2.04.151	Germline and Somatic Biomarker Testing for Targeted Treatment and Immunotherapy in Breast Cancer		
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Section:	2.0 Medicine	**Page:**	Page 1 of 40

Policy Statement

Note: This policy is not intended to address germline testing related to determining the risk of developing cancer. See instead: 2.04.02 Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers (BRCA1, BRCA2, PALB2)

BRCA1 and BRCA2 Testing

I. Genetic testing for *BRCA1* or *BRCA2* germline and/or somatic 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).

II. Genetic testing of *BRCA1* or *BRCA2* germline and/or somatic variants in individuals with breast cancer for guiding therapy is considered **investigational** in all other situations unless included in a panel approved under another policy. For comprehensive breast tumor testing panels or PIK3CA targeted testing for treatment response to alpelisib (Piqray), see Blue Shield of California Medical Policy: Oncology: Molecular Analysis Of Solid Tumors And Hematologic Malignancies

NTRK Gene Fusion Testing

III. 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).

IV. Analysis of *NTRK* gene fusions is considered **investigational** in all other situations unless included in a panel approved under another policy.

PD-L1 Testing

V. 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 (see Policy Guidelines).

VI. PD-L1 testing is considered **investigational** in all other situations, including to predict treatment response to atezolizumab (Tecentriq) unless included in a panel approved under another policy.

MSI-H/dMMR Testing

VII. 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).

VIII. MSI-H/dMMR testing is considered **investigational** in all other situations, including to predict treatment response to dostarlimab-gxly (Jemperli) unless included in a panel approved under another policy.

Ki-67 Testing

IX. Ki-67 testing to predict treatment response to abemaciclib (Verzenio) in individuals with breast cancer is considered **investigational** unless included in a panel approved under another policy.

RET Testing

X. RET testing to predict treatment response to selpercatinib (Retevmo) in individuals with breast cancer is considered **investigational** unless included in a panel approved under another policy.

BRAF Testing

XI. BRAF testing to predict treatment response to dabrafenib (Tafinlar) plus trametinib (Mekinist) in individuals with breast cancer is considered **investigational** unless included in a panel approved under another policy.

Circulating Tumor Cell Testing

XII. Analysis of circulating tumor cells to select treatment in individuals with breast cancer is considered **investigational** (see Background section). For circulating tumor DNA (liquid biopsy) testing, see Blue Shield of California Medical Policy: Oncology: Circulating Tumor DNA and Circulating Tumor Cells (Liquid Biopsy)

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

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

This policy does not address NTRK testing.

This policy does not address germline testing for inherited risk of developing cancer.

For expanded panel testing, see Blue Shield of California Medical Policy: Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies.

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

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

Breast Cancer Risk Groups

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

- Patients with triple-negative breast cancer who were treated with adjuvant chemotherapy were required to have axillary node-positive disease or an invasive primary tumor measuring at least 2 cm on pathological analysis. Patients treated with neoadjuvant chemotherapy were required to have not achieved pathological complete response.
- Patients treated with adjuvant chemotherapy for hormone receptor (HR)-positive, HER2-negative breast cancer were required to have at least 4 pathologically confirmed positive 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	
Nuclear grade 3	1

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

Paired Genetic Testing

Testing for genetic changes in tumor tissue assesses somatic changes. However, most somatic testing involves a paired blood analysis in order to distinguish whether findings in tumor tissue are acquired somatic changes or inherited germline changes. As such, simultaneous sequencing of tumor and normal tissue can recognize potential secondary germline changes that may identify risk for other cancers as well as identify risk for relatives. Thus, some laboratories offer concurrent full germline and somatic testing or paired tumor sequencing and germline sequencing, through large panels of germline and somatic variants. For paired panel testing involving germline components, see Blue Shield of California Medical Policy: Genetic Cancer Susceptibility Panels Using Next-Generation Sequencing. For paired panel testing involving somatic components, see Blue Shield of California Medical Policy: Oncology: Molecular Analysis Of Solid Tumors And Hematologic Malignancies.

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.

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.

Note: The use of PARP inhibitors (e.g., Lynparza/olaparib or talazoparib) in HER2-negative metastatic breast cancer with a germline BRCA mutation, is sometimes based on germline rather than somatic mutations in BRCA. Both may be tested as well as HER2 somatic tumor testing. Myriad myChoice (CPT 0172U) may be used for somatic BRCA testing (esp. for ovarian cancer) and BRACAnalysis CDx (Myriad Genetic Laboratories) may be used for germline BRCA testing to help determine eligible patients.

Coding

The following CPT codes may be used for this genomic sequence analysis:

- **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)

The following Molecular Pathology codes support Neurotrophic receptor tyrosine kinase (NTRK) gene testing:

- **81191:** NTRK1 (neurotrophic receptor tyrosine kinase 1) (e.g., solid tumors) translocation analysis
- **81192:** NTRK2 (neurotrophic receptor tyrosine kinase 2) (e.g., solid tumors) translocation analysis
- **81193:** NTRK3 (neurotrophic receptor tyrosine kinase 3) (e.g., solid tumors) translocation analysis
- **81194:** NTRK (neurotrophic-tropomyosin receptor tyrosine kinase 1, 2, and 3) (e.g., solid tumors) translocation analysis

The following CPT code that represents Oncosignal 7-Pathway version for Breast Cancer and Other Cancers by Protean BioDiagnostics. Per the manufacturer, this MAAA test is used after cancer diagnosis (various cancer types) to affect the course of treatment based on the activity of the signaling pathways tested by Oncosignal:

- **0262U:** Oncology (solid tumor), gene expression profiling by real-time RT-PCR of 7 gene pathways (ER, AR, PI3K, MAPK, HH, TGFB, Notch), formalin-fixed paraffin-embedded (FFPE), algorithm reported as gene pathway activity score

Description

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

The objective of this evidence review is to examine whether biomarker testing for *BRCA* variants, PD-L1, MSI-H/dMMR, Ki-67, RET, BRAF, TMB, or circulating tumor cells improves the net health outcome in patients with breast cancer who are considering targeted therapy or immunotherapy. This policy does not address PIK3CA testing, comprehensive tumor testing or circulating tumor DNA testing which are addressed in other policies.

Related Policies

- Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis in Patients with Breast Cancer
- Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers (BRCA1, BRCA2, PALB2)
- Oncology: Molecular Analysis Of Solid Tumors And Hematologic Malignancies
- Oncology: Circulating Tumor DNA and Circulating Tumor Cells (Liquid Biopsy)

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. 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.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

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. An up-to-date list of FDA cleared or approved companion diagnostics is available at https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools.

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

Treatment	Class	Indications in Breast Cancer	Companion Diagnostic
Abemaciclib (Verzenio)	Cyclin-dependent kinase (CDK) 4/6 inhibitor	• In combination with endocrine therapy (tamoxifen or an aromatase inhibitor) for the adjuvant treatment of adult patients with HR-positive, HER2-negative, node-positive, early breast cancer at high risk of recurrence and a Ki-67 score ≥20% as determined by an FDA approved test. • In combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women, and men, with HR-positive, HER2-negative advanced or metastatic breast cancer. • In combination with fulvestrant for the treatment of adult patients with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy. • 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.	Ki-67 IHC MIB-1 pharmDx (Dako Omnis)
Ado-trastuzumab emtansine (Kadcyla)[a]	HER2-targeted antibody and microtubule inhibitor conjugate	As a single agent, for: • Treatment of patients with HER2-positive, metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either: o received prior therapy for metastatic disease, or o developed disease recurrence during or within 6 months of completing adjuvant therapy. • Adjuvant treatment of patients with HER2-positive early breast cancer who have residual invasive disease after	FoundationOne CDx HER2 FISH pharmDx Kit HercepTest INFORM HER2 Dual ISH DNA Probe Cocktail PATHWAY anti-Her2/neu (4B5) Rabbit Monoclonal Primary Antibody

Treatment	Class	Indications in Breast Cancer	Companion Diagnostic
		neoadjuvant taxane and trastuzumab-based treatment.	
Alpelisib (Piqray)	Kinase inhibitor	In combination with fulvestrant for the treatment of postmenopausal women, and men, with HR positive, HER2 -negative, PIK3CA-mutated, advanced or metastatic breast cancer as detected by an FDA approved test following progression on or after an endocrine-based regimen	FoundationOne CDx FoundationOne Liquid CDx therascreen PIK3CA RGQ PCR Kit
Dabrafenib (Tafinlar) + Trametinib (Mekinist)	Kinase inhibitors	Adult and pediatric patients 6 years of age and older with unresectable or metastatic solid tumors with BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options	No FDA approved companion diagnostic
Dostarlimab-gxly (Jemperli)	PD-1 blocking antibody	Adult patients with dMMR recurrent or advanced solid tumors, as determined by an FDA-approved test, that has progressed on or following prior treatment and who have no satisfactory alternative treatment options	VENTANA MMR RxDx Panel
Entrectinib (Rozlytrek)[b]	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	No FDA approved companion diagnostic test
Fam-trastuzumab deruxtecan-nxki (Enhertu)[c]	HER-2 targeted antibody and topoisomerase inhibitor conjugate	• Adult patients with unresectable or metastatic HER2-positive breast cancer who have received a prior anti-HER2-based regimen either in the metastatic setting or in the neoadjuvant or adjuvant setting and have developed disease recurrence during or within 6 months of completing therapy • Adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer, as determined by an FDA-approved test, who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy	PATHWAY anti-Her2/neu (4B5) Rabbit Monoclonal Primary Antibody
Larotrectinib (Vitrakvi)[b]	Kinase inhibitor	Adult and pediatric patients 12 years of age and older with solid tumors that: • have an NTRK gene fusion without a known acquired resistance mutation, • are metastatic or where surgical resection is likely to result in severe morbidity, and • have progressed following treatment or have no satisfactory alternative therapy	FoundationOne CDx
Olaparib (Lynparza)	PARP inhibitor	Adult patients with deleterious or suspected deleterious germline BRCA mutated, HER2-negative metastatic breast cancer who have been treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting. Patients with HR -positive breast cancer should have been treated with a prior endocrine therapy or be considered	BRACAnalysis CDx FoundationOne CDx

Treatment	Class	Indications in Breast Cancer	Companion Diagnostic
		inappropriate for endocrine therapy. Select patients for therapy based on an FDA approved companion diagnostic for Lynparza.	
Pembrolizumab (Keytruda)	PD-L1-blocking antibody	In combination with chemotherapy, for the treatment of patients with locally recurrent unresectable or metastatic TNBC whose tumors express PD-L1 as determined by an FDA approved test	PD-L1 IHC 22C3 pharmDx
		Adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options	FoundationOne CDx
		Unresectable or metastatic tumor mutational burden-high (≥10 mutations/megabase) solid tumors, as determined by an FDA approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options.	FoundationOne CDx (Solid tumors TMB ≥ 10 mutations per megabase)
Pertuzumab (Perjeta)	HER2/neu receptor antagonist	Use in combination with trastuzumab and docetaxel for treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease. Use in combination with trastuzumab and chemotherapy as: • Neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer. • Adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence	HER2 FISH pharmDx Kit HercepTest FoundationOne CDx
Selpercatinib (Retevmo)	Kinase inhibitor	Adult patients with locally advanced or metastatic solid tumors with a RET gene fusion that have progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options	No FDA-approved companion diagnostic test
Talzenna (Talazoparib)	PARP inhibitor	Adult patients with deleterious or suspected deleterious germline BRCA-mutated HER2-negative locally advanced or metastatic breast cancer	BRACAnalysis CDx
Trastuzumab (Herceptin)[d]	HER2/neu receptor antagonist	The treatment of HER2-overexpressing breast cancer	Bond Oracle HER2 IHC System FoundationOne CDx HER2 CISH pharmDx Kit HER2 FISH pharmDx Kit HercepTest INFORM HER-2/neu INFORM HER2 Dual ISH DNA Probe Cocktail InSite Her-2/neu KIT PathVysion HER-2 DNA

Treatment	Class	Indications in Breast Cancer	Companion Diagnostic
			Probe Kit PATHWAY anti-Her2/neu (4B5) Rabbit Monoclonal Primary Antibody SPOT-LIGHT HER2 CISH Kit VENTANA HER2 Dual ISH DNA Probe Cocktail

[a] Covered in Policy 5.01.22.
[b] Covered in Policy 5.01.31.
[c] Placement of fam-trastuzumab deruxtecan-nxki (Enhertu) in the reference medical policy library is under current discussion.
[d] Covered in Policy 5.01.12.
dMMR: mismatch repair deficient; FDA: U.S. Food & Drug Administration; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; MSI-H: microsatellite instability-high; NTRK: neurotrophic-tropomyosin receptor kinase; PD-1: programmed death receptor-1; D-L1: programmed death-ligand 1 ; PIK3CA: phosphatidylinositol 3-kinase catalytic alpha polypeptide; TNBC: triple-negative breast cancer
Sources: [20,21,]

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

Rationale

Background

BRCA Variant Testing

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

Several genetic syndromes with an autosomal dominant pattern of inheritance that features breast cancer have been identified. Of these, hereditary breast and ovarian cancer (HBOC) and some cases 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. 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.[1,] 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).[1,2,3,4,] In cancer-prone families, the mean age of breast cancer diagnosis among women carrying *BRCA1* or *BRCA2* variants is in the 40s.[5,] 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.[2,] 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.[6,] 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.[7,8,9,]

In patients with "triple-negative" breast cancer (i.e., 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.[10,] 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.[11,] 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*).[12,]

Programmed Cell Death Ligand Protein-1

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

Mismatch Repair Deficiency/Microsatellite Instability

Mismatch repair deficiency (dMMR) and high levels of microsatellite instability (MSI-H) describe cells that have alterations in certain genes involved in correcting errors made when DNA is replicated. dMMR tumors are characterized by a high tumor mutational load and potential responsiveness to anti-PD-L1-immunotherapy. MMR deficiency is most common in colorectal cancer, other types of gastrointestinal cancer, and endometrial cancer, but it may also be found in other cancers including breast cancer. Microsatellite instability testing is generally performed using polymerase chain reaction (PCR) for 5 biomarkers, although other biomarker panels and next generation sequencing are sometimes performed. High microsatellite instability is defined as 2 or more of the 5 biomarkers showing instability or more than 30% of the tested biomarkers showing instability depending on what panel is used. Microsatellite instability testing is generally paired with immunohistochemistry (IHC) assessing lack of protein expression from 4 DNA mismatch repair genes thereby reflecting dMMR.[13,]

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.[14,]

Rearranged During Transfection

The REarranged during Transfection (RET) proto-oncogene encodes a receptor tyrosine kinase growth factor.[15,] 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.[16,]

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.[17,] BRAF mutations occur in approximately 1% of breast cancer cases.[18,]

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.

Literature Review

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.

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 patients who have advanced cancer is to inform a decision regarding treatment selection (e.g., whether to select a targeted treatment or standard treatment).

The question addressed in this evidence review is: Does biomarker testing of tumor tissue for PD-L1, MSI-H/dMMR, Ki-67, RET, BRAF or germline testing for *BRCA* variants improve the net health outcome in individuals with breast cancer?

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

Populations

The relevant population of interest is patients 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, PD-L1, MSI-H/dMMR, 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 patients with refractory solid tumors. ORR can be measured by the proportion of patients 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),[22,] or Response Assessment in Neuro-Oncology criteria,[23,] as appropriate by a blinded and independent adjudication committee.

There are clearly defined quantitative thresholds for the follow-up of patients 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, PD-L1, MIS-H/dMMR, Ki-67, RET, and BRAF*)* and by recommended therapy.

Review of Evidence

BRCA Variants

Food and Drug Administration Companion Diagnostic Tests

BRACAnalysis CDx is an FDA-approved companion diagnostic test for olaparib and talazoparib, and FoundationOne CDx has FDA approval as a companion diagnostic for olaparib.

Randomized Controlled Trials

Numerous clinical trials have been conducted to evaluate the effectiveness of PARP inhibitors in individuals with hereditary breast and ovarian cancer (HBOC) Syndrome or other high-risk cancers confirmed to have a *BRCA1/2* mutation. Summarized below are the pivotal trials that supported the *BRCA* mutation-related FDA approved indications.

Olaparib

Tutt et al (2021) published results from the phase 3 multicenter, multinational, and double-blind OlympiA RCT, which evaluated the safety and efficacy of olaparib in patients with germline *BRCA1* or *BRCA2* pathogenic or likely pathogenic variants and high-risk, human epidermal growth factor receptor 2 (*HER2*)-negative primary early-stage breast cancer after definitive local treatment and neoadjuvant or adjuvant chemotherapy.[24,] Patients with triple-negative disease comprised 82.2% of

the trial population. Patients were randomized 1:1 to treatment with twice daily 300 mg olaparib (n = 921) or placebo (n=915) for 52 weeks. The 3-year invasive disease-free survival was 85.9% in the olaparib group and 77.1% in the placebo group (difference, 8.8%; 95% CI, 4.5% to 13.0%). Invasive disease-free survival was significantly longer among patients receiving olaparib (hazard ratio [HR], 0.58; 99.5% CI, 0.41 to 0.82; p<.001). Distant disease-free survival at 3 years was 87.5% in the olaparib group and 80.4% in the placebo group (difference, 7.1%; 95% CI, 3.0% to 11.1%). This outcome was significantly longer among patients assigned to receive olaparib (HR, 0.57; 99.5% CI, 0.39 to 0.83; p<.001). While fewer deaths were reported in the olaparib group (59 versus 86) with a HR of 0.68 (99% CI, 0.44 to 1.05; p=.02), the between-group difference did not cross the prespecified multiple-testing procedure boundary for significance of p<.01. Subgroup analysis of invasive disease-free survival revealed treatment effects for olaparib over placebo that were consistent with those in the overall analysis population across all stratification groups and prespecified subgroups. Serious adverse events occurred in 8.7% and 8.4% of patients treated with olaparib and placebo, respectively. Adverse events leading to trial regimen discontinuation occurred in 9.9% and 4.2% of patients treated with olaparib and placebo, respectively.

OlympiAD is a phase 3 RCT in which patients with HER2-negative metastatic breast cancer and a germline *BRCA* variant were randomized to olaparib (n=205) or standard therapy (n=97).[25,] *BRCA1/2* mutation was detected by BRACAnalysis testing. In its initial publication, Robson et al (2017) reported that after a median follow-up of 14.5 months, patients receiving olaparib experienced significantly longer progression-free survival (PFS) compared with patients receiving standard therapy (HR, 0.6; 95% CI, 0.4 to 0.8).[26,] The rate of grade 3 or higher adverse events was lower in the group receiving olaparib (37%) compared with the group receiving standard therapy (51%). However, regarding overall survival, in their subsequent publication, Robson et al (2019) further reported that although improvement with olaparib was not significant overall (19.3 vs 17.1 months; HR, 0.90; 95% CI, 0.66 to 1.23) there may be a benefit in the subgroup of patients who had not received chemotherapy for metastatic disease (HR, 0.51; 95% CI, 0.29-0.90).[27,]

Talazoparib

Litton et al (2018) published results from a phase 3, randomized, open-label trial of 431 patients with advanced breast cancer and a germline *BRCA1/2* mutation that compared talazoparib 1 mg once daily to standard single-agent therapy (EMBRACA).[28,] *BRCA1/2* mutation was detected by BRAC Analysis testing. The primary endpoint was PFS. Median duration of follow-up for that endpoint was 11.2 months. Progression-free survival was significantly longer in the talazoparib group (8.6 months vs. 5.6 months; HR 0.54, 95% CI, 0.41 to 0.71). The rate of overall grade 3 or higher adverse events was similar for talazoparib compared with the standard care (25.5% vs. 25.4%), but hematologic grade 3 to 4 adverse events (primarily anemia) were more frequent for talazoparib (55% vs. 38%) compared with nonhematologic grade 3 to 4 adverse events (32% vs. 38%). Based on the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30), compared to baseline, there was a significant improvement in the talazoparib group (+3.0; 95% CI, 1.2 to 4.8) and a significant decline in the standard therapy group (-5.4; 95% CI, -8.8 to -2.0). Although the trial was open-label, assessment of the primary outcome was based on blinded independent central review.

Section Summary: *BRCA* Variant Testing

No studies were identified that have directly compared health outcomes in patients with breast cancer who did and did not use *BRCA1* and *BRCA2* variant testing to guide systemic treatment decisions. Evidence for the use of testing for *BRCA1* and *BRCA2* variants in individuals with breast cancer consists of several placebo-controlled RCTs of PARP inhibitor drugs that have consistently demonstrated that, in individuals identified by genetic testing as having a *BRCA1* or *BRCA2* variant, treatment with PARP inhibitor drugs significantly improve PFS time. In individuals with a *BRCA1/2* mutation and either HER2-negative metastatic breast cancer or other advanced breast cancer who were followed for 11 to 12 months, treatment with a PARP inhibitor drug resulted in a 40% to 46% lower risk of disease progression or death. In individuals with a *BRCA1/2* mutation and early-

stage breast cancer at high-risk for recurrence, treatment with olaparib resulted in a 9% improvement in 3-year invasive disease-free survival.

PD-L1 Testing

Food and Drug Administration Companion Diagnostic Tests

PD-L1 IHC 22C3 pharmDx is an approved companion diagnostic test to select patients with triple negative breast cancer for treatment with pembrolizumab.

Randomized Controlled Trials

Pembrolizumab

Randomized Controlled Trials

The efficacy of pembrolizumab plus chemotherapy compared to placebo plus chemotherapy for previously untreated, locally recurrent inoperable or metastatic triple-negative breast cancer (N=847) was evaluated in the KEYNOTE-355 study (Table 4).Dual primary efficacy endpoints were PFS and overall survival in patients with PD-L1 combined positive score ≥1. Interim study results were published in 2020,[30,] and final results were published in 2022.[31,] Study results are summarized in Table 5. This study formed the basis of pembrolizumab accelerated approval in patients with unresectable or metastatic triple-negative breast cancer and PD-L1 CPS ≥10.

Table 4. Pembrolizumab in Patients with PD-L1 Positive Triple Negative Breast Cancer - Randomized Study Characteristics

Study	Design	Participants	Interventions		Endpoints
			Active	Comparator	
Cortes et al (2020 [30,] and 2022)[31,] KEYNOTE-355 NCT02819518	Randomized, placebo-controlled, double-blind, multicenter, phase 3	847 patients with previously untreated, locally recurrent inoperable or metastatic triple-negative breast cancer	n=566 Pembrolizumab + chemotherapy • PD-L1 CPS ≥1, 425 (75%) • PD-L1 CPS ≥10, 220 (39%)	n=566 Placebo + chemotherapy • PD-L1 CPS ≥1, 210 (75%) • PD-L1 CPS ≥10, 220 (37%)	Primary: PFS, OS Secondary: Safety

CPS: combined positive score; OS: overall survival; PD-L1: programmed death ligand-1; PFS: progression-free survival.

Table 5. Pembrolizumab in Patients with PD-L1 Positive Triple Negative Breast Cancer - Randomized Study Results

Study	Median OS, months			Median PFS, months			Grade ≥3 Adverse Events
Cortes et al (2022)[31,]	ITT	PD-L1 CPS≥1	PD-L1 CPS≥10	ITT	PD-L1 CPS≥1	PD-L1 CPS≥10	
N	847	636	323				
Pembrolizumab + chemotherapy	17.2	17.6	23.0	7.5	7.6	9.7	Any adverse event: 77.9% (438/562) Treatment-related adverse events: 68.1% (383/562) Immune-mediated adverse events: 5.3% (30/562)
Placebo + chemotherapy	15.5	16.0	16.1	5.6	5.6	5.6	Any adverse event: 73.7%

Study	Median OS, months			Median PFS, months			Grade ≥3 Adverse Events
							(207/281) Treatment-related adverse events: 66.9% (188/281) Immune-mediated adverse events: 0% (0/ 281)
HR (95% CI)	0.89 (0.76 to 1.05)	0.86 (0.72 to 1.04)	0.71 (0.54 to 0.93)	0.82 (0.70 to 0.98)[a]	0.75 (0.62 to 0.92)[a]	0.66 (0.50 to 0.88)[a]	

[a] HR for progression or death.
CPS: combined positive score; HR: hazard ratio; ITT: intention-to-treat; PD-L1: programmed death ligand-1; OS: overall survival; PFS: progression-free survival.

Nonrandomized Trials

Two nonrandomized, single-arm trials reported outcomes in a total of 111 patients with PD-L1 positive triple negative breast cancer treated with pembrolizumab (Tables 6 and 7).[32,33,]

Table 6. Pembrolizumab in Patients with PD-L1-Positive Triple Negative Breast Cancer - Study Characteristics

Study	Design	Participants	Intervention	Endpoints
Adams et al (2019)[32,] KEYNOTE-086 NCT02447003	Nonrandomized, multicohort, phase 2	84 patients with metastatic triple-negative breast cancer; 86.9% received prior (neo)adjuvant therapy; none had prior systemic therapy for metastatic disease	Pembrolizumab monotherapy	Primary: Safety Secondary: Objective response, disease control rate, duration of response, PFS, OS
Nanda et al (2016)[33,] KEYNOTE-012 NCT01848834	Nonrandomized, multicohort, phase Ib	27 patients with recurrent or metastatic PD-L1 positive triple-negative breast cancer. Most were heavily pretreated, having received therapy in both the early and advanced disease settings.	Pembrolizumab monotherapy	Primary: OR : defined as percentage of patients with a best overall response of complete response or partial response Secondary: PFS, duration of response, OS

OS: overall survival; PD-L1: programmed death-ligand 1; PFS: progression-free survival

Table 7. Pembrolizumab in Patients with PD-L1-Positive Triple Negative Breast Cancer - Study Results

Study	Response	Median PFS	Duration of Response	OS	Adverse Events
Adams et al (2019);[32,] NCT02447003					
N analyzed	84	84			84
Targeted therapy	Objective response rate: 21.4% (95% CI 13.9 to 31.4)	Median: 2.1 months (95% CI, 2.0 to 2.2) Rate at 6 months: 27.0%	Median: 10.4 months (range 4.2 to 19.2+)	Median 18.0 months (95% CI 12.9 to 23.0) 6-month rate 81.0% 12-month rate: 61.7%	53 (63.1%) patients experienced 1 or more treatment-related AEs, 8 (9.5%) with 1 or more grade 3 event. No grade 4 events, no AEs that led to death, 1 (1.2%) discontinued

Study	Response	Median PFS	Duration of Response	OS	Adverse Events
					due to AEs. Most common treatment-related AEs were fatigue (26.2%), nausea (13.1%), and diarrhea (11.9%)
Nanda et al (2016);[33] KEYNOTE-012 (NCT01848834)					
N Analyzed	27	22			
Targeted therapy	Overall response rate:18.5% (95% CI, 6.3 to 38.1) Complete response: 1 (3.7%) Partial response: 4 (14.8%) PD 13: (48.1%)	Median 1.9 months (95% CI, 1.7 to 5.5) 6 months PFS: 24.4%	Median not yet reached (range 15.0 to ≥47.3 weeks)	Median : 11.2 months (95% CI, 5.3 to [not reached]) 6 month rate: 66.7% 12-month OS: 43.1%	56.3% of patients experienced at least one treatment-related toxicity, including 15.6% who experienced at least one grade 3 to 5 event. One patient died as a result of DIC accompanied by grade 4 decreased blood fibrinogen, both of which were considered by the investigator to be treatment related.

AE: adverse events; DIC: disseminated intravascular coagulation; CI: confidence interval; OS: overall survival; PD: progressive disease; PD-L1: programmed death-ligand 1; PFS: progression-free survival.

Section Summary: PD-L1 Testing

Two nonrandomized trials of pembrolizumab for patients with PD-L1 positive triple negative breast cancer reported objective response rates of 21.4% (95% CI, 13.9 to 31.4) and 18.5% (95% CI, 6.3 to 38.1).

MSI-H/dMMR Testing

Food and Drug Administration Companion Diagnostic Tests

The Ventana MMR RxDx Panel is an FDA-approved test for the detection of dMMR to guide the use of dostarlimab-gxly (Jemperli) in solid tumors. FoundationOne CDx is an FDA-approved test for the detection of MSI-H or dMMR for pembrolizumab (Keytruda). In clinical trials, the identification of MSI-H or dMMR tumor status for the majority of patients (135/149) was prospectively determined using local laboratory-developed, polymerase chain reaction (PCR) tests for MSI-H status or immunohistochemistry (IHC) tests for dMMR.

Nonrandomized Trials of Immunotherapy

Pembrolizumab

Marabelle et al (2020) reported results of a phase 2 trial of pembrolizumab in 233 previously treated patients with MSI-H solid tumors (Tables 8 and 9), 5 of whom had breast cancer.[34] The overall response rate, the primary outcome, was 34.3% (95% CI, 28.3% to 40.8%). Median PFS was 4.1 months (95% CI, 2.4 to 4.9 months) and median overall survival was 23.5 months (95% CI, 13.5 months to not reached). Treatment-related adverse events occurred in 151 patients (64.8%). Earlier, Le et al (2015) reported on a small (N = 41) phase 2 trial that compared response to pembrolizumab in patients with solid tumors that did or did not have mismatch repair.[35] Most of the patients had colorectal cancer, but a cohort of 9 patients with dMMR tumors that were not colorectal was included. In the full cohort,

mismatch-repair status predicted clinical benefit of pembrolizumab, and patients with dMMR noncolorectal cancer had responses similar to those of patients with dMMR colorectal cancer.

Table 8. Pembrolizumab in Patients with MSI-H/dMMR-Positive Solid Tumors - Study Characteristics

Study	Countries	Sites	Dates	Design	Participants	Intervention	Outcomes
Marabelle et al (2020); [34], KEYNOTE-158 (NCT02628067)	Multiple (N=21)	81	Feb 2016-May 2018	Nonrandomized, open-label, multisite phase 2	233 patients 18 years or older with unresectable and/or metastatic incurable noncolorectal solid tumor with disease progression on or intolerance to prior standard therapy. 27 tumor types 5 patients had breast cancer (2.1%)	Pembrolizumab	Primary: Overall response rate Secondary: duration of response, PFS, OS, safety

dMMR: mismatch repair deficient; MSI-H: microsatellite instability-high; N: sample size; OS: overall survival; PFS: progression-free survival

Table 9. Pembrolizumab in Patients with MSI-H/dMMR-Positive Solid Tumors - Study Results

Study	Response	Duration of Response	PFS	OS	Adverse events
Marabelle et al (2020)[34], KEYNOTE-158 NCT02628067					
N analyzed	233				233
Targeted therapy	Overall response rate: 34.3% (95% CI, 28.3% to 40.8%) Complete: 23 (9.9%) Partial: 57 (24.5%)	Median: not reached, range, 2.9 to 31.3+ months Response 12 months or longer: 86.9% 24 months or longer: 77.6%	Median: 4.1 months (95% CI, 2.4 to 4.9 months) 12 months: 33.9% 24 months: 29.3%	Median: 23.5 months (95% CI, 13.5 months to not reached) 12 months: 60.7% 24 months: 48.9%	Overall, 151 patients (64.8%) had treatment-related adverse events and 34 (14.6%) had grade 3 to 5 treatment-related adverse events, one of which was grade 5 (pneumonia). Eighteen patients (7.7%) had serious treatment-related adverse events, and 22 (9.4%) discontinued treatment because of a treatment-related adverse event Deaths: 113 (48.5%)

CI: confidence interval; dMMR: mismatch repair deficient; MSI-H: microsatellite instability-high; N: sample size; OS: overall survival; PFS: progression-free survival

Dostarlimab-gxly

Patients with dMMR/MSI-H endometrial cancer (EC; n=103) or dMMR/MSI-H and/or polymerase epsilon (POLE)-mutant non-endometrial solid cancers (n=106) who had experienced disease progression for recurrent or advanced disease with no satisfactory alternative treatment options were evaluated in the multicenter, open-label GARNET trial, a phase 1 dose escalation and cohort expansion study of dostarlimab-gxly (Jemperli).[36] Laboratory-developed tests using immunohistochemistry (IHC), polymerase chain reaction (PCR), or next generation sequencing (NGS) were used to prospectively determine patient variant status, and dMMR status was retrospectively

confirmed with the marketed companion diagnostic test, the Ventana MMR RxDx Panel, a qualitative IHC test. Accelerated drug approval was based on an overall response rate of 41.6% (95% CI, 34.9%, 48.6%) for the full cohort, the primary efficacy outcome, as assessed at data cutoff with a median follow-up duration of 13.5 months. The median duration of response was 34.7 months, with 95.4% of patients achieving a duration of response of at least 6 months. The confirmed overall response rate was 44.7% (95% CI, 34.9% to 54.8%) and 38.7% (29.4% to 48.6%) for EC and non-EC cohorts, respectively. One patient with breast cancer was enrolled in the study and achieved a complete response and ongoing duration of response of 16.8 months. Continued drug approval is subject to the results of confirmatory trials.

Section Summary: MSI-H/dMMR Testing

In a phase 2 trial of pembrolizumab in 233 previously treated patients with MSI-H solid tumors, the overall response rate was 34.3% (95% CI, 28.3% to 40.8%). Median PFS was 4.1 months (95% CI, 2.4 to 4.9 months) and median overall survival was 23.5 months (95% CI, 13.5 months to not reached). Treatment-related adverse events occurred in 151 patients (64.8%). A phase 1 dose escalation study of dostarlimab-gxly reported an overall response rate of 41.6% with a median duration of response of 34.7 months for a combined cohort of 209 patients with endometrial cancer and non-endometrial cancer solid cancers; however, enrollment of patients with breast cancer was limited to 1 individual.

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).[37,] Adult men and women with 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 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 (HR, 0.75; 95% 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 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%). [38,] 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 ALNs, 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.[39] 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). 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, additional analyses 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 preliminary results that were not subject to peer review. 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).[40] 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 10). *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 polymerase-chain-reaction (PCR) assay.[41] 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 11). LIBRETTO-001 is ongoing, and continued selpercatinib approval in this population is subject to the results of confirmatory trials.

Table 10. Selpercatinib in Patients with RET Fusion-Positive Solid Tumors - Study Characteristics

Study	Countries	Sites	Dates	Design	Participants	Intervention	Outcomes
Subbiah et al (2022)[40], LIBRETTO-	Denmark, France, Germany,	30	Dec 2017-	Nonrandomized, open-label phase 1/2	N=45 (n=2 with breast cancer) RET fusion-positive,	Selpercatinib 20-240 mg/day	Primary: overall response

Study	Countries	Sites	Dates	Design	Participants	Intervention	Outcomes
001 (NCT03157128)	Israel, Japan, Singapore, Switzerland, USA		Aug 2021		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		(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 11. 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)[40], 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: 100% (15.8 to 100)	Total cohort: 24.5 months (9.2 months to not evaluable) Breast cancer subgroup: 17.3 months (17.3 to 17.3)	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) 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.

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 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.[42,] 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).[43,] 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 12. 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 13. 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 12. 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)[44,] 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)[45,] 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 options available • Mean age 57 years • 56% female • 93% white, 7% Asian	Dabrafenib 150 mg 2x/day and trametinib 2 mg/day	Primary: ORR Secondary: PFS, duration of response, OS, safety
Wen et al (2022)[46,] BRF117019 (NCT02034110)	13 countries (Austria, Belgium, Canada,	27	Apr 2014-Jul 2018	Open-label, single-arm,	N=58 (none with breast cancer; 45 high-grade glioma, 13 low-grade	Dabrafenib 150 mg 2x/day and trametinib 2 mg/day	Primary: ORR Secondary: PFS,

Study	Countries	Sites	Dates	Design	Participants	Intervention	Outcomes
	France, Germany, Italy, Japan, the Netherlands, Norway, South Korea, Spain, Sweden, USA)			phase 2 basket trial	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		duration of response, OS, safety

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

Table 13. 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)[44], 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)[45], 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)[46], 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	High-grade cohort: 31% (18 to 47; 7% had	High-grade cohort: median 13.6	High-grade cohort: median 4.5 months (1.8 to	High-grade cohort: median 17.6 months (9.5	Serious treatment-related adverse events: 12% (7/45)

Study	Overall Response (95% CI)	Duration of Response (95% CI)	PFS (95% CI)	OS (95% CI)	Treatment-related adverse events
dabrafenib + trametinib	complete response) Low-grade cohort: 69% (39 to 91; 8% had complete response)	months (4.6 to 43.4) Low-grade cohort: median 27.5 months (3.8 to 39.5)	7.4) Low-grade cohort: median 14.0 months (4.7 to 46.9)	to 45.2) Low-grade cohort: median NR	

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

In addition to the results reported in Table 13, the FDA reported pooled efficacy data from the 2 trials, finding an objective response rate of 41% (95% CI, 33% to 50%).[42,] Response varied according to tumor type, ranging from 0% (for various adenocarcinomas and gastrointestinal stromal tumors) to 80% (for serous ovarian cancer).[43,]

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, and continued dabrafenib plus trametinib approval in this population is subject to the results of confirmatory trials.

Circulating Tumor Cell Testing to Select Targeted Treatment

Clinical Context and Test Purpose

The purpose of testing circulating tumor cells (CTC) in patients who have breast cancer is to inform a decision about selecting targeted treatment.

The question addressed in this evidence review is: Does CTC testing improve the net health outcome in individuals with breast cancer?

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 patients 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.[51,52,]

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 16 and 17).

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.[53,]. 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=0.98). 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.[54,] 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 16. RCTs of CTC-Guided Treatment in Breast Cancer- Characteristics

Study	Countries	Sites	Dates	Participants	Interventions		Endpoints
					Active	Comparator	
Smerage et al (2014);[53,] NCT00382018			Oct 2006-Mar 2012	Women with histologically confirmed breast cancer and clinical and/or radiographic	Changing chemotherapy after 1 cycle of first-line chemotherapy (n=59)	Continued initial therapy (n=64)	OS, PFS

Study	Countries	Sites	Dates	Participants	Interventions		Endpoints
				evidence of metastatic disease Persistent increased CTCs following 1 cycle of chemotherapy			
Bidard et al (2021)[54,]	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; HER2: human epidermal growth factor receptor 2; OS: overall survival; PFS: progression-free survival; RCTs: randomized controlled trials.

Table 17. RCTs of CTC-Guided Treatment in Breast Cancer- Results

Study	OS	PFS
Smerage et al (2014)[53,]		
N analyzed		
CTC-Directed Treatment	12.5 months	4.6 months
Standard care	10.7 months	3.5 months
HR (95% CI)	1.00 (0.69 to 1.47)	0.92 (0.64 to 1.32)
p	.98	.64
Bidard et al (2021)[54,]		
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).

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.[55,] The guideline recommended the following biomarker tests:

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

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

Detailed recommendations are as follows:

- Patients with locally recurrent unresectable or metastatic hormone receptor-positive and human epidermal growth factor receptor 2 (HER2)-negative breast cancer who are candidates for a treatment regimen that includes a phosphatidylinositol 3-kinase inhibitor and a hormonal therapy should undergo testing for PIK3CA mutations using next-generation sequencing of tumor tissue or circulating tumor DNA (ctDNA) in plasma to determine their eligibility for treatment with the phosphatidylinositol 3-kinase inhibitor alpelisib plus fulvestrant. If no mutation is found in ctDNA, testing in tumor tissue, if available, should be used as this will detect a small number of additional patients with PIK3CA mutations (Type of recommendation: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).
- There are insufficient data at present to recommend routine testing for ESR1 mutations to guide therapy in hormone receptor–positive, HER2-negative MBC. Existing data suggest reduced efficacy of aromatase inhibitors (AIs) compared with the selective estrogen receptor degrader fulvestrant in patients who have tumor or ctDNA with ESR1 mutations (Type of recommendation: informal consensus; Evidence quality: insufficient; Strength of recommendation: moderate).
- Patients with metastatic HER2-negative breast cancer who are candidates for treatment with a poly (ADP-ribose) polymerase (PARP) inhibitor should undergo testing for germline BRCA1 and BRCA2 pathogenic or likely pathogenic mutations to determine their eligibility for treatment with the PARP inhibitors olaparib or talazoparib (Type of recommendation: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).
- There is insufficient evidence to support a recommendation either for or against testing for a germline PALB2 pathogenic variant for the purpose of determining eligibility for treatment with PARP inhibitor therapy in the metastatic setting. This recommendation is independent of the indication for testing to assess cancer risk (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).
    - Small single-arm studies show that oral PARP inhibitor therapy demonstrates high response rates in MBC encoding DNA repair defects, such as germline PALB2 pathogenic variants and somatic BRCA1/2 mutations. It should also be noted that the randomized PARP inhibitor trials made no direct comparison with taxanes, anthracyclines, or platinums; comparative efficacy against these compounds is

unknown. There are insufficient data at present to recommend routine testing of tumors for homologous recombination deficiency to guide therapy for MBC (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

- Patients with locally recurrent unresectable or metastatic hormone receptor-negative and HER2-negative breast cancer who are candidates for a treatment regimen that includes an immune checkpoint inhibitor (ICI) should undergo testing for expression of programmed cell death ligand-1 in the tumor and immune cells with a US Food and Drug Administration–approved test to determine eligibility for treatment with the ICI pembrolizumab plus chemotherapy (Type of recommendation: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).
- Patients with metastatic cancer who are candidates for a treatment regimen that includes an ICI should undergo testing for deficient mismatch repair/microsatellite instability-high to determine eligibility for dostarlimab-gxly or pembrolizumab (Type of recommendation: informal consensus; Evidence quality: low; Strength of recommendation: moderate).
- Patients with metastatic cancer who are candidates for treatment with an ICI should undergo testing for tumor mutational burden to determine eligibility for pembrolizumab monotherapy (Type of recommendation: informal consensus; Evidence quality: low; Strength of recommendation: moderate).
- Clinicians may test for NTRK fusions in patients with metastatic cancer who are candidates for a treatment regimen that includes a TRK inhibitor to determine eligibility for larotrectinib or entrectinib (Type of recommendation: informal consensus; Evidence quality: low; Strength of recommendation: moderate).
- There are insufficient data to recommend routine testing of tumors for TROP2 expression to guide therapy with an anti-TROP2 antibody-drug conjugate for hormone receptor-negative, HER2-negative MBC (Type of recommendation: informal consensus; Evidence quality: low; Strength of recommendation: moderate).
- There are insufficient data to recommend routine use of ctDNA to monitor response to therapy among patients with MBC (Type of recommendation: informal consensus; Evidence quality: low; Strength of recommendation: moderate).
- There are insufficient data to recommend routine use of circulating tumor cells to monitor response to therapy among patients with MBC (Type of recommendation: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

National Comprehensive Cancer Network

Table 18 summarizes National Comprehensive Cancer Network guidelines (v. 4.2022) on biomarker testing for the biomarkers included in this policy.[56,] The guidelines state that the use of circulating tumor cells or circulating tumor DNA in metastatic breast cancer is not yet included in algorithms for disease assessment and monitoring. For patients being considered for treatment with alpelisib, testing for *PIK3CA* with either tissue or liquid biopsy is recommended (category of evidence 2A).

Table 18. 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	1	Preferred

Biomarker	Breast Cancer Subtype	FDA Approved Agents	Testing Recommendation	Targeted Therapy Category of Evidence	Targeted Therapy Category of Preference
			talazoparib are FDA-indicated in HER2-negative disease, NCCN supports use in any breast cancer subtype associated with a germline *BRCA1* or *BRCA2* mutation.		
PIK3CA	HR-positive/HER2-negative	Alpelisib + fulvestrant	For HR-positive/HER2-negative breast cancer, assess for *PIK3CA* mutations with tumor or liquid biopsy to identify candidates for alpelisib plus fulvestrant. *PIK3CA* mutation testing can be done on tumor tissue or ctDNA in peripheral blood (liquid biopsy). If liquid biopsy is negative, tumor tissue testing is recommended.	1	Preferred second-or subsequent-line therapy
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
TMB-H (≥10 mut/mb)	Any	Pembrolizumab	Biomarker detection via NGS is indicated in patients with unresectable or metastatic TMB-H tumors that have progressed following prior treatment and who have no satisfactory treatment options.	2A	Useful in certain circumstances

Source: Adapted from National Comprehensive Cancer Network guidelines on Breast Cancer (v. 4.2022)[56,]

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

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

laboratory AND the test has approval or clearance by the U.S. Food and Drug Administration (CAG-00450R).[57,]

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

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 19.

Table 19. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT03145961[a]	c-TRAK TN: A Randomised Trial Utilising ctDNA Mutation Tracking to Detect Minimal Residual Disease and Trigger Intervention in Patients With Moderate and High Risk Early Stage Triple Negative Breast Cancer	208	Mar 2024
NCT03213041[a]	I-CURE-1: A Phase II, Single Arm Study of Pembroluzimab Combined With Carboplatin in Patients With Circulating Tumor Cells (CTCs) Positive HER-2 Negative Metastatic Breast Cancer (MBC)	100	Jul 2023 (recruiting)
NCT02965755[a]	Individualized Molecular Analyses Guide Efforts in Breast Cancer - Personalized Molecular Profiling in Cancer Treatment at Johns Hopkins (IMAGE-II)	200	Jul 2023 (recruiting)
NCT02819518[a]	A Randomized, Double-Blind, Phase III Study of Pembrolizumab (MK-3475) Plus Chemotherapy vs Placebo Plus Chemotherapy for Previously Untreated Locally Recurrent Inoperable or Metastatic Triple Negative Breast Cancer (KEYNOTE-355)	882	Nov 2023
NCT02889978[a]	The Circulating Cell-free Genome Atlas Study (CCGA)	15,254	Mar 2024
NCT02568267[a]	An Open-Label, Multicenter, Global Phase 2 Basket Study of Entrectinib for the Treatment of Patients With Locally Advanced or Metastatic Solid Tumors That Harbor NTRK1/2/3, ROS1, or ALK Gene Rearrangements (STARTRK-2)	700	Apr 2025 (recruiting)
NCT04591431	The Rome Trial - From Histology to Target: the Road to Personalize Target Therapy and Immunotherapy	384	Aug 2024 (recruiting)
NCT02693535[a]	Targeted Agent and Profiling Utilization Registry (TAPUR) Study	3641	Dec 2025 (recruiting)
NCT04720729	Chemotherapy Monitoring by Circulating Tumor DNA (ctDNA) in HER2 (Human Epidermal Growth Factor Receptor-2)-Metastatic Breast Cancer (MONDRIAN): a Phase 2 Study	214	Jun 2025 (recruiting)
NCT04526587	The Roswell Park Ciclib Study: A Prospective Study of Biomarkers and Clinical Features of Advanced/Metastatic Breast Cancer Treated With CDK4/6 Inhibitors	300	Jul 2025 (recruiting)
NCT04895358[a]	A Randomized, Double-blind, Placebo-controlled, Phase 3 Study of Pembrolizumab Plus Chemotherapy Versus Placebo Plus Chemotherapy for the Treatment of Chemotherapy-Candidate Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative (HR+/HER2-) Locally Recurrent Inoperable or Metastatic Breast Cancer (KEYNOTE-B49)	800	Oct 2027 (recruiting)
NCT02306096	SCAN-B: The Sweden Cancerome Analysis Network - Breast Initiative	20000	Aug 2031 (recruiting)
Unpublished			
NCT04098640	Molecular Profiling Using FoundationOne CDx in Young (<50 Years of Age) Patients With Metastatic Breast Cancer (ML41263)	200	Jul 2021 (unknown)

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

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Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or consultation notes including:
  - Clinical findings (i.e., pertinent symptoms and duration)
  - Current diagnoses and status (i.e., type of cancer, stage)
  - Family history, if applicable
  - Reason for test when applicable
  - Pertinent past procedural and surgical history (i.e., biopsies, resections, etc.)
  - Pertinent past genetic tests (i.e., somatic/tumor or germline test results including but not limited to HER2, PD-L1, MSI, BRCA, etc.)

Post Service (in addition to the above, please include the following):

- Results/reports of tests performed
- Procedure report(s)

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	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 Foundation One 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],

Type	Code	Description
		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
	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.)
	0262U	Oncology (solid tumor), gene expression profiling by real-time RT-PCR of 7 gene pathways (ER, AR, PI3K, MAPK, HH, TGFB, Notch), formalin-fixed paraffin-embedded (FFPE), algorithm reported as gene pathway activity score
	81191	NTRK1 (neurotrophic receptor tyrosine kinase 1) (e.g., solid tumors) translocation analysis
	81192	NTRK2 (neurotrophic receptor tyrosine kinase 2) (e.g., solid tumors) translocation analysis
	81193	NTRK3 (neurotrophic receptor tyrosine kinase 3) (e.g., solid tumors) translocation analysis
	81194	NTRK (neurotrophic-tropomyosin receptor tyrosine kinase 1, 2, and 3) (e.g., solid tumors) translocation analysis
	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
	81449	Targeted genomic sequence analysis panel, solid organ neoplasm, 5-50 genes (e.g., ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, MET, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed; RNA analysis ***(Code effective 1/1/2023)***
	81456	Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes (e.g., ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MET, MLL, NOTCH1, NPM1, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; RNA analysis ***(Code effective 1/1/2023)***
	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
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
02/01/2021	New policy
06/01/2021	Coding update
11/01/2021	Coding update
03/01/2022	Annual review. Policy statement, guidelines and literature review updated. Policy title changed from Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Breast Cancer to current one.
03/01/2023	Annual review. Policy statement, guidelines and literature review updated. Coding update.
06/01/2023	Policy review. Policy statement, guidelines and literature review updated. Policy title changed from Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Breast Cancer to current one. Coding update.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT	
BEFORE Red font: Verbiage removed	**AFTER** Blue font: Verbiage Changes/Additions
Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Breast Cancer 2.04.151 **Policy Statement:** ***BRCA1 and BRCA2* Testing** I. 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). II. Genetic testing of *BRCA1* or *BRCA2* germline or somatic variants in individuals with breast cancer for guiding therapy is considered **investigational** in all other situations unless included in a panel approved under another policy. ***PIK3CA* Testing** III. *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 (see Policy Guidelines). IV. *PIK3CA* testing of tissue is considered **investigational** in all other situations unless included in a panel approved under another policy.	**Germline and Somatic Biomarker Testing for Targeted Treatment and Immunotherapy in Breast Cancer 2.04.151** **Policy Statement:** Note: This policy is not intended to address germline testing related to determining the risk of developing cancer. See instead: 2.04.02 Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers (BRCA1, BRCA2, PALB2) ***BRCA1 and BRCA2* Testing** I. Genetic testing for *BRCA1* or *BRCA2* germline and/or somatic 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). II. Genetic testing of *BRCA1* or *BRCA2* germline and/or somatic variants in individuals with breast cancer for guiding therapy is considered **investigational** in all other situations unless included in a panel approved under another policy. For comprehensive breast tumor testing panels or PIK3CA targeted testing for treatment response to alpelisib (Piqray), see Blue Shield of California Medical Policy: Oncology: Molecular Analysis Of Solid Tumors And Hematologic Malignancies

POLICY STATEMENT	
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	***NTRK* Gene Fusion Testing** III. 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). IV. Analysis of *NTRK* gene fusions is considered **investigational** in all other situations unless included in a panel approved under another policy.
PD-L1 Testing V. 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 (see Policy Guidelines). VI. PD-L1 testing is considered **investigational** in all other situations, including to predict treatment response to atezolizumab (Tecentriq) unless included in a panel approved under another policy.	**PD-L1 Testing** V. 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 (see Policy Guidelines). VI. PD-L1 testing is considered **investigational** in all other situations, including to predict treatment response to atezolizumab (Tecentriq) unless included in a panel approved under another policy.
MSI-H/dMMR Testing VII. 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). VIII. MSI-H/dMMR testing is considered **investigational** in all other situations, including to predict treatment response to dostarlimab-gxly (Jemperli) unless included in a panel approved under another policy.	**MSI-H/dMMR Testing** VII. 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). VIII. MSI-H/dMMR testing is considered **investigational** in all other situations, including to predict treatment response to dostarlimab-gxly (Jemperli) unless included in a panel approved under another policy.

POLICY STATEMENT	
BEFORE Red font: Verbiage removed	AFTER Blue font: Verbiage Changes/Additions
Ki-67 Testing IX. Ki-67 testing to predict treatment response to abemaciclib (Verzenio) in individuals with breast cancer is considered **investigational** unless included in a panel approved under another policy.	**Ki-67 Testing** IX. Ki-67 testing to predict treatment response to abemaciclib (Verzenio) in individuals with breast cancer is considered **investigational** unless included in a panel approved under another policy.
RET Testing X. RET testing to predict treatment response to selpercatinib (Retevmo) in individuals with breast cancer is considered **investigational** unless included in a panel approved under another policy.	**RET Testing** X. RET testing to predict treatment response to selpercatinib (Retevmo) in individuals with breast cancer is considered **investigational** unless included in a panel approved under another policy.
BRAF Testing XI. BRAF testing to predict treatment response to dabrafenib (Tafinlar) plus trametinib (Mekinist) in individuals with breast cancer is considered **investigational** unless included in a panel approved under another policy.	**BRAF Testing** XI. BRAF testing to predict treatment response to dabrafenib (Tafinlar) plus trametinib (Mekinist) in individuals with breast cancer is considered **investigational** unless included in a panel approved under another policy.
Tumor Mutational Burden Testing XII. Tumor mutational burden testing to predict response to immunotherapy in individuals with breast cancer may be considered **medically necessary** when all standard treatments have failed and testing is being done to assess the potential efficacy of pembrolizumab (Keytruda). XIII. Tumor mutational burden testing to predict response to immunotherapy in individuals with breast cancer is considered **investigational.**	
Circulating Tumor DNA Testing (Liquid Biopsy) XIV. *PIK3CA* testing using FoundationOne Liquid CDx (FDA approved companion test) 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 (see Policy Guidelines) when there is insufficient tissue to be	

POLICY STATEMENT	
BEFORE **Red font: Verbiage removed**	**AFTER** **Blue font: Verbiage Changes/Additions**
tested and an additional invasive procedure would be required otherwise. XV. Circulating tumor DNA testing is considered **investigational** in all other situations unless included in a panel approved under another policy, such as use in Non-Small Cell Lung Cancer (NSCLC). **Circulating Tumor Cell Testing** XVI. Analysis of circulating tumor cells to select treatment in individuals with breast cancer is considered **investigational** (see Background section).	**Circulating Tumor Cell Testing** XII. Analysis of circulating tumor cells to select treatment in individuals with breast cancer is considered **investigational** (see Background section). For circulating tumor DNA (liquid biopsy) testing, see Blue Shield of California Medical Policy: Oncology: Circulating Tumor DNA and Circulating Tumor Cells (Liquid Biopsy)