BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

FEP 2.04.151 Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Breast Cancer (BRCA1, BRCA2, PIK3CA, Ki-67, RET, BRAF, ESR1)

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Related Policies:

2.04.02 - Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers (BRCA1, BRCA2, PALB2)
2.04.115 - Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies
2.04.141 - Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy)
2.04.157 - Somatic Biomarker Testing for Immune Checkpoint Inhibitor Therapy (BRAF, MSI/MMR, PD-L1, TMB)
2.04.36 - Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis in Patients with Breast Cancer
5.01.12 - Trastuzumab
5.01.22 - Ado-Trastuzumab Emtansine (Trastuzumab-DM1) for Treatment of HER2-Positive Malignancies
5.01.31 - Tropomyosin Receptor Kinase Inhibitors for Locally Advanced or Metastatic Solid Tumors Harboring an NTRK Gene Fusion
5.21.134-Rozlytrek (entrectinib); 5.21.122- Vitrakvi (larotrectinib); 5.21.80- Keytruda (pembrolizumab); 5.21.128-Piqray (alpelisib); 5.21.037- Tafinlar (dabrafenib)
5.21.52- Lynparza (olaparib); 5.21.119- Talenza (talazopaarib); 5.21.174-Jemperli (dostarlimab-gxly); 5.21.104- Verzenio (abemaciclib); 5.21.148 Retevmo- (selpercatinib)

Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Breast Cancer (BRCA1, BRCA2, PIK3CA, Ki-67, RET, BRAF, ESR1)

Description

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

PIK3CA Testing

Alterations in the protein coding gene *PIK3CA* (Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha) occur in approximately 40% of patients with hormone receptor (HR)-positive, HER2-negative breast cancer.[16,]

Ki-67

Ki-67 is a nuclear protein used to detect and quantify the rate of tumor cell proliferation and has been investigated as a prognostic biomarker for breast cancer.[17,]

Rearranged During Transfection

The REarranged during Transfection (RET) proto-oncogene encodes a receptor tyrosine kinase growth factor.[18,] Translocations that result in fusion genes with several partners have been reported, and occur in about 5-10% of thyroid cancer cases (primarily papillary thyroid carcinoma) and 1%-2% of non-small-cell lung cancer cases. RET fusions in breast cancer, occur in less than 1% of cases.[19,]

BRAF

RAF proteins are serine/threonine kinases that are downstream of RAS in the RAS-RAF-ERK-MAPK pathway. The most common mutation locus is found in codon 600 of exon 15 (V600E) of the BRAF gene, causing constitutive hyperactivation, proliferation, differentiation, survival, and oncogenic transformation.[20,] BRAF mutations occur in approximately 1% of breast cancer cases.[21,]

ESR1

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

Circulating Tumor DNA

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

Circulating Tumor Cells

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

OBJECTIVE

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

POLICY STATEMENT

BRCA1 and BRCA2 Testing

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

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.

PIK3CA Testing

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

- 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 individuals with breast cancer is considered **investigational** in all other situations.

Ki-67 Testing

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

RET Testing

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

BRAF Testing

BRAF testing to predict treatment response to dabrafenib (Tafinlar) plus trametinib (Mekinist) in individuals 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 individuals with hormone receptor-positive, HER2 negative advanced or metastatic breast cancer who have progressed on or after an endocrine-based regimen (see Policy Guidelines).

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

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

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

Circulating Tumor Cell Testing

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

Other

Testing for other variants may become available between policy updates.

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. The use of tropomyosin receptor kinase (TRK) inhibitors for individuals with neurotrophic tyrosine receptor kinase (NTRK) gene fusion-positive solid tumors is addressed separately in evidence review 5.01.31.

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

This policy does not address HER2 testing. Agents targeted against HER2 with approved companion diagnostic tests include monoclonal antibodies (margetuximab, pertuzumab, trastuzumab) and antibody-drug conjugates (ado-trastuzumab emtansine, fam-trastuzumab deruxtecan), which are not true targeted therapies. The use of ado-trastuzumab emtansine is addressed separately in evidence review 5.01.22.

For expanded panel testing, see evidence review 2.04.115.

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.

FDA approves tests in between policy review cycles. As such, newly approved tests might need to be considered per local Plan discretion. 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.

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.

BENEFIT APPLICATION

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

Some Plans may have contract or benefit exclusions for genetic testing.

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 breast cancer (including immunotherapy) and the FDA cleared or approved companion diagnostic tests associated with each. The information in Table 1 was current as of October 25, 2023. An up-to-date list of FDA cleared or approved companion diagnostics is available at https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools.

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

Treatment	Class	Indications in Breast Cancer	Companion Diagnostic	Pivotal Studies	NCCN Breast Cancer Guideline (V4.2023) Recommendation Level[24,]
Abemaciclib (Verzenio)[a]	Cyclin-dependent kinase (CDK) 4/6 inhibitor	• In combination with endocrine therapy (tamoxifen or an aromatase inhibitor) for the adjuvant treatment of adult patients with HR-positive, HER2-negative, node-positive, early breast cancer at high risk of recurrence. • In combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women, and men, with HR-positive, HER2-negative advanced or metastatic breast cancer. • In combination with fulvestrant for the treatment of adult patients with HR-positive, HER2-negative advanced or metastatic breast cancer with disease 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)	Adjuvant therapy: monarchE (NCT03155997)[25,26,] Initial endocrine-based therapy for advanced or metastatic disease: MONARCH 3 (NCT02246621)[27,] With fulvestrant for progressive advanced or metastatic disease: MONARCH 2 (NCT02107703)[28,29,] Monotherapy for progressive advanced or metastatic disease: MONARCH 1 (NCT02102490)[30,]	Adjuvant therapy: 1 (Ki-67 testing is not required - see footnote[a]) Initial endocrine-based therapy for advanced or metastatic disease: 1 (in combination with fulvestrant), 2A (in combination with aromatase inhibitor) With fulvestrant for progressive advanced or metastatic disease: 1 Monotherapy for progressive advanced or metastatic disease: 2A
Ado-trastuzumab emtansine (Kadcyla)[b]	HER2-targeted antibody and microtubule inhibitor conjugate	As a single agent, for: • Treatment of patients with HER2-positive, metastatic breast cancer who previously	FoundationOne CDx HER2 FISH pharmDx Kit HercepTest	Metastatic disease: EMILIA (NCT00829166)[31,] Adjuvant therapy:	Metastatic disease: 2A Adjuvant therapy: 1

		received trastuzumab and a taxane, separately or in combination. Patients should have either: ○ received prior therapy for metastatic disease, or ○ developed disease recurrence during or within 6 months of completing adjuvant therapy. • Adjuvant treatment of patients with HER2-positive early breast cancer who have residual invasive disease after neoadjuvant taxane and trastuzumab-based treatment.	INFORM HER2 Dual ISH DNA Probe Cocktail PATHWAY anti-Her2/neu (4B5) Rabbit Monoclonal Primary Antibody	KATHERINE (NCT01772472)[32,]	
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	SOLAR-1 (NCT02437318)[33,]	1
Dabrafenib (Tafinlar) + Trametinib (Mekinist)	Kinase inhibitors	Adult and pediatric patients 1 year of age and older with unresectable or metastatic solid tumors with BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options	No FDA approved companion diagnostic	ROAR (NCT02034110)[34,] NCI-MATCH arm H (NCT02465060)[35,]	N/A
Dostarlimab-gxly (Jemperli)[c]	PD-1 blocking antibody	Adult patients with dMMR recurrent or advanced solid tumors, as determined by an FDA-approved test, that has progressed on or following prior treatment and who have no satisfactory alternative treatment options	VENTANA MMR RxDx Panel	GARNET (NCT02715284)[36,]	2A

Elacestrant (Orserdu)	ER antagonist/SERD	Postmenopausal women or adult men with ER-positive, HER2-negative, *ESR1*-mutated advanced or metastatic breast cancer with disease progression following at least 1 line of endocrine therapy	Guardant360 CDx	EMERALD (NCT03778931)[37],	2A
Entrectinib (Rozlytrek)[d]	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	ALKA (EudraCT 2012-000148-88), STARTRK-1 (NCT02097810), and STARTRK-2 (NCT02568267)[38],	2A
Fam-trastuzumab deruxtecan-nxki (Enhertu)[e]	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	HER2-positive metastatic disease: DESTINY-Breast03 (NCT03529110)[39], HER2-low metastatic disease: DESTINY-Breast04 (NCT03734029)[40],	1

Larotrectinib (Vitrakvi)[d]	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	LOXO-TRK-14001 (NCT02122913), SCOUT (NCT02637687), and NAVIGATE (NCT02576431)[41],	2A
Olaparib (Lynparza)	PARP inhibitor	• Adjuvant treatment of adults with deletrious or suspected deleterious germline BRCA mutated, HER2-negative high risk early breast cancer who have been treated with neoadjuvant or adjuvant chemotherapy • Treatment of adults with deleterious or suspected deleterious germline BRCA mutated, HER-negative metastatic breast cancer who have been treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic setting. Patients with HR-positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine therapy.	BRACAnalysis CDx FoundationOne CDx	Adjuvant therapy: OlympiA (NCT02032823)[42], Metastatic disease: OlympiAD (NCT02000622)[43],	Adjuvant therapy: 2A Metastatic disease: 1
Pembrolizumab (Keytruda)[c]	PD-L1-blocking antibody	• Neoadjuvant treatment of high-risk, early-stage TNBC in combination with chemotherapy, then continued as a single	PD-L1 IHC 22C3 pharmDx	Neoadjuvant/adjuvant therapy: KEYNOTE-522 (NCT03036488)[44], Unresectable/metastatic disease: KEYNOTE-355 (NCT02819518)[45],	Neoadjuvant/adjuvant therapy: 2A Unresectable/metastatic disease: 1

		agent as adjuvant therapy • 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			
		Adult and pediatric patients with unresectable or metastatic, microsatellite instability-high or mismatch repair deficient solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options	FoundationOne CDx	KEYNOTE-158 (NCT02628067)[46],	2A
		Adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (≥10 mutations/megabase) solid tumors, as determined by an FDA approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options.	FoundationOne CDx (Solid tumors TMB ≥ 10 mutations per megabase)	KEYNOTE-158 (NCT02628067)[47],	2A
Pertuzumab (Perjeta)[f]	HER2/neu receptor antagonist	Use in combination with trastuzumab and docetaxel for treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease. Use in combination with trastuzumab and chemotherapy as: • Neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer.	HER2 FISH pharmDx Kit HercepTest FoundationOne CDx	Metastatic disease: CLEOPATRA (NCT00567190)[48], Neoadjuvant therapy: NeoSphere (NCT00545688)[49], Adjuvant therapy: APHINITY (NCT01358877)[50],	Metastatic disease: 1 Neoadjuvant/adjuvant therapy: 1 or 2A (regimen-specific)

		• Adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence			
Selpercatinib (Retevmo)	Kinase inhibitor	Adult patients with locally advanced or metastatic solid tumors with a RET gene fusion that have progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options	No FDA-approved companion diagnostic test	LIBRETTO-001 (NCT03157128)[51],	2A
Talazoparib (Talzenna)	PARP inhibitor	Adult patients with deleterious or suspected deleterious germline BRCA-mutated HER2-negative locally advanced or metastatic breast cancer	BRACAnalysis CDx	EMBRACA (NCT01945775)[52],	1
Trastuzumab (Herceptin)[g]	HER2/neu receptor antagonist	• Adjuvant treatment of HER2-overexpressing node-positive or node-negative (HR-negative or with 1 high-risk feature) breast cancer as part of a regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel; as part of a regimen with docetaxel and carboplatin; or as a single agent following multi-modality anthracycline-based therapy • Treatment of metastatic HER2-overexpressing breast cancer in combination with paclitaxel (first-line treatment) or as a single agent (after 1 or more chemotherapy regimens for metastatic disease)	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	Adjuvant therapy: BCIRG-006 (NCT00021255)[53], Metastatic disease: CLEOPATRA (NCT00567190)[48],	Adjuvant therapy: 1 or 2A (regimen-specific) Metastatic disease: 1 or 2A (regimen-specific)

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

[b] Covered in Policy 5.01.22.

[c] Covered in Policy 2.04.157.

[d] Covered in Policy 5.01.31.

[e] Placement of fam-trastuzumab deruxtecan-nxki (Enhertu) in the reference medical policy library is under current discussion.

[f] Covered in Policy 5.01.20.

[g] Covered in Policy 5.01.12.

dMMR: mismatch repair deficient; ER: estrogen receptor; FDA: U.S. Food & Drug Administration; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; MSI-H: microsatellite instability-high; N/A: not applicable;NCCN: National Comprehensive Cancer Network; NTRK: neurotrophic-tropomyosin receptor kinase; PD-1: programmed death receptor-1; PD-L1: programmed death-ligand 1; PIK3CA: phosphatidylinositol 3-kinase catalytic alpha polypeptide; SERD: selective estrogen receptor degrader; TNBC: triple-negative breast cancer

Sources: [54,55,]

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

Summary of Evidence

For individuals with metastatic or high-risk, early stage HER2-negative breast cancer being considered for systemic therapy (ie, poly(adenosine diphosphate - ribose) polymerase [PARP] inhibitors) who receive genetic testing for a *BRCA1* or *BRCA2* germline variant, the evidence includes FDA-approved therapeutics with National Comprehensive Cancer Network (NCCN) recommendations of 2A or higher and was not extensively evaluated. The evidence includes the pivotal studies leading to the U.S. Food and Drug Administration (FDA) and National Comprehensive Cancer Network (NCCN) recommendations.

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 FDA-approved therapeutics with NCCN recommendations of 2A or higher and was not extensively evaluated. The evidence includes the pivotal studies leading to the FDA and NCCN recommendations.

For individuals with breast cancer who are being considered for abemaciclib therapy who receive Ki-67 testing, the evidence includes a randomized, controlled, open-label trial. Relevant outcomes include overall survival, disease-specific survival, test validity, quality of life, and treatment-related morbidity. Among patients with hormone receptor-positive, HER2-negative, node-positive, early breast cancer with clinical and pathological features consistent with a high risk of recurrence (n=5637), abemaciclib plus endocrine therapy demonstrated superior invasive disease-free survival compared to endocrine therapy alone (hazard ratio [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 intention-to-treat (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 'high' versus 'low' status. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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

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

For individuals with hormone receptor-positive, HER2-negative advanced or metastatic breast cancer who receive circulating tumor DNA testing to select targeted treatment, the evidence includes FDA-approved therapeutics with NCCN recommendations of 2A or higher and was not extensively evaluated. The evidence includes the pivotal studies leading to the FDA and NCCN recommendations.

For individuals with metastatic breast cancer who receive circulating tumor cell (CTC) testing to guide treatment decisions, the evidence includes randomized controlled trials (RCTs) , observational studies, and systematic reviews. Relevant outcomes include overall survival, disease-specific survival, test validity, quality of life, and treatment-related morbidity. Systematic reviews and meta-analyses have described an association between CTCs and poor prognosis in metastatic breast cancer, but evidence that CTC-driven treatment improves health outcomes is lacking. One RCT found no improvement in overall survival or progression-free survival (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% confidence interval 0.81 to 1.09). The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given 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.[70,] The guideline recommended the following biomarker tests:

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

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

Detailed recommendations are as follows:

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

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

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

A rapid update to the ASCO guideline was published in March 2023 to address *ESR1* testing (which was not recommended in the previous version).[71,] The guideline recommended routine testing for *ESR1* mutations at the time of disease recurrence or progression while receiving endocrine therapy, with or without a concomitant CDK4/6 inhibitor, in patients with estrogen receptor-positive, HER2-negative metastatic breast cancer (Type of recommendation: evidence-based; Evidence quality: high; Strength of recommendation: strong). Testing should be performed with blood or tissue obtained at the time of progression, as *ESR1* alterations develop via selective pressure from treatment and are unlikely to be detected in the primary tumor. Blood-based ctDNA is preferred due to greater sensitivity.

National Comprehensive Cancer Network

Table 2 summarizes National Comprehensive Cancer Network guidelines (v. 4.2023) on biomarker testing for the biomarkers included in this policy.[24,] The guidelines state that the use of circulating tumor cells or circulating tumor DNA in metastatic breast cancer is not yet included in algorithms for disease assessment and monitoring. For patients being considered for treatment with alpelisib, testing for *PIK3CA* with either tissue or liquid biopsy is recommended (category 1 recommendation). For patients being considered for treatment with elacestrant, testing for *ESR1* with liquid biopsy is recommended (category 2A recommendation).

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

Biomarker	Breast Cancer Subtype	FDA Approved Agents	Testing Recommendation	Targeted Therapy Category of Evidence	Targeted Therapy Category of Preference
BRCA1/2 mutations	Any	Olaparib Talazoparib	Patients with recurrent or metastatic breast cancer should be assessed for *BRCA1/2* mutations with germline sequencing to identify candidates for PARP inhibitor therapy. While olaparib and talazoparib are FDA-indicated in HER2-negative	1	Preferred

			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
ESR1 mutation	HR-positive/HER2-negative	Elacestrant	For postmenopausal females or adult males with ER-positive, HER2-negative, *ESR1*-mutated disease after progression on one or two prior lines of endocrine therapy, including one line containing a CDK4/6 inhibitor. Blood testing is recommended.	2A	Other recommended regimen
PD-L1 expression (combined positive score ≥10)	Triple negative	Pembrolizumab + chemotherapy (albumin-bound paclitaxel, or gemcitabine and carboplatin)	For triple-negative breast cancer, assess PD-L1 expression using 22C3 antibody via immunohistochemistry. While available data are in the first-line setting, this regimen can be used for second and subsequent lines of therapy if PD-1/PD-L1 inhibitor therapy has not been previously used.	1	Preferred first-line therapy
MSI-H/dMMR	Any	Pembrolizumab Dostarlimab-gxly	Biomarker detection via immunohistochemistry or PCR tissue block is recommended. If a patient with unresectable or metastatic MSI-H/dMMR breast cancer has progressed on or following prior treatment with no satisfactory alternative treatment options, pembrolizumab or dostarlimab-gxly are indicated.	2A	Useful in certain circumstances
TMB-H (≥10 mut/mb)	Any	Pembrolizumab	Biomarker detection via NGS is indicated in patients with unresectable or metastatic TMB-H tumors that have progressed following prior treatment and who have no satisfactory treatment options.	2A	Useful in certain circumstances
RET-fusion	Any	Selpercatinib	Biomarker detection via NGS is recommended in adult patients with locally advanced or metastatic solid tumors that have progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options.	2A	Useful in certain circumstances

Source: Adapted from National Comprehensive Cancer Network guidelines on Breast Cancer (v. 4.2023)[24,]

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).[72,]

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.

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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.
March 2022	Replace policy	Policy updated with literature review through November 8, 2021; references added. Investigational policy statements added for MSI-H/dMMR testing for dostarlimab-gxly, and PD-L1 testing for atezolizumab. Medically necessary policy statements and rationale for BRCA1/2 testing to predict treatment response to PARP inhibitors were migrated into this policy from evidence review 2.04.02. Medically necessary policy statement added for Ki-67 testing for abemaciclib to correlate with FEP pharmacy policy 5.20.104. Policy title updated to reflect both germline and somatic biomarker testing.
March 2023	Replace policy	Policy updated with literature review through October 24, 2022; references added. Evidence on the use of atezolizumab in individuals with triple negative PD-L1 positive breast cancer removed from policy, as in 2021 Genentech voluntarily withdrew accelerated approval of atezolizumab for use in these individuals.
March 2024	Replace policy	Policy updated with literature review through October 25, 2023; references added. Evidence review extensively pruned. Evidence on PD-L1, MSI-H/dMMR, and tumor mutational burden testing for immunotherapy removed as it is covered in evidence review 2.04.157. Pivotal studies and NCCN recommendations added to Table 1. Minor editorial change to PIK3CA policy statement; intent unchanged. Liquid biopsy testing for ESR1 incorporated into circulating tumor DNA indication, with corresponding updates to policy statements and guidelines. Other policy statements unchanged. Language added to policy guidelines to clarify that HER2 testing is not addressed in this review. Policy title and objective updated to reflect that only testing for targeted therapy is reviewed.