



FEP Medical Policy Manual

FEP 2.04.151 Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Breast Cancer

Effective Policy Date: April 1, 2021

Original Policy Date: March 2021

Related Policies:

2.04.02 - Genetic Testing for BRCA1 or BRCA2 for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers	5.21.134 Rozlytrek (entrectinib)
2.04.115 - Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies	5.21.122 Vittrakvi (larotrectinib)
2.04.141 - Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy)	5.21.80 Tecentriq (atezolizumab)
2.04.36 - Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis in Patients with Breast Cancer	5.21.50 Keytruda (pembrolizumab)
	5.021.128 Piqray (alpelisib)

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

Description

Description

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

PIK3CA Testing

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

NTRK Gene Fusions

Neurotrophic-tropomyosin receptor kinase (*NTRK*) gene fusions encode tropomyosin receptor kinase fusion proteins that act as oncogenic drivers for solid tumors including lung, salivary gland, thyroid, and sarcoma. *NTRK* gene fusion findings might be more highly

The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.

associated with rare breast cancer subtypes (eg secretory carcinoma).¹

Programmed Cell Death Ligand Protein-1

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

Mismatch Repair Deficiency/Microsatellite Instability

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

Tumor Mutational Burden

Tumor mutational burden (TMB), a measure of gene mutations within cancer cells, is an emerging biomarker of outcomes with immunotherapy in multiple tumor types. Initially, assessments of TMB involved whole exome sequencing (WES). More recently, targeted next generation sequencing (NGS) panels are being adapted to estimate TMB. Currently FoundationOne CDx is the only U.S. Food and Drug Administration (FDA) approved panel for estimating TMB, but others are in development.³

Circulating Tumor DNA

Normal and tumor cells release small fragments of DNA into the blood, which is referred to as cell-free DNA. Cell-free DNA from nonmalignant cells is released by apoptosis. Most cell-free tumor DNA is derived from apoptotic and/or necrotic tumor cells, either from the primary tumor, metastases, or CTCs.¹ Unlike apoptosis, necrosis is considered a pathologic process and generates larger DNA fragments due to incomplete and random digestion of genomic DNA. The length or integrity of the circulating DNA can potentially distinguish between apoptotic and necrotic origin. Circulating tumor DNA can be used for genomic characterization of the tumor.

Circulating Tumor Cells

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

OBJECTIVE

The objective of this evidence review is to determine whether biomarker testing using tissue biopsy, circulating tumor DNA testing, or circulating tumor cells improves the net health outcome in patients with metastatic, inoperable, or recurrent breast cancer. This policy does not address testing of germline variants (see 2.04.02).

POLICY STATEMENT

PIK3CA Testing

PIK3CA testing may be **medically necessary** to predict treatment response to alpelisib (Piqray) in patients with hormone receptor-positive, HER2 negative advanced or metastatic breast cancer who have progressed on or after an endocrine-based regimen (see Policy Guidelines).

- When tumor tissue is available, use of tissue for testing is preferred but is not required (see Circulating Tumor DNA Testing below).

PIK3CA testing of tissue in patients with breast cancer is considered **investigational** in all other situations.

NTRK Gene Fusion Testing

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).

Analysis of *NTRK* gene fusions in patients with breast cancer is considered **investigational** in all other situations.

PD-L1 Testing

PD-L1 testing may be considered **medically necessary** to predict treatment response to atezolizumab (Tecentriq) in patients with hormone receptor-negative/HER2-negative (triple negative) metastatic or unresectable breast cancer (see Policy Guidelines).

PD-L1 testing may be considered **medically necessary** to predict treatment response to pembrolizumab (Keytruda) in patients with hormone receptor-negative/HER2-negative (triple negative) recurrent or metastatic breast cancer (see Policy Guidelines).

PD-L1 testing in patients with breast cancer is considered **investigational** in all other situations

MSI-H/dMMR Testing

MSI-H/dMMR testing may be considered **medically necessary** to predict treatment response to pembrolizumab (Keytruda) in patients with unresectable or metastatic breast cancer that has progressed following standard treatment and who have no alternative treatment option (see Policy Guidelines).

MSI-H/dMMR testing in patients with breast cancer is considered **investigational** in all other situations.

Tumor Mutational Burden Testing

Tumor mutational burden testing to predict response to immunotherapy in patients with breast cancer is considered **investigational**.

Circulating Tumor DNA Testing (Liquid Biopsy)

PIK3CA testing using FoundationOne Liquid CDx may be considered **medically necessary** to predict treatment response to alpelisib (Piqray) in patients with hormone receptor-positive, HER2 negative advanced or metastatic breast cancer who have progressed on or after an endocrine-based regimen(see Policy Guidelines).

- When tumor tissue is available, use of tissue for testing is preferred but is not required.

The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.

Circulating tumor DNA testing in patients with breast cancer is considered **investigational** in all other situations.

Circulating Tumor Cell Testing

Analysis of circulating tumor cells to select treatment in patients with breast cancer is considered **investigational**.

POLICY GUIDELINES

This policy does not address testing of germline variants (see 2.04.02).

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

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

FDA 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 recurrent or metastatic breast cancer (including immunotherapy) and the FDA approved companion diagnostic tests associated with each.

The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.

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

Treatment	Class	Indications in Breast Cancer	Companion Diagnostic
ado-trastuzumab emtansine (Kadcyla)	HER2-targeted antibody and microtubule inhibitor conjugate	As a single agent, for: <ul style="list-style-type: none"> Treatment of patients with HER2-positive, metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either: <ul style="list-style-type: none"> received prior therapy for metastatic disease, or developed disease recurrence during or within 6 months of completing adjuvant therapy. Adjuvant treatment of patients with HER2-positive early breast cancer who have residual invasive disease after neoadjuvant taxane and trastuzumab-based treatment. 	FoundationOne CDx HER2 FISH pharmDx Kit HercepTest INFORM HER2 Dual ISH DNA Probe Cocktail PATHWAY anti-Her2/neu (4B5) Rabbit Monoclonal Primary Antibody
Alpelisib (Piqray)	Kinase inhibitor	In combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA-mutated, advanced or metastatic breast cancer as detected by an FDA approved test following progression on or after an endocrine-based regimen	FoundationOne CDx FoundationOne Liquid CDx therascreen PIK3CA RGQ PCR Kit
Atezolizumab (Tecentri)	PD-L1 blocking antibody	In combination with paclitaxel protein-bound for the treatment of adult patients with unresectable locally advanced or metastatic TNBC whose tumors express PD-L1, as determined by an FDA approved test.	VENTANA PD-L1(SP142) Assay
Entrectinib (Rozlytrek)	Kinase inhibitor	Adult and pediatric patients 12 years of age and older with solid tumors that: <ul style="list-style-type: none"> have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have progressed following treatment or have no satisfactory alternative therapy 	No FDA approved companion diagnostic test
Larotrectinib (Vitrakvi)	Kinase inhibitor	Adult and pediatric patients 12 years of age and older with solid tumors that: <ul style="list-style-type: none"> have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have progressed following treatment or have no satisfactory alternative therapy 	FoundationOne CDx
Olaparib (Lynparza)	PARP inhibitor	Adult patients with deleterious or suspected deleterious germline BRCA mutated, HER2-negative metastatic breast cancer who have been treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting. Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine therapy. Select patients for therapy based on an FDA approved companion diagnostic for Lynparza.	BRACAnalysis CDx

The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.

Pembrolizumab (Keytruda)	PD-L1-blocking antibody	<ul style="list-style-type: none"> 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
		<ul style="list-style-type: none"> 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 	No FDA approved companion diagnostic test
		<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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 <ul style="list-style-type: none"> 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
Talzenna (Talazoparib)	PARP inhibitor	Adult patients with deleterious or suspected deleterious germline BRCA-mutated HER2-negative locally advanced or metastatic breast cancer.	BRACAnalysis CDx
Trastuzumab (Herceptin)	HER2/neu receptor antagonist	The treatment of HER2-overexpressing breast cancer	Bond Oracle HER2 IHC System FoundationOne CDx HER2 CISH pharmDx Kit HER2 FISH pharmDx Kit HercepTest INFORM HER-2/neu INFORM HER2 Dual ISH DNA Probe Cocktail InSite Her-2/neu KIT PathVysion HER-2 DNA Probe Kit PATHWAY anti-Her2/neu (4B5) Rabbit Monoclonal Primary Antibody SPOT-LIGHT HER2 CISH Kit VENTANA HER2 Dual ISH DNA Probe Cocktail

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

The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.

triple-negative breast cancer

Sources: [4,5](#)

RATIONALE

Summary of Evidence

For individuals with hormone receptor-positive, HER2 negative advanced or metastatic breast cancer who receive *PIK3CA* gene testing to select targeted treatment, the evidence includes a randomized, placebo-controlled trial of alpelisib compared to placebo in men and postmenopausal women with advanced breast cancer who had previously received endocrine therapy. Relevant outcomes include overall survival, disease-specific survival, test validity, quality of life, and treatment-related morbidity. Among patients with *PIK3CA*-positive tumors who received targeted therapy, PFS was 11.0 months (95% CI, 7.5 to 14.5), compared to 5.7 months (95% CI, 3.7 to 7.4) in *PIK3CA*-positive patients who received standard care. In contrast, the hazard ratio for PFS in the cohort without *PIK3CA*-mutated cancer was not significantly different for the active vs placebo groups. The overall response rate was higher in patients with *PIK3CA*-positive tumors compared to the rate in the standard care group (26.6% [95% CI [20.1- 34.0] vs 12.8% [8.2-18.7%]). The evidence is sufficient to determine that the technology results in an improvement in the net health outcomes.

For individuals with locally advanced or metastatic breast cancer being considered for immunotherapy who receive *NTRK* gene fusion testing, the evidence includes integrated analyses of nonrandomized trials of larotrectinib and entrectinib in patients with *NTRK*-fusion positive solid tumors. Relevant outcomes are OS, disease-specific survival, test validity, QOL, and treatment-related morbidity. In an analysis of 159 patients with *NTRK*-fusion positive solid tumors who received larotrectinib, including 5 patients with breast tumors, the overall response rate was 79% (95% CI 72 to 85). The median PFS was 283 months (95% CI 22.1 to not estimable), and 67% of patients were progression-free at 12 months (95% CI 58 - 76). In an integrated analysis of 3 phase 1-2 trials in 54 patients with *NTRK*-positive solid tumors who received entrectinib, 6 of whom had breast cancer, the overall response rate was 57% (95% CI 43.2 - 70.8). At data cutoff, 16 (30%) of 54 patients had died, and the estimated median overall survival was 21 months (95% CI 14.9 to not estimable). Responses were observed regardless of tumor type or age of the patient. The evidence is sufficient to determine that the technology results in an improvement in the net health outcomes.

For individuals with recurrent, metastatic, or unresectable hormone receptor-negative, HER2 negative (triple negative) breast cancer being considered for immunotherapy who receive PD-L1 testing, the evidence includes a RCT of atezolizumab and nonrandomized trials of pembrolizumab. Relevant outcomes include overall survival, disease-specific survival, test validity, quality of life, and treatment-related morbidity. In a placebo controlled trial of atezolizumab in combination with nab-paclitaxel for patients with PD-L1 positive TNBC, median PFS (HR 0.62; 95% CI, 0.49 to 0.78) and OS 0.62 (95% CI, 0.45 - 0.86) were longer among patients who received the targeted immunotherapy. In 2 nonrandomized trials of pembrolizumab for patients with PD-L1 positive TNBC, the objective response rate was 21.4% (95% CI, 13.9 to 31.4) and 18.5% (95% CI, 6.3 to 38.1). The evidence is sufficient to determine that the technology results in an improvement in the net health outcomes.

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

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

The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.

receiving immunotherapy. These results need to be confirmed in additional, well-designed prospective studies. The evidence is insufficient to determine that the technology results in an improvement in the net health outcomes.

For individuals with hormone receptor-positive, HER2 negative advanced or metastatic breast cancer who receive circulating tumor DNA testing to select targeted treatment, the evidence includes a randomized, placebo-controlled trial of alpelisib compared to placebo in men and postmenopausal women with advanced breast cancer who had previously received endocrine therapy. Relevant outcomes include overall survival, disease-specific survival, test validity, quality of life, and treatment-related morbidity. Clinical validity of the FoundationOne Liquid CDx test was demonstrated through retrospective testing of plasma samples of patients enrolled in the SOLAR-1 trial. The positive predictive agreement and negative predictive agreement between FoundationOne Liquid CDx and the tissue-based assay were 71.7% (95% CI 65.4%, 77.5%) and 100% (97.2%, 100%), respectively. Among the circulating tumor DNA-positive population, there was an estimated 54% risk reduction in disease progression or death in the alpelisib plus fulvestrant arm compared to the placebo plus fulvestrant arm (HR = 0.46, 95% CI: 0.30, 0.70). The evidence is sufficient to determine that the technology results in an improvement in the net health outcomes.

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

SUPPLEMENTAL INFORMATION

Professional Society Guidelines

National Comprehensive Cancer Network

Table 2 summarizes National Comprehensive Cancer Network guidelines (v.6.2020) on biomarker testing for the biomarkers included in this policy.¹ The guidelines state that the use of circulating tumor cells or circulating tumor DNA in metastatic breast cancer is not yet included in algorithms for disease assessment and monitoring. For patients being considered for treatment with alpelisib, testing for PIK3CA with either tissue or liquid biopsy is recommended (category of evidence 2A). The guidelines do not address TMB testing.

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

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

The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.

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

Source: Adapted from National Comprehensive Cancer Network guidelines on Breast Cancer (v.6.2020)¹

REFERENCES

1. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Breast Cancer. Version 6,2020. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed November 20, 2020.
2. Bonneville R, Krook MA, Chen HZ, et al. Detection of Microsatellite Instability Biomarkers via Next-Generation Sequencing. *Methods Mol Biol.* 2020; 2055: 119-132. PMID 31502149
3. Merino DM, McShane LM, Fabrizio D, et al. Establishing guidelines to harmonize tumor mutational burden (TMB): in silico assessment of variation in TMB quantification across diagnostic platforms: phase I of the Friends of Cancer Research TMB Harmonization Project. *J Immunother Cancer.* Mar 2020; 8(1). PMID 32217756
4. US Food & Drug Administration. Drugs@FDA: FDA-Approved Drugs. <https://www.accessdata.fda.gov/scripts/cder/daf/>. Accessed February 15, 2021.
5. US Food & Drug Administration. List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools). <https://www.fda.gov/medical-devices/vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-vitro-and-imaging-tools>. Accessed November 30, 2020.
6. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer.* Jan 2009; 45(2): 228-47. PMID 19097774
7. Wen PY, Macdonald DR, Reardon DA, et al. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. *J Clin Oncol.* Apr 10 2010; 28(11): 1963-72. PMID 20231676
8. Andre F, Ciruelos E, Rubovszky G, et al. Alpelisib for PIK3CA -Mutated, Hormone Receptor-Positive Advanced Breast Cancer. *N Engl J Med.* May 16 2019; 380(20): 1929-1940. PMID 31091374
9. Doebele RC, Drilon A, Paz-Ares L, et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. *Lancet Oncol.* Feb 2020; 21(2): 271-282. PMID 31838007
10. Hong DS, DuBois SG, Kummar S, et al. Larotrectinib in patients with TRK fusion-positive solid tumours: a pooled analysis of three phase 1/2 clinical trials. *Lancet Oncol.* Apr 2020; 21(4): 531-540. PMID 32105622
11. Drilon A, Laetsch TW, Kummar S, et al. Efficacy of Larotrectinib in TRK Fusion-Positive Cancers in Adults and Children. *N Engl J Med.* Feb 22 2018; 378(8): 731-739. PMID 29466156
12. Schmid P, Adams S, Rugo HS, et al. Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer. *N Engl J Med.* Nov 29 2018; 379(22): 2108-2121. PMID 30345906
13. Adams S, Loi S, Toppmeyer D, et al. Pembrolizumab monotherapy for previously untreated, PD-L1-positive, metastatic triple-negative breast cancer: cohort B of the phase II KEYNOTE-086 study. *Ann Oncol.* Mar 01 2019; 30(3): 405-411. PMID 30475947
14. Nanda R, Chow LQ, Dees EC, et al. Pembrolizumab in Patients With Advanced Triple-Negative Breast Cancer: Phase Ib KEYNOTE-012 Study. *J Clin Oncol.* Jul 20 2016; 34(21): 2460-7. PMID 27138582

The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.

15. Marabelle A, Le DT, Ascierto PA, et al. Efficacy of Pembrolizumab in Patients With Noncolorectal High Microsatellite Instability/Mismatch Repair-Deficient Cancer: Results From the Phase II KEYNOTE-158 Study. *J Clin Oncol*. Jan 01 2020; 38(1): 1-10. PMID 31682550
16. Le DT, Uram JN, Wang H, et al. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. *N Engl J Med*. Jun 25 2015; 372(26): 2509-20. PMID 26028255
17. Ott PA, Bang YJ, Piha-Paul SA, et al. T-Cell-Inflamed Gene-Expression Profile, Programmed Death Ligand 1 Expression, and Tumor Mutational Burden Predict Efficacy in Patients Treated With Pembrolizumab Across 20 Cancers: KEYNOTE-028. *J Clin Oncol*. Feb 01 2019; 37(4): 318-327. PMID 30557521
18. Marabelle A, Fakih M, Lopez J, et al. Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study. *Lancet Oncol*. Oct 2020; 21(10): 1353-1365. PMID 32919526
19. Woodhouse R, Li M, Hughes J, et al. Clinical and analytical validation of FoundationOne Liquid CDx, a novel 324-Gene cfDNA-based comprehensive genomic profiling assay for cancers of solid tumor origin. *PLoS One*. 2020; 15(9): e0237802. PMID 32976510
20. Bidard FC, Peeters DJ, Fehm T, et al. Clinical validity of circulating tumour cells in patients with metastatic breast cancer: a pooled analysis of individual patient data. *Lancet Oncol*. Apr 2014; 15(4): 406-14. PMID 24636208
21. Smerage JB, Barlow WE, Hortobagyi GN, et al. Circulating tumor cells and response to chemotherapy in metastatic breast cancer: SWOG S0500. *J Clin Oncol*. Nov 01 2014; 32(31): 3483-9. PMID 24888818
22. Bidard FC, Jacot W, Kiavue N, et al. Efficacy of Circulating Tumor Cell Count-Driven vs Clinician-Driven First-line Therapy Choice in Hormone Receptor-Positive, ERBB2-Negative Metastatic Breast Cancer: The STIC CTC Randomized Clinical Trial. *JAMA Oncol*. Nov 05 2020. PMID 33151266

POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
March 2021	New policy	Policy created with literature review on November 20, 2020. Policy statements included for: testing for PIK3CA, NTRK Gene Fusions, PD-L1, MSI-H/dMMR, Tumor Mutational Burden, Circulating Tumor DNA, and Circulating Tumor Cells.

The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.