Medical Policy

BlueCross BlueShield Kansas
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Title: Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Breast Cancer (*BRCA1, BRCA2, PIK3CA,* Ki-67*, RET, BRAF, ESR1, NTRK)*

Related Policies:	• *Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers (BRCA1, BRCA2, PALB2)* • *Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies* • *Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy)* • *Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis in Patients with Breast Cancer*

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Populations	Interventions	Comparators	Outcomes
Individuals: • With metastatic or high-risk, early stage HER2-negative breast cancer who are being considered for systemic therapy (i.e., poly(adenosine diphosphate–ribose) polymerase [PARP] inhibitors)	Interventions of interest are: • Genetic testing for *BRCA1* or *BRCA2* germline variants	Comparators of interest are: Standard treatment without genetic testing for a *BRCA1* or *BRCA2* variant	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Quality of life • Treatment-related morbidity
Individuals: • With hormone receptor-positive, HER2 negative advanced or metastatic breast cancer	Interventions of interest are: • *PIK3CA* gene testing to select targeted treatment	Comparators of interest are: • Standard treatment without *PIK3CA* Gene Testing	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Quality of life • Treatment-related morbidity
Individuals: • With hormone receptor-positive, HER2-negative, node-positive, early breast cancer at high risk of recurrence who are being considered for adjuvant targeted therapy	Interventions of interest are: • Ki-67 testing	Comparators of interest are: • Standard treatment without Ki-67 testing	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Quality of life • Treatment-related morbidity
Individuals: • With locally advanced or metastatic breast cancer with progression following prior treatment who are being considered for selpercatinib therapy who receive RET testing	Interventions of interest are: • RET testing	Comparators of interest are: • Standard treatment without RET testing	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Quality of life Treatment-related morbidity
Individuals: • With unresectable or metastatic breast cancer with progression following prior treatment who are	Interventions of interest are: • BRAF testing	Comparators of interest are: • Standard treatment without BRAF testing	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity

Populations	Interventions	Comparators	Outcomes
being considered for dabrafenib and trametinib combination therapy who receive BRAF testing			• Quality of life Treatment-related morbidity
Individuals: • With hormone receptor-positive, HER2 negative advanced or metastatic breast cancer	Interventions of interest are: • Testing of circulating tumor DNA to select targeted treatment	Comparators of interest are: • Using tissue biopsy to select targeted treatment	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Quality of life • Treatment-related morbidity
Individuals: • With hormone receptor-positive, HER2 negative metastatic breast cancer	Interventions of interest are: • Testing of circulating tumor cells (CTCs) to select targeted treatment	Comparators of interest are: • Standard treatment without using CTCs to select treatment	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Quality of life • Treatment-related morbidity
Individuals: • With recurrent unresectable (local or regional) or stage IV breast cancer	Interventions of interest are: • *NTRK* gene fusion testing to select treatment with FDA-approved targeted therapy	Comparators of interest are: • Standard treatment without using *NTRK* gene fusion testing to select treatment	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Quality of life • Treatment-related morbidity

DESCRIPTION

Multiple biomarkers are being evaluated to predict response to targeted treatments 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 evidence review is to examine whether biomarker testing for *BRCA* variants, *PIK3CA*, *ESR1,* Ki-67, RET, BRAF, circulating tumor DNA, or circulating tumor cells improves the net health outcome in patients with breast cancer who are considering targeted therapy.

OBJECTIVE

The objective of this evidence review is to summarize the evidence and guidelines on biomarker testing using tissue biopsy, circulating tumor DNA testing, or circulating tumor cells to select targeted treatment for individuals with breast cancer.

BACKGROUND

BRCA Variant Testing

The prevalence of *BRCA* variants is approximately 0.2% to 0.3% in the general population.[1,] 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.[2,] Of these, hereditary breast and ovarian cancer (HBOC) and some cases 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. For this evidence review, BCBSA refers collectively to both as hereditary breast and/or 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.[3,] 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.[4,] 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).[4,5,6,7,] In cancer-prone families, the mean age of breast cancer diagnosis among women carrying *BRCA1* or *BRCA2* variants is in the 40s.[8,] 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.[5,] 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.[9,] 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.[10,11,12,]

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 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.[13,] 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.[14,] 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*).[15,]

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 hormone receptor (HR)-positive, HER2-negative breast cancer.[16,]

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.[17,]

Rearranged During Transfection

The REarranged during Transfection (RET) proto-oncogene encodes a receptor tyrosine kinase growth factor.[18,] 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.[19,]

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.[20,] BRAF mutations occur in approximately 1% of breast cancer cases.[21,]

ESR1

Mutations in *ESR1*, which occur in approximately 10-20% of patients with metastatic estrogen receptor-positive breast cancer, confer resistance to endocrine therapy via constitutive activation of estrogen receptor-mediated growth activity.[22,23,]

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. Most cell-free

tumor DNA is derived from apoptotic and/or necrotic tumor cells, either from the primary tumor, metastases, or 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 detecting CTCs is prognostic, through quantification of circulating levels.

Neurotrophic Receptor Tyrosine Kinase (*NTRK*) Gene Fusion Testing
The presence of *NTRK* gene fusion can be detected by multiple methods including next-generation sequencing, reverse transcription-polymerase chain reaction, fluorescence in situ hybridization and immunohistochemistry.[24,] Next-generation sequencing provides the most comprehensive view of a large number of genes and may identify *NTRK* gene fusions as well as other actionable alterations, with minimal tissue needed. The fluorescence in situ hybridization using break-apart probes can detect gene rearrangements in DNA that may generate a fusion transcript. The immunohistochemistry techniques have generally been used in the research setting. Reverse transcription-polymerase chain reaction is designed to identify only known translocation partners and breakpoints and cannot identify novel breakpoints or novel fusion partners.

REGULATORY STATUS

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 breast cancer (including immunotherapy) and the FDA cleared or approved companion diagnostic tests associated with each. The information in Table 1 was current as of October 16, 2024.. 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	Pivotal Studies	NCCN Breast Cancer Guideline (V5.2024) Recommendation Level[25,]
Abemaciclib (Verzenio)[a]	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. • 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	Ki-67 IHC MIB-1 pharmDx (Dako Omnis)	Adjuvant therapy: monarchE (NCT03155997)[26,27,] Initial endocrine-based therapy for advanced or metastatic disease: MONARCH 3 (NCT02246621)[28,] With fulvestrant for progressive advanced or metastatic disease: MONARCH 2 (NCT02107703)[29,30,] Monotherapy for progressive advanced or metastatic disease: MONARCH 1 (NCT02102490)[31,]	Adjuvant therapy: 1 (Ki-67 testing is not required - see footnote[a]) Initial endocrine-based therapy for advanced or metastatic disease: 1 (in combination with fulvestrant), 2A (in combination with aromatase inhibitor) With fulvestrant for progressive advanced or metastatic disease: 1 Monotherapy for progressive advanced or metastatic disease: 2A

Treatment	Class	Indications in Breast Cancer	Companion Diagnostic	Pivotal Studies	NCCN Breast Cancer Guideline (V5.2024) Recommendation Level[25,]
		progression following endocrine therapy. • 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)[b]	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: ○ received prior therapy for	FoundationOne CDx HER2 FISH pharmDx Kit HercepTest INFORM HER2 Dual ISH DNA Probe Cocktail PATHWAY anti-Her2/neu (4B5) Rabbit Monoclonal Primary Antibody	Metastatic disease: EMILIA (NCT00829166)[32,] Adjuvant therapy: KATHERINE (NCT01772472)[33,]	Metastatic disease: 2A Adjuvant therapy: 1

Treatment	**Class**	**Indications in Breast Cancer**	**Companion Diagnostic**	**Pivotal Studies**	**NCCN Breast Cancer Guideline (V5.2024) Recommendation Level[25,]**
		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.			
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	FoundationOne CDx FoundationOne Liquid CDx therascreen PIK3CA RGQ PCR Kit	SOLAR-1 (NCT02437318)[34,]	1

Treatment	**Class**	**Indications in Breast Cancer**	**Companion Diagnostic**	**Pivotal Studies**	**NCCN Breast Cancer Guideline (V5.2024) Recommendation Level[25,]**
		endocrine-based regimen			
Dabrafenib (Tafinlar) + Trametinib (Mekinist)	Kinase inhibitors	Adult and pediatric patients 1 year 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	ROAR (NCT02034110)[35,] NCI-MATCH arm H (NCT02465060)[36,]	N/A
Dostarlimab -gxly (Jemperli)[c]	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	GARNET (NCT02715284)[37,]	2A
Elacestrant (Orserdu)	ER antagonist/SERD	Postmenopausal women or adult men with ER-positive, HER2-negative, *ESR1*-mutated advanced or metastatic breast	Guardant360 CDx	EMERALD (NCT03778931)[38,]	2A

Treatment	**Class**	**Indications in Breast Cancer**	**Companion Diagnostic**	**Pivotal Studies**	**NCCN Breast Cancer Guideline (V5.2024) Recommendation Level[25,]**
		cancer with disease progression following at least 1 line of endocrine therapy			
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, • 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 (Foundation Medicine, Inc.) FoundationOne Liquid CDx (Foundation Medicine, Inc.)	ALKA (EudraCT 2012-000148-88), STARTRK-1 (NCT02097810), and STARTRK-2 (NCT02568267)[39,]	2A
Fam-trastuzumab deruxtecan-nxki (Enhertu) [d]	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	PATHWAY anti-Her2/neu (4B5) Rabbit Monoclonal Primary Antibody	HER2-positive metastatic disease: DESTINY-Breast03 (NCT03529110)[40,] HER2-low metastatic disease: DESTINY-Breast04 (NCT03734029)[41,]	1

Treatment	Class	Indications in Breast Cancer	Companion Diagnostic	Pivotal Studies	NCCN Breast Cancer Guideline (V5.2024) Recommendation Level[25,]
		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			
Larotrectinib (Vitrakvi)	Kinase inhibitor	Adult and pediatric patients 12 years of age and older with solid tumors that:	FoundationOne CDx	LOXO-TRK-14001 (NCT02122913), SCOUT (NCT02637687), and NAVIGATE (NCT02576431)[42,]	2A

Treatment	Class	Indications in Breast Cancer	Companion Diagnostic	Pivotal Studies	NCCN Breast Cancer Guideline (V5.2024) Recommendation Level[25,]
		• 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			
Olaparib (Lynparza)	PARP inhibitor	• Adjuvant treatment of adults with deletrious or suspected deleterious germline BRCA mutated, HER2-negative high risk early breast cancer who have been treated with neoadjuvant or adjuvant chemotherapy • Treatment of adults with deleterious or suspected deleterious germline BRCA mutated, HER-	BRACAnalysis CDx FoundationOne CDx	Adjuvant therapy: OlympiA (NCT02032823)[43,] Metastatic disease: OlympiAD (NCT02000622)[44,]	Adjuvant therapy: 2A Metastatic disease: 1

Treatment	Class	Indications in Breast Cancer	Companion Diagnostic	Pivotal Studies	NCCN Breast Cancer Guideline (V5.2024) Recommendation Level[25,]
		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.			
Pembrolizumab (Keytruda)[c]	PD-L1-blocking antibody	• Neoadjuvant treatment of high-risk, early-stage TNBC in combination with chemotherapy, then continued as a single agent as adjuvant therapy • In combination with chemotherapy, for the treatment of patients with locally recurrent unresectable or	PD-L1 IHC 22C3 pharmDx	Neoadjuvant/adjuvant therapy: KEYNOTE-522 (NCT03036488)[45,] Unresectable/metastatic disease: KEYNOTE-355 (NCT02819518)[46,]	Neoadjuvant/adjuvant therapy: 2A Unresectable/metastatic disease: 1

Treatment	Class	Indications in Breast Cancer	Companion Diagnostic	Pivotal Studies	NCCN Breast Cancer Guideline (V5.2024) Recommendation Level[25,]
		metastatic TNBC whose tumors express PD-L1 as determined by an FDA approved test			
		Adult and pediatric patients with unresectable or metastatic, microsatellite instability-high or mismatch repair deficient solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options	FoundationOne CDx	KEYNOTE-158 (NCT02628067)[47,]	2A
		Adult and pediatric patients with 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	FoundationOne CDx (Solid tumors TMB ≥ 10 mutations per megabase)	KEYNOTE-158 (NCT02628067)[48,]	2A

Treatment	Class	Indications in Breast Cancer	Companion Diagnostic	Pivotal Studies	NCCN Breast Cancer Guideline (V5.2024) Recommendation Level[25,]
		alternative treatment options.			
Pertuzumab (Perjeta) [e]	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 treatment regimen for early breast cancer.	HER2 FISH pharmDx Kit HercepTest FoundationOne CDx	Metastatic disease: CLEOPATRA (NCT00567190)[49,] Neoadjuvant therapy: NeoSphere (NCT00545688)[50,] Adjuvant therapy: APHINITY (NCT01358877)[51,]	Metastatic disease: 1 Neoadjuvant/adjuvant therapy: 1 or 2A (regimen-specific)

Treatment	**Class**	**Indications in Breast Cancer**	**Companion Diagnostic**	**Pivotal Studies**	**NCCN Breast Cancer Guideline (V5.2024) Recommendation Level[25,]**
		• 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	LIBRETTO-001 (NCT03157128)[52,]	2A
Talazoparib (Talzenna)	PARP inhibitor	Adult patients with deleterious or suspected deleterious germline BRCA-mutated HER2-negative locally advanced or metastatic breast cancer	BRACAnalysis CDx	EMBRACA (NCT01945775)[53,]	1
Trastuzumab (Herceptin) [f]	HER2/neu receptor antagonist	• Adjuvant treatment of HER2-overexpressing node-positive or node-negative (HR-negative or with 1 high-risk	Bond Oracle HER2 IHC System FoundationOne CDx HER2 CISH pharmDx Kit HER2 FISH pharmDx Kit	Adjuvant therapy: BCIRG-006 (NCT00021255)[54,] Metastatic disease: CLEOPATRA (NCT00567190)[49,]	Adjuvant therapy: 1 or 2A (regimen-specific) Metastatic disease: 1 or 2A (regimen-specific)

Treatment	Class	Indications in Breast Cancer	Companion Diagnostic	Pivotal Studies	NCCN Breast Cancer Guideline (V5.2024) Recommendation Level[25,]
		feature) breast cancer as part of a regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel; as part of a regimen with docetaxel and carboplatin; or as a single agent following multi-modality anthracycline-based therapy • Treatment of metastatic HER2-overexpressing breast cancer in combination with paclitaxel (first-line treatment) or as a single agent (after 1 or more chemotherapy regimens for metastatic disease)	HercepTest INFORM HER-2/neu INFORM HER2 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		
Itovebi (inavolisib)	Kinase inhibitor	Indicated in combination with palbociclib and fulvestrant for the treatment of adults with endocrine-resistant, *PIK3CA* -mutated, hormone	FoundationOne CDx (Foundation Medicine, Inc.) FoundationOne Liquid CDx (Foundation Medicine, Inc.) *therascreen* PIK 3CA RGQ PCR	INAVO120 (NCT04191499)[55,]	N/A

Treatment	Class	Indications in Breast Cancer	Companion Diagnostic	Pivotal Studies	NCCN Breast Cancer Guideline (V5.2024) Recommendation Level[25,]
		receptor (HR) positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer, as detected by an FDA-approved test, following recurrence on or after completing adjuvant endocrine therapy.	Kit (QIAGEN GmbH)		

[a] The FDA-approved indication for adjuvant therapy with abemaciclib was expanded in March 2023 and no longer requires Ki-67 testing. NCCN's recommendation for adjuvant abemaciclib use was similarly updated to no longer stipulate Ki-67 testing.
[b] Covered in Policy 5.01.22.
[c] Covered in Policy 2.04.157.

[d] Placement of fam-trastuzumab deruxtecan-nxki (Enhertu) in the reference medical policy library is under current discussion.
[e]Covered in Policy 5.01.20.
[f] Covered in Policy 5.01.12.
dMMR: mismatch repair deficient; ER: estrogen receptor; FDA: U.S. Food & Drug Administration; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; MSI-H: microsatellite instability-high; N/A: not applicable;NCCN: National Comprehensive Cancer Network; NTRK: neurotrophic-tropomyosin receptor kinase; PD-1: programmed death receptor-1; PD-L1: programmed death-ligand 1; PIK3CA: phosphatidylinositol 3-kinase catalytic alpha polypeptide; SERD: selective estrogen receptor degrader; TNBC: triple-negative breast cancer
Sources: [56,57,]

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.

POLICY

A. ***BRCA1 and BRCA2* Testing**

1. Genetic testing for *BRCA1* or *BRCA2* germline variants may be considered **medically necessary** to predict treatment response to PARP inhibitors (e.g., olaparib [Lynparza] and talazoparib [Talzenna]) for human epidermal receptor 2 (HER2)-negative metastatic and early stage, high-risk breast cancer (see Policy Guidelines).

2. Genetic testing of *BRCA1* or *BRCA2* germline or somatic variants in individuals with breast cancer for guiding therapy is considered **experimental / investigational** in all other situations.

B. ***PIK3CA* Testing**

1. *PIK3CA* testing may be considered **medically necessary** to predict treatment response to alpelisib (Piqray) in individuals with hormone receptor-positive, HER2-negative advanced or metastatic breast cancer who have progressed on or after an endocrine-based regimen (see Policy Guidelines).
   a. When tumor tissue is available, use of tissue for testing is preferred but is not required (see Circulating Tumor DNA Testing below).

2. *PIK3CA* testing of tissue in individuals with breast cancer is considered **experimental / investigational** in all other situations.

C. **Ki-67 testing**

1. Ki-67 testing to predict treatment response to abemaciclib (Verzenio) in individuals with breast cancer is considered **experimental / investigational**.

D. **RET Testing**

1. RET testing to predict treatment response to selpercatinib (Retevmo) in individuals with breast cancer is considered **experimental / investigational**.

E. **BRAF Testing**

1. BRAF testing to predict treatment response to dabrafenib (Tafinlar) plus trametinib (Mekinist) in individuals with breast cancer is considered **experimental / investigational**.

F. **Circulating Tumor DNA Testing (Liquid Biopsy)**
1. *PIK3CA* testing using FoundationOne Liquid CDx may be considered **medically necessary** to predict treatment response to alpelisib (Piqray) in individuals with hormone receptor-positive, HER2 negative advanced or metastatic breast cancer who have progressed on or after an endocrine-based regimen.
   a. When tumor tissue is available, use of tissue for testing is preferred but is not required.

2. *ESR1* testing using Guardant360 CDx may be considered **medically necessary** to predict treatment response to elacestrant (Orserdu) in individuals with estrogen receptor-positive, HER2-negative advanced or metastatic breast cancer with disease progression following at least 1 line of endocrine therapy (see Policy Guidelines).

3. Circulating tumor DNA testing in individuals with breast cancer is considered **experimental/ investigational** in all other situations.

G. **Circulating Tumor Cell Testing**
1. Analysis of circulating tumor cells to select treatment in individuals with breast cancer is considered **experimental/ investigational**.

H. ***NTRK* Gene Fusion Testing**
1. *NTRK* gene fusion testing may be considered **medically necessary** for individuals with recurrent unresectable (local or regional) or stage IV breast cancer to select individuals for treatment with FDA-approved therapies.

2. *NTRK* gene fusion testing in individuals with breast cancer is considered **experimental / investigational** in all other situations.

POLICY GUIDELINES

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

B. 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.

C. 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.

D. **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 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
Receptor Status	
ER-negative	1
Nuclear Grade	

Stage or Feature	Points
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.

E. 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, BCBSKS medial policy *Genetic Cancer Susceptibility Panels Using Next Generation Sequencing*. For paired panel testing involving somatic components, see BCBSKS medial policy *Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies*.

F. Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG2). The Society's nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG3 shows the recommended standard terminology- "pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"- to describe variants identified that cause Mendelian disorders.

Table PG2. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG3. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

ACMG-AMP: American College of Medical Genetics and Genomics and the Association for Molecular Pathology.

G. **Genetic Counseling**

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

RATIONALE

This evidence review has been updated using the PubMed database. The most recent literature update was performed through November 1, 2024.

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings

more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

BIOMARKER TESTING USING TISSUE BIOPSY TO SELECT TARGETED TREATMENT

Clinical Context and Test Purpose

Breast cancer treatment selection is informed by tumor type, grade, stage, patient performance status and preference, prior treatments, and the molecular characteristics of the tumor such as the presence of driver mutations. One purpose of biomarker testing of individuals who have advanced cancer is to inform a decision regarding treatment selection (eg, whether to select a targeted treatment or standard treatment).

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with advanced or metastatic breast cancer for whom the selection of treatment depends on the molecular characterization of the tumor.

Interventions

The technologies being considered are germline testing for *BRCA* variants, *PIK3CA*, Ki-67, *RET,* or *BRAF* testing using tissue biopsy.

Comparators

Decisions about treatment in breast cancer are based on clinical characteristics.

Outcomes

The general outcomes of interest in oncology are overall survival, disease-specific survival, quality of life (QOL), treatment-related mortality and morbidity.

Beneficial outcomes resulting from a true-positive test result are prolonged survival, reduced toxicity, and improved QOL associated with receiving a more effective targeted therapy. Beneficial outcomes from a true negative result are prolonged survival associated with receiving chemotherapy in those without driver mutations.

Harmful outcomes resulting from a false-negative test result include shorter survival from receiving less effective and more cytotoxic chemotherapy in those with driver mutations; possible harmful outcomes resulting from a false-positive test result are a shorter survival from receiving potentially ineffective targeted treatment and delay in initiation of chemotherapy in those without driver mutations.

The overall response rate (ORR) may be used as a surrogate endpoint reasonably likely to predict clinical benefit in individuals with refractory solid tumors. ORR can be measured by the proportion of individuals with best overall confirmed response of complete response) or partial response by the Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1),[58,] or

Response Assessment in Neuro-Oncology criteria,[59,] as appropriate by a blinded and independent adjudication committee.

There are clearly defined quantitative thresholds for the follow-up of individuals in oncology trials. A general rule is a continuation of treatment until disease progression or unacceptable toxicity. Long-term follow-up outside of a study setting is conducted to determine survival status. The duration of follow-up for the outcomes of interest is 6 months and 1 year.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for randomized controlled trials (RCTs);
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

The evidence is presented below by biomarker (*BRCA*1/2, *PIK3CA*, for pembrolizumab, *ESR1,* for selection of dostarlimab-gxly, Ki-67, *RET, BRAF)* and by recommended therapy.

REVIEW OF EVIDENCE

Testing for *PIK3CA* Variants and *BRCA* Variants

For individuals with breast cancer who receive biomarker testing of tumor tissue for *PIK3CA* variants or testing for germline *BRCA* variants, the evidence includes FDA-approved therapeutics with NCCN recommendations of 2A or higher and was not extensively evaluated. The evidence includes the pivotal studies leading to the FDA and NCCN recommendations.

KI-67 TESTING

FDA Companion Diagnostic Test

The Ki-67 IHC MIB-1 pharmDx (Dako Omnis) test is an FDA-approved companion diagnostic for abemaciclib (Verzenio).

RANDOMIZED Controlled Trial

Abemaciclib

Efficacy of abemaciclib was evaluated in the multicenter, randomized, open-label monarchE (NCT03155997) trial reported by Johnston et al (2021).[26,] Adult men and women with hormone receptor (HR) -positive, HER2-negative, node-positive, early breast cancer with clinical and pathological features consistent with a high risk of recurrence were enrolled and randomized to receive either 2 years of abemaciclib plus physician's choice of standard endocrine therapy (n=2808) or endocrine therapy (ET) alone (n=2829). The primary efficacy outcome was invasive disease-free survival (IDFS). At the preplanned interim efficacy analysis, abemaciclib plus endocrine therapy demonstrated superior IDFS compared to endocrine therapy alone (hazard

ratio [HR] , 0.75; 95% confidence interval [CI] , 0.60 to 0.93; p=.01), with 2-year IDFS rates of 92.2% versus 88.75%, respectively. Ki-67 index ≥20% was reported for 1262 (44.9%) and 1233 (43.6%) patients treated with abemaciclib plus endocrine therapy and endocrine therapy alone, respectively. In a secondary pre-planned efficacy analysis of patients with high risk of recurrence and retrospectively confirmed Ki-67 score of at least 20% (n=2003), the study also demonstrated a statistically significant improvement in the primary efficacy outcome of IDFS (HR 0.626; 95% CI, 0.488-0.803; p=.0042). For patients receiving abemaciclib plus tamoxifen or an aromatase inhibitor, IDFS at 36 months was 86.1% (95% CI, 82.8% to 88.8%) compared to 79.0% at 36 months (95% CI, 75.3% to 82.3%) in patients receiving only tamoxifen or an aromatase inhibitor. At the time of IDFS, overall survival data was immature and not reported.

Efficacy of abemaciclib in the intention-to-treat (ITT) population at median follow-up 19 months showed continued benefit in IDFS (HR=0.71, 95% CI 0.58-0.87; nominal p<.001) with an absolute improvement of 3.0% in the 2-year IDFS rates (abemaciclib + ET: 92.3% versus ET alone: 89.3%), and benefit in distant relapse-free survival (DRFS) (HR=0.69, 95% CI 0.55 to 0.86; nominal p<.001) with absolute difference of 3.0% at 2 years (abemaciclib + ET: 93.8% versus ET alone: 90.8%). [60,] At 27 months, the benefit of abemaciclib held (IDFS HR=0.70, 95% CI 0.59 to 0.82; nominal p<.0001 and DRFS HR=0.69, 95% CI 0.57 to 0.83; nominal p<.0001). When assessing Ki-67-high and -low populations, abemaciclib + ET showed an IDFS benefit regardless of the Ki-67 index and for all follow-up time periods assessed. The 3-year IDFS rates in the control arm suggested that patients with Ki-67-high tumors had a higher risk of developing an IDFS event than those with Ki-67-low tumors (79.0% versus 87.2%, respectively), thus indicating the prognostic value of Ki-67. While Ki-67 was prognostic, the abemaciclib benefit was observed regardless of Ki-67 status. The data for IDFS among patients with 1 to 3 positive axillary lymph nodes , tumor size less than 5cm, grade less than 3, and high Ki-67 index (over 20%) remained immature.

An interim analysis of overall survival, a secondary outcome in monarchE, was published in a letter to the editor by Harbeck et al in February 2022.[61,] At 27 months, overall survival in the ITT population was 3.4% (96/2808) with abemaciclib + ET versus 3.2% (90/2829) in the ET alone (HR, 1.09, 95% CI 0.82 to 1.46). When limited to the abemaciclib FDA-indicated population (HR+, HER2-negative, node-positive, early breast cancer at high risk of recurrence, Ki-67 score of ≥20%) overall survival was 4.1% (42/1017) in the abemaciclib + ET and 5.4% (53/986) in the ET alone groups (HR, 0.77, 95% CI 0.51 to 1.15). An updated interim analysis was published in 2023.[27,] With median follow-up of 42 months, median IDFS had not been reached in either group, and previously-identified IDFS (HR=0.664; 95% CI, 0.578 to 0.762) and DRFS benefits (HR=0.659; 95% CI, 0.567 to 0.767) appeared to be sustained. Subgroup analysis indicated similar IDFS and DRFS benefit with the addition of abemaciclib regardless of Ki-67 status. Overall survival data remained immature and did not indicate a difference between groups. The monarchE trial is ongoing with an estimated study completion date of June 2029.

Section Summary: Ki-67 Testing
Among patients with HR-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 of at least 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, multiple subsequent analyses with additional follow-up showed the abemaciclib benefit was observed regardless of Ki-67 status. There was no clear benefit of abemaciclib on overall survival in either the ITT population or the FDA-indicated population based on interim results. Further study is necessary to confirm whether an improved overall survival benefit is observed among patients with Ki-67 positive status.

RET TESTING

FDA Companion Diagnostic Test

There is currently no FDA approved companion diagnostic test for *RET* fusion-positive solid tumors for selpercatinib.

NONRANDOMIZED TRIALS

Selpercatinib

The efficacy of selpercatinib in patients with tumor-agnostic RET fusion-positive advanced solid tumors was evaluated in a subset of the phase 1/2 LIBRETTO-001 basket trial (NCT03157128) reported by Subbiah et al (2022).[52,] LIBRETTO-001 included adult patients with solid tumors with a life expectancy of at least 3 months and with disease progression on or after previous systemic therapies or who had no satisfactory therapeutic options (Table 2). *RET* alteration status was determined by local molecular testing performed in a certified laboratory with the use of next-generation sequencing, fluorescence in situ hybridization (FISH), or PCR assay.[62,] Of the 45 patients included in the trial, 4% (2/45) had primary breast cancer; 4 patients were excluded from efficacy analyses though none of these were breast cancer patients. The primary outcome was overall response rate (complete or partial response) assessed according to independent review using Response Evaluation Criteria in Solid Tumours (RECIST) criteria, version 1.1. In the total population, overall response was 43.9% (95% CI 28.5 to 60.3) and the median duration of response was 24.5 months. In the 2 breast cancer patients, the response rate was 100% (95% CI 15.8 to 100) and the median duration of response was 17.3 months. Harms of treatment were reported for the total cohort; 3 patients had serious, treatment-related adverse events, and elevated liver enzymes (AST and ALT) were the most common grade 3 or higher adverse events (Table 3). LIBRETTO-001 is ongoing, and continued selpercatinib approval in this population is subject to the results of confirmatory trials.

Table 2. Selpercatinib in Patients with RET Fusion-Positive Solid Tumors - Study Characteristics

Study	Countries	Sites	Dates	Design	Participants	Intervention	Outcomes
Subbiah et al (2022)[52,] LIBRETTO-001 (NCT03157128)	Denmark, France, Germany, Israel, Japan, Singapore, Switzerland, USA	30	Dec 2017-Aug 2021	Nonrandomized, open-label phase 1/2	N=45 (n=2 with breast cancer) RET fusion-positive, tumor-agnostic adults with evaluable disease per RECIST (v. 1.1), ECOG performance status 0-2, life expectancy ≥3 months • Mean age 53 years • 51% female • 69% white, 24% Asian, 4% Black, 2% other race/ethnicity	Selpercatinib 20-240 mg/day	Primary: overall response (complete or primary) Secondary: time to response, progression-free survival, overall survival

ECOG: Eastern Cooperative Oncology Group; RECIST: Response Evaluation Criteria in Solid Tumors.

Table 3. Selpercatinib in Patients with RET Fusion-Positive Solid Tumors - Study Results

Study	Overall Response (95% CI)	Duration of Response (95% CI)	PFS[a] (95% CI)	OS[a] (95% CI)	Treatment-related adverse events[a]
Subbiah et al (2022)[52,] LIBRETTO-001 (NCT03157128)	N=41 (n=2 with breast cancer)	N=41 (n=2 with breast cancer)	N=41 (n=2 with breast cancer)	N=41 (n=2 with breast cancer)	N=45 (n=2 with breast cancer)
Targeted therapy with selpercatinib	Total cohort: 43.9% (28.5 to 80.3) Breast cancer subgroup:	Total cohort: 24.5 months (9.2 months to not evaluable)	Median 13.2 months (7.4 to 26.2)	Median 18.0 months (10.7 to not evaluable)	Serious adverse events: 6.7% (3/45) Any grade 3 adverse events: 38% (17/45)

Study	Overall Response (95% CI)	Duration of Response (95% CI)	PFS[a] (95% CI)	OS[a] (95% CI)	Treatment-related adverse events[a]
	100% (15.8 to 100)	Breast cancer subgroup: 17.3 months (17.3 to 17.3)			Grade 3 elevated ALT: 16% (7/45) Grade 3 elevated AST: 11% (5/45)

[a] Data for breast cancer subgroup not available.
ALT: alanine transaminase; AST: aspartate transaminase; CI: confidence interval; OS: overall survival; PFS: progression-free survival.

Section Summary: *RET* Testing
The phase 1/2 LIBRETTO-001 trial of selpercatinib in individuals with *RET* fusion-positive solid tumors 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 currently no FDA-approved companion diagnostic test for *RET* fusion-positive solid tumors, and continued selpercatinib approval in this population is subject to the results of confirmatory trials.

BRAF TESTING

FDA Companion Diagnostic Test
There is currently no FDA approved companion diagnostic test for *BRAF* V600e positive solid tumors other than melanoma and non-small cell lung cancer for dabrafenib plus trametinib.

NONRANDOMIZED TRIALS

Dabrafenib plus Trametinib
Dabrafenib plus trametinib combination therapy received FDA approval in 2022 for treatment of patients with unresectable or metastatic solid tumors with *BRAF* V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options.[63,] Approval in this population was based on existing approval for treatment of lung cancer and melanoma, and on 3 additional basket trials of patients with BRAF V600E mutations: NCI-MATCH Subprotocol H (NCT02465060), BRF117019 (NCT02034110), and CTMT212X2101 (NCT02124772).[64,] NCI-MATCH Subprotocol H and BRF117019 were conducted in adults with various solid tumors (N=131); CTMT212X2101 was conducted in a glioma pediatric population and is not further discussed in this policy.

Study characteristics of NCI-MATCH and BRF117019 are summarized in Table 4. Both trials were uncontrolled, single-arm trials. Of note, none of the patients in either trial had breast cancer. Study results are summarized in Table 5. The primary outcome in both trials was overall response, a composite outcome that includes complete and partial response. Overall response ranged from 31% to 69%, and complete response was rare. The median duration of response (range 9 to 27.5 months), progression-free survival (range 4.5 to 14 months) and overall survival (range 14 to 28.6 months) 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

Table 4. Dabrafenib plus Trametinib in Patients with *BRAF* V600E Mutation Solid Tumors - Study Characteristics

Study	Countries	Sites	Dates	Design	Participants	Intervention	Outcomes
Salama et al (2020)[65], NCI MATCH Subprotocol H (NCT02465060	USA	Unclear for Subprotocol H	Aug 2015-Feb 2018	Open-label, single-arm, basket trial	N=35 (none with breast cancer) *BRAF* V600E mutated solid tumors, lymphoma or multiple myeloma with disease progression on at least 1 standard therapy and measurable disease according to standard practice for the tumor type • Median age 59 years • 62% female • 93% white, 1% Black, 1% mixed race, 1% NR	Dabrafenib 150 mg 2x/day and trametinib 2 mg/day	Primary: ORR Secondary: PFS, OS, safety
Subbiah et al (2020)[66], BRF117019 (NCT02034110)	9 countries (USA and Europe)	19	Mar 2014-Jul 2018	Open-label, single-arm, phase 2 basket trial	N=43 (none with breast cancer) *BRAF* V600E mutated biliary tract cancer that was unresectable, metastatic, locally advanced, or recurrent with no other standard treatment	Dabrafenib 150 mg 2x/day and trametinib 2 mg/day	Primary: ORR Secondary: PFS, duration of response, OS, safety

Study	Countries	Sites	Dates	Design	Participants	Intervention	Outcomes
					options available • Mean age 57 years • 56% female • 93% white, 7% Asian		
Wen et al (2022)[67], BRF117019 (NCT02034110)	13 countries (Austria, Belgium, Canada, France, Germany, Italy, Japan, the Netherlands, Norway, South Korea, Spain, Sweden, USA)	27	Apr 2014-Jul 2018	Open-label, single-arm, phase 2 basket trial	N=58 (none with breast cancer; 45 high-grade glioma, 13 low-grade glioma) *BRAF* V600E mutated high- or low-grade glioma High-grade glioma: • Mean age 42 years • 49% female • 76% white, 13% Asian, 4% Black, 2% American Indian or Alaska Native, 4% NR Low-grade glioma: • Mean age 33 years • 69% female • 77% white, 33% Asian	Dabrafenib 150 mg 2x/day and trametinib 2 mg/day	Primary: ORR Secondary: PFS, duration of response, OS, safety

NR: not reported; ORR: objective response rate; OS: overall survival; PFS: progression-free survival.

Table 5. Dabrafenib plus Trametinib in Patients with *BRAF* V600E Mutation Solid Tumors - Study Results

Study	Overall Response (95% CI)	Duration of Response (95% CI)	PFS (95% CI)	OS (95% CI)	Treatment-related adverse events
Salama et al (2020)[65], NCI MATCH Subprotocol H (NCT02465060)	N=29	N=29	N=29	N=29	N=35
Targeted therapy with dabrafenib + trametinib	38% (23 to 55; all partial response, no patients had complete response)	Median 25.1 months (12.8 to NA)	Median 11.4 months (7.2 to 16.3)	Median 28.6 months (NR)	Grade 4 adverse event: 3% (1/35) Grade 3 adverse event: 63% (22/35)
Subbiah et al (2020)[66], BRF117019 (NCT02034110)	N=43	N=22	N=43	N=43	N=43
Targeted therapy with dabrafenib + trametinib	47% (31 to 62; all partial response, no patients had complete response)	Median 9 months (6 to 14)	Median 9 months (5 to 10)	Median 14 months (10 to 33)	Serious treatment-related adverse event: 21% (9/43)
Wen et al (2022)[67], BRF117019 (NCT02034110)	N=45 high-grade glioma cohort N=13 low-grade glioma cohort	N=45 high-grade glioma cohort N=13 low-grade glioma cohort	N=45 high-grade glioma cohort N=13 low-grade glioma cohort	N=45 high-grade glioma cohort N=13 low-grade glioma cohort	N=58
Targeted therapy with dabrafenib + trametinib	High-grade cohort: 31% (18 to 47; 7% had complete response) Low-grade cohort: 69% (39 to 91; 8% had complete response)	High-grade cohort: median 13.6 months (4.6 to 43.4) Low-grade cohort: median 27.5 months (3.8 to 39.5)	High-grade cohort: median 4.5 months (1.8 to 7.4) Low-grade cohort: median 14.0 months (4.7 to 46.9)	High-grade cohort: median 17.6 months (9.5 to 45.2) Low-grade cohort: median NR	Serious treatment-related adverse events: 12% (7/45)

CI: confidence interval; NA: not available; NR: not reported; OS: overall survival; PFS: preservative-free survival.

In addition to the results reported in Table 5 , the FDA reported pooled efficacy data from the 2 trials, finding an objective response rate of 41% (95% CI, 33% to 50%).[63,] Response varied according to tumor type, ranging from 0% (for various adenocarcinomas and gastrointestinal stromal tumors) to 80% (for serous ovarian cancer).[64,]

Section Summary: *BRAF* Testing
The phase NCI Match and BRF117019 trials of dabrafenib plus trametinib combination therapy in individuals with *BRAF* mutated solid tumors reported overall response rates ranging from 31% to 69%, largely driven by partial responders; complete response was rare. Duration of response, PFS, 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 other than melanoma and non-small cell lung cancer, and continued dabrafenib plus trametinib approval in this population is subject to the results of confirmatory trials.

Circulating Tumor DNA Testing to Select Targeted Treatment
For individuals with hormone receptor-positive, HER2-negative advanced or metastatic breast cancer who receive biomarker testing of circulating tumor DNA for *PIK3CA* or *ESR1* variants, the evidence includes FDA-approved therapeutics with NCCN recommendations of 2A or higher and was not extensively evaluated. The evidence includes the pivotal studies leading to the FDA and NCCN recommendations.

CIRCULATING TUMOR CELL TESTING TO SELECT TARGETED TREATMENT

Clinical Context and Test Purpose
The purpose of testing circulating tumor cells (CTC) in individuals who have breast cancer is to inform a decision about selecting targeted treatment.
The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with recurrent or metastatic breast cancer.

Interventions
The test being considered is CTC testing.
The primary reason for CTCs would be to aid in decision-making about alternative treatment. CTC testing has been proposed as a method to guide the choice between chemotherapy and endocrine therapy as first-line treatment, or to change early to an alternative chemotherapy regimen in individuals for whom chemotherapy has failed to reduce CTCs.

Comparators
Decisions about first-line treatment and alternative treatments in metastatic breast cancer are based on clinical evaluation and biopsy.

Outcomes
The general outcomes of interest in oncology are overall survival, disease-specific survival, quality of life, treatment-related mortality and morbidity.
Follow-up at 6 to 12 months is of interest to monitor outcomes.

Study Selection Criteria
For the evaluation of clinical validity of the CTC test, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard (describe the reference standard)
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

Clinical Validity
Systematic reviews and meta-analyses have described an association between CTCs and poor prognosis in metastatic breast cancer.[68,69,]

CLINICAL UTILITY

Randomized Controlled Trials
Two RCTs have evaluated the clinical utility of using CTC to guide treatment decisions in patients with metastatic breast cancer (Tables 6 and 7).

Smerage et al (2014) reported on the results of an RCT of patients with metastatic breast cancer and persistently increased CTC levels to test whether changing chemotherapy after 1 cycle of first-line therapy could improve overall survival.[70,]. Level of CTCs were enumerated using the CellSearch system. Five or more CTCs per 7.5 mL whole blood was considered an increased level, and it served as the cut point for separation of favorable versus unfavorable prognosis. Patients who did not have increased CTC levels at baseline remained on initial therapy until progression (arm A), patients with initially increased CTC levels that decreased after 21 days of therapy remained on initial therapy (arm B), and patients with persistently increased CTC levels after 21 days of therapy were randomized to continue initial therapy (arm C1) or change to an alternative chemotherapy (arm C2). There were 595 eligible and evaluable patients, 276 (46%) of whom did not have increased CTC levels (arm A). Of patients with initially increased CTC levels, 31 (10%) were not retested, 165 were assigned to arm B, and 123 were randomized to arms C1 or C2. There was no difference in median overall survival between arms C1 (10.7 months) and C2 (12.5 months; p=.98). CTC levels were strongly prognostic, with a median overall survival for arms A, B, and C (C1 and C2 combined) of 35 months, 23 months, and 13 months, respectively (p<.001). While the trial showed the prognostic significance of CTCs in patients with metastatic breast cancer, changing to an alternative chemotherapeutic regimen did not improve outcomes in patients whose CTCs were not reduced after 1 cycle of first-line chemotherapy.

More recently, Bidard et al (2021) reported on a noninferiority trial comparing CTC-driven versus clinician driven first-line therapy choice in patients with metastatic breast cancer.[71,] Median PFS

was 15.5 months (95% CI, 12.7-17.3) in the CTC arm and 13.9 months (95% CI, 12.2-16.3) in the standard arm. The primary end point was met, with an HR of 0.94 (90% CI, 0.81-1.09).

Table 6. RCTs of CTC-Guided Treatment in Breast Cancer- Characteristics

Study	Countries	Sites	Dates	Participants	Interventions		Endpoints
					Active	Comparator	
Smerage et al (2014);[70,] NCT00382018			Oct 2006-Mar 2012	Women with histologically confirmed breast cancer and clinical and/or radiographic evidence of metastatic disease Persistent increased CTCs following 1 cycle of chemotherapy	Changing chemotherapy after 1 cycle of first-line chemotherapy (n=59)	Continued initial therapy (n=64)	OS, PFS
Bidard et al (2021)[71,]	France	17	Feb 2012-Jul 2016	778 women with hormone-receptor positive, HER2-negative metastatic breast	CTC-driven treatment choice (n=391)	Clinician-driven treatment choice (n=387)	PFS, OS, rate of treatment changes, AEs

AEs: adverse events; CTC: circulating tumor cell; OS: overall survival; PFS: progression-free survival; RCTs: randomized controlled trials.

Table 7. RCTs of CTC-Guided Treatment in Breast Cancer- Results

Study	OS	PFS
Smerage et al (2014)[70,]		
N analyzed		
CTC-Directed Treatment	12.5 months	4.6 months
Standard care	10.7 months	3.5 months

Study	**OS**	**PFS**
HR (95% CI)	1.00 (0.69 to 1.47)	0.92 (0.64 to 1.32)
p	.98	.64
Bidard et al (2021)[71,]		
N analyzed		
CTC-directed treatment		15.5 months (12.7-17.3)
Standard care		13.9 months (12.2-16.3)
HR (95% CI)		0.94 (0.81 to 1.09)

CI: confidence interval; CTC: circulating tumor cell; HR: hazard ratio; OS: overall survival; PFS: progression-free survival; RCTs: randomized controlled trials

Section Summary: Circulating Tumor Cell Testing
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 (PFS HR, 0.94; 95% CI, 0.81 to 1.09).

Neurotrophic Receptor Tyrosine Kinase (*NTRK*) Gene Fusion Testing to Select Targeted Treatment
For individuals with recurrent unresectable (local or regional) or stage IV breast cancer who receive *NTRK* gene fusion testing to guide treatment decisions, the evidence includes FDA-approved therapeutics with NCCN recommendations of 2A or higher and was not extensively evaluated. The evidence includes the pivotal studies leading to the FDA and NCCN recommendations.

SUPPLEMENTAL INFORMATION
The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

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

- 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 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).

A rapid update to the ASCO guideline was published in March 2023 to address *ESR1* testing (which was not recommended in the previous version).[73,] The guideline recommended routine testing for *ESR1* mutations at the time of disease recurrence or progression while receiving endocrine therapy, with or without a concomitant CDK4/6 inhibitor, in patients with estrogen receptor-positive, HER2-negative metastatic breast cancer (Type of recommendation: evidence-based; Evidence quality: high; Strength of recommendation: strong). Testing should be performed with blood or tissue obtained at the time of progression, as *ESR1* alterations develop via selective pressure from treatment and are unlikely to be detected in the primary tumor. Blood-based ctDNA is preferred due to greater sensitivity.

National Comprehensive Cancer Network

Table 8 summarizes National Comprehensive Cancer Network guidelines (v. 4.2023) on biomarker testing for the biomarkers included in this policy.[25,] 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 1 recommendation). For patients being considered for treatment with elacestrant, testing for *ESR1* with liquid biopsy is recommended (category 2A recommendation).

Table 8. 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
PIK3CA	HR-positive/HER2-negative	Alpelisib + fulvestrant	For HR-positive/HER2-negative breast cancer, assess for *PIK3CA* mutations with tumor or liquid biopsy to	1	Preferred second-or subsequent-line therapy

Biomarker	**Breast Cancer Subtype**	**FDA Approved Agents**	**Testing Recommendation**	**Targeted Therapy Category of Evidence**	**Targeted Therapy Category of Preference**
			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.		
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 two prior lines of endocrine therapy, including one line containing a CDK4/6 inhibitor. Blood testing is recommended.	2A	Other recommended regimen
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
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 progressed on or following prior treatment with no satisfactory alternative treatment options, pembrolizumab or dostarlimab-gxly are indicated.	2A	Useful in certain circumstances

Biomarker	Breast Cancer Subtype	FDA Approved Agents	Testing Recommendation	Targeted Therapy Category of Evidence	Targeted Therapy Category of Preference
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
RET-fusion	Any	Selpercatinib	Biomarker detection via NGS is recommended in adult patients with locally advanced or metastatic solid tumors that have progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options.	2A	Useful in certain circumstances

Source: Adapted from National Comprehensive Cancer Network guidelines on Breast Cancer (v. 5.2024)[25,]

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

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 9.

Table 9. 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
NCT02965755[a]	Individualized Molecular Analyses Guide Efforts in Breast Cancer - Personalized Molecular Profiling in Cancer Treatment at Johns Hopkins (IMAGE-II)	200	Jul 2026
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	534	Apr 2025

	Advanced or Metastatic Solid Tumors That Harbor NTRK1/2/3, ROS1, or ALK Gene Rearrangements (STARTRK-2)		
NCT04591431	The Rome Trial - From Histology to Target: the Road to Personalize Target Therapy and Immunotherapy	400	Jun 2025
NCT02693535[a]	Targeted Agent and Profiling Utilization Registry (TAPUR) Study	3791	Jun 2027
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	Oct 2026
NCT04526587	The Roswell Park Ciclib Study: A Prospective Study of Biomarkers and Clinical Features of Advanced/Metastatic Breast Cancer Treated With CDK4/6 Inhibitors	400	Jul 2025
NCT02306096	SCAN-B: The Sweden Cancerome Analysis Network - Breast Initiative	20000	Aug 2031
Unpublished			
NCT04098640	Molecular Profiling Using FoundationOne CDx in Young (<50 Years of Age) Patients With Metastatic Breast Cancer (ML41263)	200	Jul 2021

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

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. This may not be a comprehensive list of procedure codes applicable to this policy.

Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.

CPT/HCPCS	
0037U	Targeted genomic sequence analysis, solid organ neoplasm, DNA analysis of 324 genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden (PLA for the FoundationOne CDx™ (F1CDx®) test)
0048U	Oncology (solid organ neoplasia), DNA, targeted sequencing of protein-coding exons of 468 cancer-associated genes, including interrogation for somatic mutations and microsatellite instability, matched with normal specimens, utilizing formalin-fixed paraffin-embedded tumor tissue, report of clinically significant mutation(s) (PLA code for the MSK–IMPACT™ (Integrated Mutation Profiling of Actionable Cancer Targets), Memorial Sloan Kettering Cancer Center)
0155U	Oncology (breast cancer), DNA, PIK3CA (phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha) (e.g., breast cancer) gene analysis (i.e., p.C420R, p.E542K, p.E545A, p.E545D [g.1635G>T only], p.E545G, p.E545K, p.Q546E, p.Q546R, p.H1047L, p.H1047R, p.H1047Y), utilizing formalin-fixed paraffin-embedded breast tumor tissue, reported as PIK3CA gene mutation status (PLA code for the therascreen® PIK3CA RGQ PCR Kit from QIAGEN)
0177U	Oncology (breast cancer), DNA, PIK3CA (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha) gene analysis of 11 gene variants utilizing plasma, reported as PIK3CA gene mutation status (PLA code for the therascreen® PIK3CA RGQ PCR Kit test from QIAGEN) (eff 7/1/2020)
0211U	Oncology (pan-tumor), DNA and RNA by next-generation sequencing, utilizing formalin-fixed paraffin-embedded tissue, interpretative report for single nucleotide variants, copy number alterations, tumor mutational burden, and microsatellite instability, with therapy association (PLA code for the MI Cancer Seek™ – NGS Analysis from Caris MPI d/b/a Caris Life Sciences.)
0239U	Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free DNA, analysis of 311 or more genes, interrogation for sequence variants, including substitutions, insertions, deletions, select rearrangements, and copy number variations
0242U	Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free circulating DNA analysis of 55-74 genes, interrogation for sequence variants, gene

CPT/HCPCS	
	copy number amplifications, and gene rearrangements (PLA for Guardant360® CDx)
0338U	Oncology (solid tumor), circulating tumor cell selection, identification, morphological characterization, detection and enumeration based on differential EpCAM, cytokeratins 8, 18, and 19, and CD45 protein biomarkers, and quantification of HER2 protein biomarker–expressing cells, peripheral blood. CellSearch® HER2 Circulating Tumor Cell
81162	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis (i.e., detection of large gene rearrangements)
81163	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis
81164	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (i.e., detection of large gene rearrangements)
81165	BRCA1 (BRCA1, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis
81166	BRCA1 (BRCA1, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (i.e., detection of large gene rearrangements)
81167	BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (i.e., detection of large gene rearrangements)
81191	NTRK1 (neurotrophic receptor tyrosine kinase 1) (eg, solid tumors) translocation analysis
81192	NTRK (neurotrophic receptor tyrosine kinase 2) (eg, solid tumors) translocation analysis
81193	NTRK3 (neurotrophic receptor tyrosine kinase 3) (eg, solid tumors) translocation analysis
81194	NTRK (neurotrophic-tropomyosin receptor tyrosine kinase 1, 2, and 3) (eg, solid tumors) translocation analysis
81212	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; 185delAG, 5385insC, 6174delT variants
81215	BRCA1 (BRCA1, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; known familial variant
81216	BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis
81217	BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; known familial variant
81301	Microsatellite instability analysis (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) of markers for mismatch repair deficiency (e.g., BAT25, BAT26), includes comparison of neoplastic and normal tissue, if performed

CPT/HCPCS	
81309	PIK3CA (phosphatidylinositol-4, 5-biphosphate 3-kinase, catalytic subunit alpha) (e.g., colorectal and breast cancer) gene analysis, targeted sequence analysis (e.g., exons 7, 9, 20)
81445	Solid organ neoplasm, genomic sequence analysis panel, 5-50 genes, interrogation for sequence variants and copy number variants or rearrangements, if performed; DNA analysis or combined DNA and RNA analysis
81455	Solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes, interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; DNA analysis or combined DNA and RNA analysis
88360	Morphometric analysis, tumor immunohistochemistry (e.g., Her-2/neu, estrogen receptor/progesterone receptor), quantitative or semiquantitative, per specimen, each single antibody stain procedure; manual
88361	Morphometric analysis, tumor immunohistochemistry (e.g., Her-2/neu, estrogen receptor/progesterone receptor), quantitative or semiquantitative, per specimen, each single antibody stain procedure; using computer-assisted technology
81479	Unlisted molecular pathology procedure

REVISIONS	
03-10-2022	Policy added to the bcbsks.com web site.
10-28-2022	Updated Coding Section ▪ Added 0338U (effective 10-01-2022)
05-25-2023	Updated Description Section
	Updated Policy Section ▪ Removed Section: C. *NTRK Gene Fusion Testing* 1. Analysis of NTRK gene fusions may be considered medically necessary 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 (see Policy Guidelines). 2. Analysis of NTRK gene fusions in patients with breast cancer is considered experimental / investigational in all other situations. ▪ Added Sections: F. *RET Testing* 1. RET testing to predict treatment response to selpercatinib (Retevmo) in individuals with breast cancer is considered experimental / investigational. G. *BRAF Testing* 1. BRAF testing to predict treatment response to dabrafenib (Tafinlar) plus trametinib (Mekinist) in individuals with breast cancer is considered experimental / investigational.
	Updated Policy Guideline Section ▪ Added: B. Testing for individual genes (not gene panels) associated with FDA-approved therapeutics (i.e., as companion diagnostic tests) for therapies

REVISIONS	
	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. C. 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.
	Updated Rationale Section
	Updated Coding Section ▪ Updated nomenclature for 81445 and 81455 ▪ Added 0242U, 81456, 81162, 81163, 81164, 81165, 81166, 81167, 81212, 81215, 81216, 81217 ▪ Removed 81191, 81192, 81193, 81194 ▪ Removed ICD-10 Codes
	Updated References Section
01-23-2024	Updated Title to: "Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Breast Cancer (BRCA1, BRCA2, PIK3CA, Ki-67, RET, BRAF, ESR1)"
	Updated Description Section
	Updated Policy Section ▪ Removed Section B, C, and G B. *"PD-L1 Testing* 1. PD-L1 testing may be considered medically necessary to predict treatment response to pembrolizumab (Keytruda) in individuals with hormone receptor-negative/HER2-negative (triple negative) recurrent or metastatic breast cancer. 2. PD-L1 testing in individuals with breast cancer is considered experimental/ investigational in all other situations, including to predict treatment response to atezolizumab (Tecentriq). C. MSI-H/dMMR Testing 1. MSI-H/dMMR testing may be considered medically necessary to predict treatment response to pembrolizumab (Keytruda) in individuals with unresectable or metastatic breast cancer that has progressed following standard treatment and who have no alternative treatment option (see Policy Guidelines). 2. MSI-H/dMMR testing in individuals with breast cancer is considered experimental/ investigational in all other situations, including to predict treatment response to dostarlimab-gxly (Jemperli). G. Tumor Mutational Burden Testing 1. Tumor mutational burden testing to predict response to immunotherapy in individuals with breast cancer is considered experimental/ investigational."

REVISIONS	
	▪ Added Section F2 2. *"ESR1* testing using Guardant360 CDx may be considered medically necessary to predict treatment response to elacestrant (Orserdu) in individuals with estrogen receptor-positive, HER2-negative advanced or metastatic breast cancer with disease progression following at least 1 line of endocrine therapy (see Policy Guidelines)."
	Updated Rationale Section
	Updated Coding Section ▪ Updated nomenclature for 81445 and 81455 (eff. 01-01-2024) ▪ Removed 81456
	Updated References Section
07-10-2025	Updated Description Section
	Updated Policy Section ▪ Added Section H: H. *NTRK* Gene Fusion Testing 1. *NTRK* gene fusion testing may be considered medically necessary for individuals with recurrent unresectable (local or regional) or stage IV breast cancer to select individuals for treatment with FDA-approved therapies. 2. *NTRK* gene fusion testing in individuals with breast cancer is considered experimental / investigational in all other situations.
	Updated Rationale Section
	Updated Coding Section ▪ Added 81191, 81192, 81193 and 81194
	Updated References Section

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