidelines).

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***PIK3CA* Testing**
Based on review of available data, the Company may consider *PIK3CA* gene testing to predict treatment response to FDA-approved treatment (e.g., alpelisib [Piqray]) in individuals with hormone receptor-positive, HER2 negative recurrent 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 tumor tissue analysis of *NTRK* gene fusions to predict treatment response to FDA-approved treatment (e.g., entrectinib [Rozlytrek] or larotrectinib [Vitrakvi[) in individuals with recurrent or metastatic breast cancer that has progressed following standard treatment or who have no alternative treatment option to be **eligible for coverage**** (see Policy Guidelines).

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

When Services May Be 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.*

MSI-H/dMMR Testing and Tumor Mutational Burden (TMB) Testing
Based on review of available data, the Company may consider tumor tissue analysis for deficiency of DNA mismatch repair protein expression (dMMR by IHC) and/or detection of high levels of

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tumor microsatellite instability (MSI-H by PCR or validated NGS) or TMB testing for selecting FDA-approved immunotherapy when patient selection criteria are met to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for MSI-H, dMMR or TMB testing for selecting treatment with FDA-approved treatment (e.g., pembrolizumab [Keytruda] or dostarlimab [Jemperli]) will be considered when **ALL** of the following criteria are met:

- Individual has recurrent unresectable or metastatic breast cancer that has progressed following standard treatment and who has no alternative treatment options (see Policy Guidelines section); **AND**
- The panel test is designated for TMB assessment (provides a TMB score) and has a U.S. Food and Drug Administration (FDA) approved or cleared indication as an in vitro companion diagnostic (i.e., FoundationOne CDx™‡ assay).

Circulating Tumor DNA Testing (Liquid Biopsy)

Based on review of available data, the Company may consider FDA-approved companion diagnostic circulating tumor DNA (ctDNA) or liquid biopsy testing when coverage criteria are met to be **eligible for coverage**.**

Patient Selection Criteria

Coverage eligibility for FDA-approved companion diagnostic liquid biopsy testing will be considered when **ALL** of the following criteria are met:

- Individual was diagnosed with hormone receptor positive, HER2- negative recurrent or metastatic breast cancer who have progressed on or after an endocrine-based regimen; **AND**
- Individual has not been previously tested for PIK3CA activating mutation and/or ESR1 gene missense mutations (or results are not available); **AND**
- Liquid biopsy test must have a U.S. Food and Drug Administration (FDA) approved or cleared indication as an in vitro companion diagnostic for use in the individual's cancer, i.e., FoundationOne®‡ Liquid CDx, therascreen®‡ PIK3CA, or Guardant360 CDx (see Policy Guidelines section); **AND**
- Tissue-based testing is not feasible (tumor tissue testing is preferred when available); **AND**

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- Treatment is considered with genomic biomarker-linked therapies approved by regulatory agencies for individual's cancer (e.g., alpelisib [Piqray], elacestrant [Orserdu]); **AND**
- Follow-up tissue-based genotyping will be considered if no genetic alteration is detected by plasma genotyping, or if ctDNA is insufficient (not detected).

When Services Are Considered Investigational

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

***BRCA, PIK3CA, NTRK, MSI-H/dMMR and TMB* Testing**

Based on review of available data, the Company considers *BRCA* (germline or somatic), *PIK3CA, NTRK, MSI-H/dMMR and TMB* gene testing for guiding therapy in individuals with breast cancer in all other situations, including but not limited to repeat testing when previous results of these variants are available, to be **investigational.***

PD-L1 Testing

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

Ki-67, RET, BRAF and Other Gene Testing

Based on review of available data, the Company considers other gene testing in individuals with breast cancer, including but not limited to Ki-67, RET and BRAF, to be **investigational.***

Circulating Tumor DNA Testing (Liquid Biopsy)

Based on review of available data, the Company considers liquid biopsy testing when selection criteria are not met and in all other situations not mentioned above, including but not limited to repeat liquid biopsy testing and use of concurrent liquid based test in addition to tumor based genomic profiling, to be **investigational.***

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

Policy Guidelines

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

Testing for individual genes (not gene panels) associated with FDA-approved therapeutics (i.e., as companion diagnostic tests) for therapies with National Comprehensive Cancer Network (NCCN) recommendations of 2A or higher are not subject to extensive evidence review. Note that while the FDA approval of companion diagnostic tests for genes might include tests that are conducted as panels, the FDA approval is for specific genes (such as driver mutations) and not for all of the genes on the test panel.

For guidance on testing criteria between policy updates, refer to the FDA's List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools) (https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools) for an updated list of FDA-approved tumor markers and consult the most current version of NCCN management algorithms.

Breast Cancer Risk Groups
In the OlympiA trial, patients with HER2-negative early-stage breast cancer (Clinical Stage I-III) and germline *BRCA1/2* mutations treated with (neo)adjuvant chemotherapy were considered at high risk of recurrent disease when the following eligibility criteria were met for treatment with olaparib (Tutt et al, 2021; PMID 34081848):

- Patients with triple-negative breast cancer who were treated with adjuvant chemotherapy were required to have axillary node-positive disease or an invasive primary tumor measuring at least 2 cm on pathological analysis. Patients treated with neoadjuvant chemotherapy were required to have not achieved pathological complete response.
- Patients treated with adjuvant chemotherapy for hormone receptor (HR)-positive, HER2-negative breast cancer were required to have at least 4 pathologically confirmed positive

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lymph nodes. Those treated with neoadjuvant chemotherapy were required to have not achieved a pathological complete response with a clinical stage, pathologic stage, estrogen receptor status, and tumor grade (CPS+EG) score of 3 or higher (Table PG1). This scoring system estimates relapse probability on the basis of clinical and pathological stage (CPS) and estrogen-receptor status and histologic grade (EG). Scores range from 0 to 6, with higher scores reflecting a worse prognosis.

Table PG1. CPS+EG Score[a,b]

Stage or Feature	Points
Clinical Stage (AJCC Staging)	
I	0
IIA	0
IIB	1
IIIA	1
IIIB	2
IIIC	2
Pathologic Stage (AJCC Staging)	
0	0
I	0
IIA	1
IIB	1
IIIA	1
IIIB	1
IIIC	2

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Receptor Status	
ER-negative	1
Nuclear Grade	
Nuclear grade 3	1

AJCC: American Joint Committee on Cancer; CPS+EG: clinical stage, pathologic stage, ER status, and tumor grade; ER: estrogen receptor.
[a] Adapted from Tung et al (2021; PMID 34343058).
[b] Add points for clinical stage, pathologic stage, ER status, and nuclear grade to yield a sum between 0 and 6.

Paired Genetic Testing
Testing for genetic changes in tumor tissue assesses somatic changes. However, most somatic testing involves a paired blood analysis in order to distinguish whether findings in tumor tissue are acquired somatic changes or inherited germline changes. As such, simultaneous sequencing of tumor and normal tissue can recognize potential secondary germline changes that may identify risk for other cancers as well as identify risk for relatives. Thus, some laboratories offer concurrent full germline and somatic testing or paired tumor sequencing and germline sequencing, through large panels of germline and somatic variants. For paired panel testing involving germline components, see medical policy 00423 - Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies.

Background/Overview

BRCA Variant Testing
The prevalence of *BRCA* variants is approximately 0.1% to 0.2% in the general population. The prevalence may be much higher for particular ethnic groups with characterized founder mutations (eg, 2.5% [1/40] in the Ashkenazi Jewish population). Family history of breast and ovarian cancer is an important risk factor for the *BRCA* variant; additionally, age and ethnicity could be independent risk factors.

Several genetic syndromes with an autosomal dominant pattern of inheritance that features breast cancer have been identified. Of these, hereditary breast and ovarian cancer (HBOC) and some cases

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of hereditary site-specific breast cancer have in common causative variants in *BRCA* (breast cancer susceptibility) genes. Families suspected of having HBOC syndrome are characterized by an increased susceptibility to breast cancer occurring at a young age, bilateral breast cancer, male breast cancer, ovarian cancer at any age, as well as cancer of the fallopian tube and primary peritoneal cancer. Other cancers, such as prostate cancer, pancreatic cancer, gastrointestinal cancers, melanoma, and laryngeal cancer, occur more frequently in HBOC families. Hereditary site-specific breast cancer families are characterized by early-onset breast cancer with or without male cases, but without ovarian cancer.

Germline variants in the *BRCA1* and *BRCA2* genes are responsible for the cancer susceptibility in most HBOC families, especially if ovarian cancer or male breast cancer are features. However, in site-specific cancer, BRCA variants are responsible only for a proportion of affected families. *BRCA* gene variants are inherited in an autosomal dominant fashion through maternal or paternal lineage. It is possible to test for abnormalities in *BRCA1* and *BRCA2* genes to identify the specific variant in cancer cases and to identify family members at increased cancer risk. Family members without existing cancer who are found to have *BRCA* variants can consider preventive interventions for reducing risk and mortality.

Young age of onset of breast cancer, even in the absence of family history, is a risk factor for *BRCA1* variants. Winchester (1996) estimated that hereditary breast cancers account for 36% to 85% of patients diagnosed before age 30. In several studies, BRCA variants were independently predicted by early age at onset, being present in 6% to 10% of breast cancer cases diagnosed at ages younger than various premenopausal age cutoffs (age range, 35-50 years). In cancer-prone families, the mean age of breast cancer diagnosis among women carrying *BRCA1* or *BRCA2* variants is in the 40s. In the Ashkenazi Jewish population, Frank et al (2002) reported that 13% of 248 cases with no known family history and diagnosed before 50 years of age had *BRCA* variants. In a similar study by Gershoni-Baruch et al (2000), 31% of Ashkenazi Jewish women, unselected for family history, diagnosed with breast cancer at younger than 42 years of age had *BRCA* variants. Other studies have indicated that early age of breast cancer diagnosis is a significant predictor of BRCA variants in the absence of family history in this population.

In patients with "triple-negative" breast cancer (ie, negative for expression of estrogen, progesterone, and overexpression of human epidermal growth factor receptor 2 [HER2] receptors), there is an

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increased prevalence of *BRCA* variants. Pathophysiologic research has suggested that the physiologic pathway for the development of triple-negative breast cancer is similar to that for *BRCA*-associated breast cancer. Young et al (2009) studied 54 women with high-grade, triple-negative breast cancer with no family history of breast or ovarian cancer, representing a group that previously was not recommended for *BRCA* testing. Six BRCA variants (5 *BRCA1,* 1 *BRCA2*) were found, for a variant rate of 11%. Finally, Gonzalez-Angulo et al (2011) in a study of 77 patients with triple-negative breast cancer, reported that 15 patients (19.5%) had BRCA variants (12 in *BRCA1*, 3 in *BRCA2*).

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.

ESR1 mutations

Estrogen receptor 1 (ESR1) activating mutations are frequently detected in patients with prior exposure to aromatase inhibitors (Ais). Tumors with these mutations are generally resistant to both AIs and tamoxifen. Certain tumors with these mutations retain sensitivity to fulvestrant. All may benefit by adding one of the following to fulvestrant - a CDK 4/6-inhibitor, or an mTOR-inhibitor, or alpelisib, if the tumor has PIK3CA mutation. The acquisition of ligand-independent *ESR1* mutations during aromatase inhibitor therapy in metastatic estrogen receptor-positive breast cancer is a common mechanism of hormonal therapy resistance.

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.

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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.

Ki-67
Ki-67 is a nuclear protein used to detect and quantify the rate of tumor cell proliferation and has been investigated as a prognostic biomarker for breast cancer.

Rearranged During Transfection
The REarranged during Transfection (RET) proto-oncogene encodes a receptor tyrosine kinase growth factor. Translocations that result in fusion genes with several partners have been reported, and occur in about 5-10% of thyroid cancer cases (primarily papillary thyroid carcinoma) and 1%-2% of non-small-cell lung cancer cases. RET fusions in breast cancer, occur in less than 1% of cases.

BRAF
RAF proteins are serine/threonine kinases that are downstream of RAS in the RAS-RAF-ERK-MAPK pathway. The most common mutation locus is found in codon 600 of exon 15 (V600E) of the BRAF gene, causing constitutive hyperactivation, proliferation, differentiation, survival, and oncogenic transformation. BRAF mutations occur in approximately 1% of breast cancer cases.

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

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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 circulating tumor cells (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.

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Table 1 summarizes available targeted treatments with FDA approval for breast cancer (including immunotherapy) and the FDA cleared or approved companion diagnostic tests associated with each. An up-to-date list of FDA cleared or approved companion diagnostics is available at https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools.

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

Treatment	Class	Indications in Breast Cancer	Companion Diagnostic
Abemaciclib (Verzenio)	Cyclin-dependent kinase (CDK) 4/6 inhibitor	• In combination with endocrine therapy (tamoxifen or an aromatase inhibitor) for the adjuvant treatment of adult patients with HR-positive, HER2-negative, node-positive, early breast cancer at high risk of recurrence and a Ki-67 score ≥20% as determined by an FDA approved test. • In combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women, and men, with HR-positive, HER2-negative advanced or metastatic breast cancer. • In combination with fulvestrant for the treatment of adult patients with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy.	Ki-67 IHC MIB-1 pharmDx (Dako Omnis)

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		• As monotherapy for the treatment of adult patients with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting.	
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 combination. Patients should have either: o received prior therapy for metastatic disease, or o 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	FoundationOne CDx HER2 FISH pharmDx Kit HercepTest INFORM HER2 Dual ISH DNA Probe Cocktail PATHWAY anti-Her2/neu (4B5) Rabbit Monoclonal Primary Antibody

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		after neoadjuvant taxane and trastuzumab-based treatment.	
Alpelisib (Piqray)	Kinase inhibitor	In combination with fulvestrant for the treatment of postmenopausal women, and men, with HR positive, 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
Dabrafenib (Tafinlar) + Trametinib (Mekinist)	Kinase inhibitors	Adult and pediatric patients 6 years of age and older with unresectable or metastatic solid tumors with BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options	No FDA approved companion diagnostic
Dostarlimab-gxly (Jemperli)	PD-1 blocking antibody	Adult patients with dMMR recurrent or advanced solid tumors, as determined by an FDA-approved test, that has progressed on or following prior treatment and who have no satisfactory alternative treatment options	VENTANA MMR RxDx Panel
Entrectinib (Rozlytrek)	Kinase inhibitor	Adult and pediatric patients 12 years of age and older with solid tumors that: • have an NTRK gene fusion without a known acquired resistance mutation,	No FDA approved companion diagnostic test

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		• are metastatic or where surgical resection is likely to result in severe morbidity, and • have progressed following treatment or have no satisfactory alternative therapy	
Fam-trastuzumab deruxtecan-nxki (Enhertu)	HER-2 targeted antibody and topoisomerase inhibitor conjugate	• Adult patients with unresectable or metastatic HER2-positive breast cancer who have received a prior anti-HER2-based regimen either in the metastatic setting or in the neoadjuvant or adjuvant setting and have developed disease recurrence during or within 6 months of completing therapy • Adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer, as determined by an FDA-approved test, who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy	PATHWAY anti-Her2/neu (4B5) Rabbit Monoclonal Primary Antibody

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Larotrectinib (Vitrakvi)	Kinase inhibitor	Adult and pediatric patients 12 years of age and older with solid tumors that: • have an 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 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 FoundationOne 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

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		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 satisfactory alternative treatment options	FoundationOne CDx
		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: • Neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or node positive) as part of a complete	HER2 FISH pharmDx Kit HercepTest FoundationOne CDx

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		treatment regimen for early breast cancer. • Adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence	
Selpercatinib (Retevmo)	Kinase inhibitor	Adult patients with locally advanced or metastatic solid tumors with a RET gene fusion that have progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options	No FDA-approved companion diagnostic test
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

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			Dual ISH DNA Probe Cocktail InSite Her-2/neu KIT PathVysion HER-2 DNA Probe Kit PATHWAY anti-Her2/neu (4B5) Rabbit Monoclonal Primary Antibody SPOT-LIGHT HER2 CISH Kit VENTANA HER2 Dual ISH DNA Probe Cocktail

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

Sources

On January 27, 2023, the FDA has approved elacestrant (Orserdu) for the treatment of postmenopausal women or adult men with estrogen receptor-positive, HER2-negative, *ESR1*-mutated advanced or metastatic breast cancer with disease progression following at least 1 line of endocrine therapy. The FDA also approved the Guardant360 CDx as a companion diagnostic to identify patients who are eligible to receive elacestrant. The regulatory decision was based on data from the randomized, open-label, active-controlled, multicenter phase 3 EMERALD trial

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(NCT03778931), in which the oral selective estrogen degrader (SERD; n=115) reduced the risk of disease progression or death by 45% compared with fulvestrant (Faslodex) or an aromatase inhibitor (n=113) in this population. The median progression-free survival with elacestrant was 3.8 months vs 1.9 months with the control (HR 0.55; 95% CI 0.39-0.77; p=.0005). An exploratory analysis of PFS in the 250 (52%) patients without ESR1 mutations showed a HR 0.86 (95% CI: 0.63, 1.19) indicating that the improvement in the ITT population was primarily attributed to the results seen in the ESR1 mutated population.

In August 2021, Genentech voluntarily withdrew accelerated approval of atezolizumab (Tecentriq) for use in patients with PD-L1 positive, triple-negative breast cancer following FDA assessment of confirmatory trial results.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Multiple biomarkers are being evaluated to predict response to targeted treatments and immunotherapy for patients with advanced or high-risk 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 review is to examine whether biomarker testing for *BRCA* variants, *PIK3CA*, *NTRK gene fusions*, PD-L1, MSI-H/dMMR, Ki-67, TMB, circulating tumor DNA, or circulating tumor cells improves the net health outcome in patients with breast cancer who are considering targeted therapy or immunotherapy.

Summary of Evidence

For individuals with metastatic or high-risk, early stage HER2-negative breast cancer being considered for systemic therapy (ie, poly(adenosine diphosphate–ribose) polymerase [PARP] inhibitors) who receive genetic testing for a *BRCA1* or *BRCA2* germline variant, the evidence includes randomized, placebo-controlled trials of olaparib and talazoparib. Relevant outcomes are

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overall survival, disease-specific survival, test validity, quality of life, and treatment-related morbidity. In individuals with a *BRCA1/2* mutation and either HER2-negative metastatic breast cancer or other advanced breast cancer who were followed for 11-12 months, treatment with a PARP inhibitor drug resulted in a 40% to 46% lower risk of disease progression or death. In individuals with a *BRCA1/2* mutation and early-stage breast cancer at high-risk for recurrence, treatment with olaparib resulted in a 9% improvement in 3-year invasive disease-free survival. Therefore, knowledge of *BRCA* variant status in individuals diagnosed with breast cancer may impact treatment decisions. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

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 *PIK3CA*-positive tumors who received targeted therapy, progression-free survival (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*-mutated 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 outcome.

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 overall survival, disease-specific survival, test validity, quality of life, 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

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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 outcome.

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 triple negative breast cancer (TNBC), median PFS (hazard ratio [HR] 0.62; 95% CI, 0.49 to 0.78) and overall survival 0.62 (95% CI, 0.45–0.86) were longer among patients who received the targeted immunotherapy. However, these findings were not confirmed in a designated confirmatory trial and accelerated approval was withdrawn for atezolizumab. 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). In 1 randomized trial of pembrolizumab plus chemotherapy versus placebo plus chemotherapy for patients with TNBC and PD-L1 combined positive score ≥10, the median PFS was 9.7 and 5.6 months, respectively (HR, 0.65; 95% CI, 0.49 to 0.86). The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with unresectable or metastatic breast cancer who are being considered for pembrolizumab therapy who receive high levels of microsatellite instability (MSI-H)/mismatch repair deficiency (dMMR) testing, the evidence includes nonrandomized trials 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 overall survival 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 outcome.

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

Policy # 00731
Original Effective Date: 03/08/2021
Current Effective Date: 09/11/2023

For individuals with recurrent or advanced breast cancer who are being considered for dostarlimab-gxly therapy who receive dMMR testing, the evidence includes nonrandomized trials in patients with solid tumors. Relevant outcomes include overall survival, disease-specific survival, test validity, quality of life, and treatment-related morbidity. A phase 1 dose escalation study of dostarlimab-gxly reported an overall response rate of 41.6% with a median duration of response of 34.7 months for a combined cohort of 209 patients with endometrial cancer and non-endometrial cancer solid cancers; however, enrollment of patients with breast cancer was limited to 1 individual. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with breast cancer who are being considered for abemaciclib therapy who receive Ki-67 testing, the evidence includes a randomized, controlled, open-label trial. Relevant outcomes include overall survival, disease-specific survival, test validity, quality of life, and treatment-related morbidity. Among patients with hormone receptor-positive, HER2-negative, node-positive, early breast cancer with clinical and pathological features consistent with a high risk of recurrence (n=5637), abemaciclib plus endocrine therapy demonstrated superior invasive disease-free survival compared to endocrine therapy alone (HR=0.75; p=.01). For the cohort of patients with Ki-67 score ≥ 20% (n=2003 [35.5%]), secondary analysis of invasive disease-free survival was also superior for the group receiving abemaciclib (HR=0.626; p=.0042). However, additional analyses showed the abemaciclib benefit was observed regardless of Ki-67 status. Further study is necessary to confirm whether an improved overall survival benefit is observed among patients with Ki-67 'high' versus 'low' status. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with breast cancer who are being considered for selpercatinib therapy who receive RET testing, the evidence includes a nonrandomized, basket trial of individuals with solid tumors with a life expectancy of at least 3 months and disease progression on or after previous systemic therapies or who had no satisfactory therapeutic options. Relevant outcomes include overall survival, disease-specific survival, test validity, quality of life, and treatment-related morbidity. Of 45 enrolled individuals, 2 (4%) had a primary breast tumor. The trial reported an overall response rate of 43.9% in the total population and 100% in the breast cancer population (n=2). Corresponding median duration of response was 24.5 months and 17.3 months. There is no FDA-approved companion

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diagnostic for use with RET fusion-positive solid tumors. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with breast cancer who are being considered for dabrafenib and trametinib therapy who receive BRAF testing, the evidence includes 2 nonrandomized basket trials of individuals with unresectable or metastatic solid tumors with BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options. Relevant outcomes include overall survival, disease-specific survival, test validity, quality of life, and treatment-related morbidity. The NCI Match and BRF117019 trials reported overall response rates ranging from 31% to 69%, largely driven by partial responders. Duration of response, progression-free survival, and overall survival ranged widely and appeared to be dependent on tumor type. Serious and grade 3 or worse adverse events were common, occurring in up to 63% of study participants. No breast cancer patients were included in either trial. There is currently no FDA-approved companion diagnostic test for BRAF mutated solid tumors for use with dabrafenib plus trametinib. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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 overall survival in patients receiving immunotherapy. These results need to be confirmed in additional, well-designed prospective studies enrolling patients with breast cancer. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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

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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 outcome. 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 circulating tumor cell (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 overall survival 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 (HR 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 outcome.

Supplemental Information

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in ‘Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given

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to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Society of Clinical Oncology

In 2022, the American Society of Clinical Oncology published an updated guideline on biomarker testing to guide systemic therapy in patients with metastatic breast cancer.[55,] The guideline recommended the following biomarker tests:

- PIK3CA (Type of recommendation: evidence-based; Evidence quality: high; Strength of recommendation: strong)
- Germline BRCA1 and BRCA2 (Type of recommendation: evidence-based; Evidence quality: high; Strength of recommendation: strong)
- PD-L1 (Type of recommendation: evidence-based; Evidence quality: intermediate; Strength of recommendation: strong)
- MSI-H/dMMR (Type of recommendation: informal consensus-based; Evidence quality: low; Strength of recommendation: moderate)
- TMB (Type of recommendation: informal consensus-based; Evidence quality: low; Strength of recommendation: moderate)
- NTRK fusions (Type of recommendation: informal consensus-based; Evidence quality: low; Strength of recommendation: moderate)

The following biomarker tests were not recommended by ASCO: ERI1, PALB2, TROP2 expression, circulating tumor DNA, circulating tumor cell.

Detailed recommendations are as follows:

- Patients with locally recurrent unresectable or metastatic hormone receptor-positive and human epidermal growth factor receptor 2 (HER2)-negative breast cancer who are candidates for a treatment regimen that includes a phosphatidylinositol 3-kinase inhibitor and a hormonal therapy should undergo testing for PIK3CA mutations using next-generation sequencing of tumor tissue or circulating tumor DNA (ctDNA) in plasma to determine their eligibility for treatment with the phosphatidylinositol 3-kinase inhibitor alpelisib plus fulvestrant. If no mutation is found in ctDNA, testing in tumor tissue, if available, should be used as this will detect a small number of additional patients with PIK3CA mutations (Type

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of recommendation: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

- There are insufficient data at present to recommend routine testing for ESR1 mutations to guide therapy in hormone receptor–positive, HER2-negative MBC. Existing data suggest reduced efficacy of aromatase inhibitors (AIs) compared with the selective estrogen receptor degrader fulvestrant in patients who have tumor or ctDNA with ESR1 mutations (Type of recommendation: informal consensus; Evidence quality: insufficient; Strength of recommendation: moderate).
- Patients with metastatic HER2-negative breast cancer who are candidates for treatment with a poly (ADP-ribose) polymerase (PARP) inhibitor should undergo testing for germline BRCA1 and BRCA2 pathogenic or likely pathogenic mutations to determine their eligibility for treatment with the PARP inhibitors olaparib or talazoparib (Type of recommendation: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).
- There is insufficient evidence to support a recommendation either for or against testing for a germline PALB2 pathogenic variant for the purpose of determining eligibility for treatment with PARP inhibitor therapy in the metastatic setting. This recommendation is independent of the indication for testing to assess cancer risk (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).
    - Small single-arm studies show that oral PARP inhibitor therapy demonstrates high response rates in MBC encoding DNA repair defects, such as germline PALB2 pathogenic variants and somatic BRCA1/2 mutations. It should also be noted that the randomized PARP inhibitor trials made no direct comparison with taxanes, anthracyclines, or platinums; comparative efficacy against these compounds is unknown. There are insufficient data at present to recommend routine testing of tumors for homologous recombination deficiency to guide therapy for MBC (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).
- Patients with locally recurrent unresectable or metastatic hormone receptor-negative and HER2-negative breast cancer who are candidates for a treatment regimen that includes an immune checkpoint inhibitor (ICI) should undergo testing for expression of programmed cell death ligand-1 in the tumor and immune cells with a US Food and Drug Administration–approved test to determine eligibility for treatment with the ICI pembrolizumab plus

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chemotherapy (Type of recommendation: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

- Patients with metastatic cancer who are candidates for a treatment regimen that includes an ICI should undergo testing for deficient mismatch repair/microsatellite instability-high to determine eligibility for dostarlimab-gxly or pembrolizumab (Type of recommendation: informal consensus; Evidence quality: low; Strength of recommendation: moderate).
- Patients with metastatic cancer who are candidates for treatment with an ICI should undergo testing for tumor mutational burden to determine eligibility for pembrolizumab monotherapy (Type of recommendation: informal consensus; Evidence quality: low; Strength of recommendation: moderate).
- Clinicians may test for NTRK fusions in patients with metastatic cancer who are candidates for a treatment regimen that includes a TRK inhibitor to determine eligibility for larotrectinib or entrectinib (Type of recommendation: informal consensus; Evidence quality: low; Strength of recommendation: moderate).
- There are insufficient data to recommend routine testing of tumors for TROP2 expression to guide therapy with an anti-TROP2 antibody-drug conjugate for hormone receptor-negative, HER2-negative MBC (Type of recommendation: informal consensus; Evidence quality: low; Strength of recommendation: moderate).
- There are insufficient data to recommend routine use of ctDNA to monitor response to therapy among patients with MBC (Type of recommendation: informal consensus; Evidence quality: low; Strength of recommendation: moderate).
- There are insufficient data to recommend routine use of circulating tumor cells to monitor response to therapy among patients with MBC (Type of recommendation: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

National Comprehensive Cancer Network

Table 2 summarizes National Comprehensive Cancer Network guidelines (v.4.2022) 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).

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

Policy # 00731
Original Effective Date: 03/08/2021
Current Effective Date: 09/11/2023

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
BRCA1/2 mutations	Any	Olaparib Talazoparib	Patients with recurrent or metastatic breast cancer should be assessed for *BRCA1/2* mutations with germline sequencing to identify candidates for PARP inhibitor therapy. While olaparib and talazoparib are FDA-indicated in HER2-negative disease, NCCN supports use in any breast cancer subtype associated with a germline *BRCA1* or *BRCA2* mutation.	1	Preferred

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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-or subsequent-line therapy
ESR1 mutation	HR-positive/ HER2-negative	Elacestrant	For postmenopausal females or adult males with ER-positive, HER2-negative, *ESR1*-mutated disease after progression on one or tow prior	2A	Other recommended regimen

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			lines of endocrine therapy, including one line containing a CDK4/6 inhibitor (NGS, PCR [blood])		
PD-L1 expression (combined positive score ≥ 10)	Triple negative	Pembrolizumab + chemotherapy (albumin-bound paclitaxel, or gemcitabine and carboplatin)	For triple-negative breast cancer, assess PD-L1 expression using 22C3 antibody via immunohistochemistry. While available data are in the first-line setting, this regimen can be used for second and subsequent lines of therapy if PD-1/PD-L1 inhibitor therapy has not been previously used.	1	Preferred first-line therapy

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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 Dostarlimab-gxly	Biomarker detection via immunohistochemistry or PCR tissue block is recommended. If a patient with unresectable or metastatic MSI-H/dMMR breast cancer has	2A	Useful in certain circumstances

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			progressed on or following prior treatment with no satisfactory alternative treatment options, pembrolizumab or dostarlimab-gxly are indicated.		
TMB-H (≥10 mut/mb)	Any	Pembrolizumab	Biomarker detection via NGS is indicated in patients with unresectable or metastatic TMB-H tumors that have progressed following prior treatment and who have no satisfactory treatment options.	2A	Useful in certain circumstances

Source: Adapted from National Comprehensive Cancer Network guidelines on Breast Cancer (v.1.2022)

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
In January 2020, the Centers for Medicare and Medicaid Services (CMS) determined that next-generation sequencing (NGS) is covered for patients with breast or ovarian cancer when the diagnostic test is performed in a Clinical Laboratory Improvement Amendments (CLIA)-certified

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laboratory AND the test has approval or clearance by the U.S. Food and Drug Administration (CAG-00450R).

CMS states that local Medicare carriers may determine coverage of NGS for management of the patient for any cancer diagnosis with a clinical indication and risk factor for germline testing of hereditary cancers when performed in a CLIA-certified laboratory.

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			
NCT03145961[a]	c-TRAK TN: A Randomised Trial Utilising ctDNA Mutation Tracking to Detect Minimal Residual Disease and Trigger Intervention in Patients With Moderate and High Risk Early Stage Triple Negative Breast Cancer	208	Mar 2024
NCT03213041[a]	I-CURE-1: A Phase II, Single Arm Study of Pembroluzimab Combined With Carboplatin in Patients With Circulating Tumor Cells (CTCs) Positive HER-2 Negative Metastatic Breast Cancer (MBC)	100	Jul 2023 (recruiting)
NCT02965755[a]	Individualized Molecular Analyses Guide Efforts in	200	Jul 2023 (recruiting)

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	Breast Cancer - Personalized Molecular Profiling in Cancer Treatment at Johns Hopkins (IMAGE-II)		
NCT02819518[a]	A Randomized, Double-Blind, Phase III Study of Pembrolizumab (MK-3475) Plus Chemotherapy vs Placebo Plus Chemotherapy for Previously Untreated Locally Recurrent Inoperable or Metastatic Triple Negative Breast Cancer (KEYNOTE-355)	882	Nov 2023
NCT02889978[a]	The Circulating Cell-free Genome Atlas Study (CCGA)	15,254	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 Solid Tumors That Harbor NTRK1/2/3, ROS1, or ALK Gene Rearrangements (STARTRK-2)	700	Apr 2025 (recruiting)
NCT04591431	The Rome Trial - From Histology to Target: the Road to Personalize Target Therapy and Immunotherapy	384	Aug 2024 (recruiting)
NCT02693535[a]	Targeted Agent and Profiling Utilization Registry (TAPUR) Study	3641	Dec 2025 (recruiting)

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NCT04720729	Chemotherapy Monitoring by Circulating Tumor DNA (ctDNA) in HER2 (Human Epidermal Growth Factor Receptor-2)- Metastatic Breast Cancer (MONDRIAN): a Phase 2 Study	214	Jun 2025 (recruiting)
NCT04526587	The Roswell Park Ciclib Study: A Prospective Study of Biomarkers and Clinical Features of Advanced/Metastatic Breast Cancer Treated With CDK4/6 Inhibitors	300	Jul 2025 (recruiting)
NCT04895358[a]	A Randomized, Double-blind, Placebo-controlled, Phase 3 Study of Pembrolizumab Plus Chemotherapy Versus Placebo Plus Chemotherapy for the Treatment of Chemotherapy-Candidate Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative (HR+/HER2-) Locally Recurrent Inoperable or Metastatic Breast Cancer (KEYNOTE-B49)	800	Oct 2027 (recruiting)
NCT02306096	SCAN-B: The Sweden Cancerome Analysis Network – Breast Initiative	20000	Aug 2031 (recruiting)

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Unpublished			
NCT04098640	Molecular Profiling Using FoundationOne CDx in Young (<50 Years of Age) Patients With Metastatic Breast Cancer (ML41263)	200	Jul 2021 (unknown)

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

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Policy History

Original Effective Date: 03/08/2021
Current Effective Date: 09/11/2023

02/04/2021 Medical Policy Committee review
02/10/2021 Medical Policy Implementation Committee approval. New policy.
02/22/2021 Coding update
03/03/2022 Medical Policy Committee review
03/09/2022 Medical Policy Implementation Committee approval. Title changed from "Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Breast Cancer" to "Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Breast Cancer". Eligible for coverage statements and rationale for *BRCA*1/2 testing to predict treatment response to PARP inhibitors were added. Removed eligible for coverage statement for 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. Added an investigational statement for genetic testing of *BRCA1* or *BRCA2*

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	germline or somatic variants in patients with breast cancer for guiding therapy in all other situations. Added "…,including to predict treatment response to atezolizumab (Tecentriq)" to the investigational statement for PD-L1 testing in patients with breast cancer in all other situations. Added "…, including to predict treatment response to dostarlimab-gxly (Jemperli) to the investigational statement for MSI-H/dMMR (immunohistochemistry) testing in patients with breast cancer in all other situations. Added an investigational statement for Ki-67 testing to predict treatment response to abemaciclib (Verzenio) in patients with breast cancer. Added sections on Breast Cancer Risks Groups and Paired Genetic Testing to the Policy Guidelines.
04/01/2022	Coding update
06/07/2022	Coding update
09/01/2022	Medical Policy Committee review
09/14/2022	Medical Policy Implementation Committee approval. Extensive revisions made to coverage and Policy Guidelines sections.
11/22/2022	Coding update
03/02/2023	Medical Policy Committee review
03/08/2023	Medical Policy Implementation Committee approval. Replaced "patients" with "individuals" in the coverage section. Removed the investigational statement for Ki-67 gene testing in patients with breast cancer. Added an investigational policy statement for other gene testing in individuals with breast cancer, including but not limited to Ki-67, RET and BRAF.
08/03/2023	Medical Policy Committee review
08/09/2023	Medical Policy Implementation Committee approval. Extensive revisions to the policy. Coverage eligibility statements added for FDA-approved companion diagnostic circulating tumor DNA (ctDNA) or liquid biopsy testing when coverage criteria are met including Gaurdant360 CDx testing. Policy updated with literature review through 7/2023 background information to include *ESR1* mutations; NCCN reference updated.
12/13/2023	Coding update

Next Scheduled Review Date: 08/2024

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

Policy # 00731
Original Effective Date: 03/08/2021
Current Effective Date: 09/11/2023

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

Code Type	Code
CPT	0037U, 0155U, 0177U, 0239U, 0242U, 0326U, 81162, 81191, 81192, 81193, 81194, 81309, 81445, 86152, 86153 Delete code effective 01/01/2023: 0172U Add codes effective 01/01/2024: 0428U, 81457, 81458, 81459, 81462, 81463, 81464
HCPCS	No codes
ICD-10 Diagnosis	C50.011-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 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,

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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.

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