

Medical Policy



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

Related Policies:	<ul style="list-style-type: none">• Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers (BRCA1, BRCA2, PALB2)• Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies• Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy)• Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis in Patients with Breast Cancer
-------------------	--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

Professional / Institutional
Original Effective Date: March 10, 2022
Latest Review Date: January 23, 2024
Current Effective Date: January 23, 2024

State and Federal mandates and health plan member contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. To verify a member's benefits, contact [Blue Cross and Blue Shield of Kansas Customer Service](#).

The BCBSKS Medical Policies contained herein are for informational purposes and apply only to members who have health insurance through BCBSKS or who are covered by a self-insured group plan administered by BCBSKS. Medical Policy for FEP members is subject to FEP medical policy which may differ from BCBSKS Medical Policy.

The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents of Blue Cross and Blue Shield of Kansas and are solely responsible for diagnosis, treatment and medical advice.

If your patient is covered under a different Blue Cross and Blue Shield plan, please refer to the Medical Policies of that plan.

Populations	Interventions	Comparators	Outcomes
<p>Individuals:</p> <ul style="list-style-type: none"> • With metastatic or high-risk, early stage HER2-negative breast cancer who are being considered for systemic therapy (i.e., poly(adenosine diphosphate–ribose) polymerase [PARP] inhibitors) 	<p>Interventions of interest are:</p> <ul style="list-style-type: none"> • Genetic testing for <i>BRCA1</i> or <i>BRCA2</i> germline variants 	<p>Comparators of interest are:</p> <p>Standard treatment without genetic testing for a <i>BRCA1</i> or <i>BRCA2</i> variant</p>	<p>Relevant outcomes include:</p> <ul style="list-style-type: none"> • Overall survival • Disease-specific survival • Test validity • Quality of life • Treatment-related morbidity
<p>Individuals:</p> <ul style="list-style-type: none"> • With hormone receptor-positive, HER2 negative advanced or metastatic breast cancer 	<p>Interventions of interest are:</p> <ul style="list-style-type: none"> • <i>PIK3CA</i> gene testing to select targeted treatment 	<p>Comparators of interest are:</p> <ul style="list-style-type: none"> • Standard treatment without <i>PIK3CA</i> Gene Testing 	<p>Relevant outcomes include:</p> <ul style="list-style-type: none"> • Overall survival • Disease-specific survival • Test validity • Quality of life • Treatment-related morbidity
<p>Individuals:</p> <ul style="list-style-type: none"> • With hormone receptor-positive, HER2-negative, node-positive, early breast cancer at high risk of recurrence who are being considered for adjuvant targeted therapy 	<p>Interventions of interest are:</p> <ul style="list-style-type: none"> • Ki-67 testing 	<p>Comparators of interest are:</p> <ul style="list-style-type: none"> • Standard treatment without Ki-67 testing 	<p>Relevant outcomes include:</p> <ul style="list-style-type: none"> • Overall survival • Disease-specific survival • Test validity • Quality of life • Treatment-related morbidity
<p>Individuals:</p> <ul style="list-style-type: none"> • With locally advanced or metastatic breast cancer with progression following prior treatment who are being considered for selpercatinib therapy who receive RET testing 	<p>Interventions of interest are:</p> <ul style="list-style-type: none"> • RET testing 	<p>Comparators of interest are:</p> <ul style="list-style-type: none"> • Standard treatment without RET testing 	<p>Relevant outcomes include:</p> <ul style="list-style-type: none"> • Overall survival • Disease-specific survival • Test validity • Quality of life • Treatment-related morbidity
<p>Individuals:</p> <ul style="list-style-type: none"> • With unresectable or metastatic breast cancer with progression following prior treatment who are 	<p>Interventions of interest are:</p> <ul style="list-style-type: none"> • BRAF testing 	<p>Comparators of interest are:</p> <ul style="list-style-type: none"> • Standard treatment without BRAF testing 	<p>Relevant outcomes include:</p> <ul style="list-style-type: none"> • Overall survival • Disease-specific survival • Test validity

Populations	Interventions	Comparators	Outcomes
being considered for dabrafenib and trametinib combination therapy who receive BRAF testing			<ul style="list-style-type: none"> Quality of life Treatment-related morbidity
Individuals: <ul style="list-style-type: none"> With hormone receptor-positive, HER2 negative advanced or metastatic breast cancer 	Interventions of interest are: <ul style="list-style-type: none"> Testing of circulating tumor DNA to select targeted treatment 	Comparators of interest are: <ul style="list-style-type: none"> Using tissue biopsy to select targeted treatment 	Relevant outcomes include: <ul style="list-style-type: none"> Overall survival Disease-specific survival Test validity Quality of life Treatment-related morbidity
Individuals: <ul style="list-style-type: none"> With hormone receptor-positive, HER2 negative metastatic breast cancer 	Interventions of interest are: <ul style="list-style-type: none"> Testing of circulating tumor cells (CTCs) to select targeted treatment 	Comparators of interest are: <ul style="list-style-type: none"> Standard treatment without using CTCs to select treatment 	Relevant outcomes include: <ul style="list-style-type: none"> Overall survival Disease-specific survival Test validity Quality of life Treatment-related morbidity

DESCRIPTION

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

The objective of this evidence review is to examine whether biomarker testing for *BRCA* variants, *PIK3CA*, *ESR1*, Ki-67, *RET*, *BRAF*, circulating tumor DNA, or circulating tumor cells improves the net health outcome in patients with breast cancer who are considering targeted therapy.

OBJECTIVE

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

BACKGROUND

***BRCA* Variant Testing**

The prevalence of *BRCA* variants is approximately 0.2% to 0.3% in the general population.¹ The prevalence may be much higher for particular ethnic groups with characterized founder mutations (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.² Of these, hereditary breast and ovarian cancer (HBOC) and some cases of hereditary site-specific breast cancer have in common causative variants in *BRCA* (breast cancer susceptibility) genes. Families suspected of having HBOC syndrome are characterized by an increased susceptibility to breast cancer occurring at a young age, bilateral breast cancer, male breast cancer, ovarian cancer at any age, as well as cancer of the fallopian tube and primary peritoneal cancer. Other cancers, such as prostate cancer, pancreatic cancer, gastrointestinal cancers, melanoma, and laryngeal cancer, occur more frequently in HBOC families. Hereditary site-specific breast cancer families are characterized by early-onset breast cancer with or without male cases, but without ovarian cancer. For this evidence review, BCBSKS refers collectively to both as *hereditary breast and/or ovarian cancer*.

Germline variants in the *BRCA1* and *BRCA2* genes are responsible for the cancer susceptibility in most HBOC families, especially if ovarian cancer or male breast cancer are features.³ However, in site-specific cancer, *BRCA* variants are responsible only for a proportion of affected families. *BRCA* gene variants are inherited in an autosomal dominant fashion through maternal or paternal lineage. It is possible to test for abnormalities in *BRCA1* and *BRCA2* genes to identify the specific variant in cancer cases and to identify family members at increased cancer risk. Family members without existing cancer who are found to have *BRCA* variants can consider preventive interventions for reducing risk and mortality.

Young age of onset of breast cancer, even in the absence of family history, is a risk factor for *BRCA1* variants. Winchester (1996) estimated that hereditary breast cancers account for 36% to 85% of patients diagnosed before age 30.⁴ In several studies, *BRCA* variants were independently predicted by early age at onset, being present in 6% to 10% of breast cancer cases diagnosed at ages younger than various premenopausal age cutoffs (age range, 35-50 years).^{4,5,6,7} In cancer-prone families, the mean age of breast cancer diagnosis among women carrying *BRCA1* or *BRCA2* variants is in the 40s.⁸ In the Ashkenazi Jewish population, Frank et al (2002) reported that 13% of 248 cases with no known family history and diagnosed before 50 years of age had *BRCA* variants.⁵ In a similar study by Gershoni-Baruch et al (2000), 31% of Ashkenazi Jewish women, unselected for family history, diagnosed with breast cancer at younger than 42 years of age had *BRCA* variants.⁹ Other studies have indicated that early age of breast cancer diagnosis is a significant predictor of *BRCA* variants in the absence of family history in this population.^{10,11,12}

In patients with "triple-negative" breast cancer (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.¹³ Young et al (2009) studied 54 women with high-grade, triple-negative breast cancer with no family history of breast or ovarian cancer, representing a group that previously was not recommended for *BRCA* testing.¹⁴ Six *BRCA* variants (5 *BRCA1*, 1 *BRCA2*) were found, for a variant rate of 11%. Finally, Gonzalez-Angulo et al (2011) in a study of 77 patients with triple-negative breast cancer, reported that 15 patients (19.5%) had *BRCA* variants (12 in *BRCA1*, 3 in *BRCA2*).¹⁵

***PIK3CA* Testing**

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

Ki-67

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

Rearranged During Transfection

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

BRAF

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

ESR1

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

Circulating Tumor DNA

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

Circulating Tumor Cells

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

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	<ul style="list-style-type: none"> In combination with endocrine therapy (tamoxifen or an aromatase inhibitor) for the adjuvant treatment of adult patients with HR-positive, HER2-negative, node- 	Ki-67 IHC MIB-1 pharmDx (Dako Omnis)	<p>Adjuvant therapy: monarchE (NCT03155997)^{25,26},</p> <p>Initial endocrine-based therapy for advanced or metastatic disease: MONARCH 3 (NCT02246621)²⁷,</p> <p>With fulvestrant for progressive advanced or metastatic disease: MONARCH 2</p>	<p>Adjuvant therapy: 1 (Ki-67 testing is not required - see footnote^a)</p> <p>Initial endocrine-based therapy for advanced or metastatic disease: 1 (in combination with fulvestrant), 2A (in combination with aromatase inhibitor)</p> <p>With fulvestrant for progressive</p>

Treatment	Class	Indications in Breast Cancer	Companion Diagnostic	Pivotal Studies	NCCN Breast Cancer Guideline (V4.2023) Recommendation Level ²⁴ ,
		<p>positive, early breast cancer at high risk of recurrence.</p> <ul style="list-style-type: none"> 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 		<p>(NCT02107703)^{28,29}</p> <p>Monotherapy for progressive advanced or metastatic disease: MONARCH 1 (NCT02102490)³⁰,</p>	<p>advanced or metastatic disease: 1</p> <p>Monotherapy for progressive advanced or metastatic disease: 2A</p>

Treatment	Class	Indications in Breast Cancer	Companion Diagnostic	Pivotal Studies	NCCN Breast Cancer Guideline (V4.2023) Recommendation Level ²⁴ ,
		<p>endocrine therapy.</p> <ul style="list-style-type: none"> As monotherapy for the treatment of adult patients with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting. 			
Ado-trastuzumab emtansine (Kadcyla) ^b	HER2-targeted antibody and microtubule inhibitor conjugate	<p>As a single agent, for:</p> <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: 	<p>Foundation One CDx HER2 FISH pharmDx Kit HercepTest INFORM HER2 Dual ISH DNA Probe Cocktail PATHWAY anti-Her2/neu (4B5) Rabbit Monoclonal Primary Antibody</p>	<p>Metastatic disease: EMILIA (NCT00829166)³¹, Adjuvant therapy: KATHERINE (NCT01772472)³²,</p>	<p>Metastatic disease: 2A Adjuvant therapy: 1</p>

Treatment	Class	Indications in Breast Cancer	Companion Diagnostic	Pivotal Studies	NCCN Breast Cancer Guideline (V4.2023) Recommendation Level ²⁴ ,
		<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. 			
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	Foundation One CDx Foundation One Liquid CDx therascreen PIK3CA RGQ PCR Kit	SOLAR-1 (NCT02437318) ³³ ,	1

Treatment	Class	Indications in Breast Cancer	Companion Diagnostic	Pivotal Studies	NCCN Breast Cancer Guideline (V4.2023) Recommendation Level ²⁴ ,
		by an FDA approved test following progression on or after an endocrine-based regimen			
Dabrafenib (Tafinlar) + Trametinib (Mekinist)	Kinase inhibitors	Adult and pediatric patients 1 year of age and older with unresectable or metastatic solid tumors with BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options	No FDA approved companion diagnostic	ROAR (NCT02034110) 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/S ERD	Postmenopausal women or adult men with ER-positive, HER2-negative, <i>ESR1</i> -mutated advanced or metastatic breast cancer with disease progression following at least 1 line of endocrine therapy	Guardant360 CDx	EMERALD (NCT03778931) ³⁷ ,	2A

Treatment	Class	Indications in Breast Cancer	Companion Diagnostic	Pivotal Studies	NCCN Breast Cancer Guideline (V4.2023) Recommendation Level ²⁴ ,
Entrectinib (Rozlytrek) ^d	Kinase inhibitor	<p>Adult and pediatric patients 12 years of age and older with solid tumors that:</p> <ul style="list-style-type: none"> • 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-xki (Enhertu) ^e	HER-2 targeted antibody and topoisomerase inhibitor conjugate	<ul style="list-style-type: none"> • Adult patients with unresectable or metastatic HER2-positive breast cancer who have received a prior anti-HER2-based regimen either in the metastatic 	PATHWAY anti-Her2/neu (4B5) Rabbit Monoclonal Primary Antibody	<p>HER2-positive metastatic disease: DESTINY-Breast03 (NCT03529110)³⁹,</p> <p>HER2-low metastatic disease: DESTINY-Breast04 (NCT03734029)⁴⁰,</p>	1

Treatment	Class	Indications in Breast Cancer	Companion Diagnostic	Pivotal Studies	NCCN Breast Cancer Guideline (V4.2023) Recommendation Level ²⁴ ,
		setting or in the neoadjuvant or adjuvant setting and have developed disease recurrence during or within 6 months of completing therapy <ul style="list-style-type: none"> • 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 			

Treatment	Class	Indications in Breast Cancer	Companion Diagnostic	Pivotal Studies	NCCN Breast Cancer Guideline (V4.2023) Recommendation Level ²⁴ ,
Larotrectinib (Vitrakvi) ^d	Kinase inhibitor	<p>Adult and pediatric patients 12 years of age and older with solid tumors that:</p> <ul style="list-style-type: none"> • 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 	Foundation One CDx	LOXO-TRK-14001 (NCT02122913), SCOUT (NCT02637687), and NAVIGATE (NCT02576431) ⁴¹ ,	2A
Olaparib (Lynparza)	PARP inhibitor	<ul style="list-style-type: none"> • Adjuvant treatment of adults with deleterious or suspected deleterious germline BRCA mutated, HER2-negative high risk early breast cancer who have 	BRCAAnalysis CDx Foundation One CDx	<p>Adjuvant therapy: OlympiA (NCT02032823)⁴²,</p> <p>Metastatic disease: OlympiAD (NCT02000622)⁴³,</p>	<p>Adjuvant therapy: 2A</p> <p>Metastatic disease: 1</p>

Treatment	Class	Indications in Breast Cancer	Companion Diagnostic	Pivotal Studies	NCCN Breast Cancer Guideline (V4.2023) Recommendation Level ²⁴ ,
		<p>been treated with neoadjuvant or adjuvant chemotherapy</p> <ul style="list-style-type: none"> 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. 			
Pembrolizumab (Keytruda) ^c	PD-L1-blocking antibody	<ul style="list-style-type: none"> Neoadjuvant treatment of high-risk, early-stage TNBC in combination 	PD-L1 IHC 22C3 pharmDx	Neoadjuvant/adjuvant therapy: KEYNOTE-522 (NCT03036488) ⁴⁴ , Unresectable/meta	Neoadjuvant/adjuvant therapy: 2A Unresectable/metastatic disease: 1

Treatment	Class	Indications in Breast Cancer	Companion Diagnostic	Pivotal Studies	NCCN Breast Cancer Guideline (V4.2023) Recommendation Level ²⁴ ,
		<p>with chemotherapy, then continued as a single agent as adjuvant therapy</p> <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 		<p>static disease: KEYNOTE-355 (NCT02819518)⁴⁵,</p>	
		<p>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</p>	<p>Foundation One CDx</p>	<p>KEYNOTE-158 (NCT02628067)⁴⁶,</p>	<p>2A</p>
		<p>Adult and pediatric patients with</p>	<p>Foundation One CDx</p>	<p>KEYNOTE-158 (NCT02628067)⁴⁷,</p>	<p>2A</p>

Treatment	Class	Indications in Breast Cancer	Companion Diagnostic	Pivotal Studies	NCCN Breast Cancer Guideline (V4.2023) Recommendation Level ²⁴ ,
		<p>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.</p>	<p>(Solid tumors TMB ≥ 10 mutations per megabase)</p>		
<p>Pertuzumab (Perjeta)^f</p>	<p>HER2/neu receptor antagonist</p>	<p>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.</p> <p>Use in combination with trastuzumab and chemotherapy as:</p> <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 	<p>HER2 FISH pharmDx Kit HerceptTest Foundation One CDx</p>	<p>Metastatic disease: CLEOPATRA (NCT00567190)⁴⁸,</p> <p>Neoadjuvant therapy: NeoSphere (NCT00545688)⁴⁹,</p> <p>Adjuvant therapy: APHINITY (NCT01358877)⁵⁰,</p>	<p>Metastatic disease: 1</p> <p>Neoadjuvant/adjuvant therapy: 1 or 2A (regimen-specific)</p>

Treatment	Class	Indications in Breast Cancer	Companion Diagnostic	Pivotal Studies	NCCN Breast Cancer Guideline (V4.2023) Recommendation Level ²⁴ ,
		<p>node positive) as part of a complete treatment regimen for early breast cancer.</p> <ul style="list-style-type: none"> 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) ⁹	HER2/neu receptor antagonist	<ul style="list-style-type: none"> Adjuvant treatment of HER2-overexpressing node-positive or 	Bond Oracle HER2 IHC System Foundation One CDx HER2 CISH	<p>Adjuvant therapy: BCIRG-006 (NCT00021255)⁵³,</p> <p>Metastatic disease:</p>	<p>Adjuvant therapy: 1 or 2A (regimen-specific)</p> <p>Metastatic disease:</p>

Treatment	Class	Indications in Breast Cancer	Companion Diagnostic	Pivotal Studies	NCCN Breast Cancer Guideline (V4.2023) Recommendation Level ²⁴ ,
		<p>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</p> <ul style="list-style-type: none"> • Treatment of metastatic HER2-overexpressing breast cancer in combination with paclitaxel (first-line treatment) or as a single agent (after 1 or more chemotherap 	<p>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</p>	<p>CLEOPATRA (NCT00567190)⁴⁸,</p>	<p>1 or 2A (regimen-specific)</p>

Treatment	Class	Indications in Breast Cancer	Companion Diagnostic	Pivotal Studies	NCCN Breast Cancer Guideline (V4.2023) Recommendation Level ²⁴ ,
		y regimens for metastatic disease)			

^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.

POLICY

A. *BRCA1* and *BRCA2* Testing

1. Genetic testing for *BRCA1* or *BRCA2* germline variants may be considered **medically necessary** to predict treatment response to PARP inhibitors (e.g., olaparib [Lynparza] and talazoparib [Talzenna]) for human epidermal receptor 2 (HER2)-negative metastatic and early stage, high-risk breast cancer (see Policy Guidelines).
2. Genetic testing of *BRCA1* or *BRCA2* germline or somatic variants in individuals with breast cancer for guiding therapy is considered **experimental / investigational** in all other situations.

B. *PIK3CA* Testing

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

C. Ki-67 testing

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

D. *RET* Testing

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

E. *BRAF* Testing

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

F. Circulating Tumor DNA Testing (Liquid Biopsy)

1. *PIK3CA* testing using FoundationOne Liquid CDx may be considered **medically necessary** to predict treatment response to alpelisib (Piqray) in individuals with hormone receptor-positive, HER2 negative advanced or metastatic breast cancer who have progressed on or after an endocrine-based regimen.
 - a. When tumor tissue is available, use of tissue for testing is preferred but is not required.
2. *ESR1* testing using Guardant360 CDx may be considered **medically necessary** to predict treatment response to elacestrant (Orserdu) in individuals with estrogen receptor-positive, HER2-negative advanced or metastatic breast cancer with disease progression following at least 1 line of endocrine therapy (see Policy Guidelines).
3. Circulating tumor DNA testing in individuals with breast cancer is considered **experimental/ investigational** in all other situations.

G. Circulating Tumor Cell Testing

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

POLICY GUIDELINES

- A. See U.S. Food and Drug Administration labels, clinical trials, and NCCN guidelines for specific population descriptions. Descriptions varied slightly across sources.
- B. Testing for individual genes (not gene panels) associated with FDA-approved therapeutics (i.e., as companion diagnostic tests) for therapies with National Comprehensive Cancer Network (NCCN) recommendations of 2A or higher are not subject to extensive evidence review. Note that while the FDA approval of companion diagnostic tests for genes might include tests that are conducted as panels, the FDA approval is for specific genes (such as driver mutations) and not for all of the genes on the test panel.
- C. For guidance on testing criteria between policy updates, refer to the FDA's List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools) (<https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools>) for an updated list of FDA-approved tumor markers and consult the most current version of NCCN management algorithms.
- D. **Breast Cancer Risk Groups**
In the OlympiA trial, patients with HER2-negative early-stage breast cancer (Clinical Stage I-III) and germline *BRCA1/2* mutations treated with (neo)adjuvant chemotherapy were considered at high risk of recurrent disease when the following eligibility criteria were met for treatment with olaparib (Tutt et al, 2021; PMID 34081848):
 - Patients with triple-negative breast cancer who were treated with adjuvant chemotherapy were required to have axillary node-positive disease or an invasive primary tumor

measuring at least 2 cm on pathological analysis. Patients treated with neoadjuvant chemotherapy were required to have not achieved pathological complete response.

- Patients treated with adjuvant chemotherapy for hormone receptor (HR)-positive, HER2-negative breast cancer were required to have at least 4 pathologically confirmed positive lymph nodes. Those treated with neoadjuvant chemotherapy were required to have not achieved a pathological complete response with a clinical stage, pathologic stage, estrogen receptor status, and tumor grade (CPS+EG) score of 3 or higher (Table PG1). This scoring system estimates relapse probability on the basis of clinical and pathological stage (CPS) and estrogen-receptor status and histologic grade (EG). Scores range from 0 to 6, with higher scores reflecting a worse prognosis.

Table PG1. CPS+EG Score^{a,b}

Stage or Feature	Points
<i>Clinical Stage (AJCC Staging)</i>	
I	0
IIA	0
IIB	1
IIIA	1
IIIB	2
IIIC	2
<i>Pathologic Stage (AJCC Staging)</i>	
0	0
I	0
IIA	1
IIB	1
IIIA	1
IIIB	1
IIIC	2
<i>Receptor Status</i>	
ER-negative	1
<i>Nuclear Grade</i>	
Nuclear grade 3	1

AJCC: American Joint Committee on Cancer; CPS+EG: clinical stage, pathologic stage, ER status, and tumor grade; ER: estrogen receptor.

^a Adapted from Tung et al (2021; PMID 34343058).

^b Add points for clinical stage, pathologic stage, ER status, and nuclear grade to yield a sum between 0 and 6.

E. Paired Genetic Testing

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

F. Genetics Nomenclature Update

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

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

Table PG2. Nomenclature to Report on Variants Found in DNA

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

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

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

Variant Classification	Definition
Benign	Benign change in the DNA sequence

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

G. Genetic Counseling

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

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

RATIONALE

This evidence review has been updated regularly with searches of the PubMed database. The most recent literature update was performed through October 25, 2023.

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

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

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

BIOMARKER TESTING USING TISSUE BIOPSY TO SELECT TARGETED TREATMENT

Clinical Context and Test Purpose

Breast cancer treatment selection is informed by tumor type, grade, stage, patient performance status and preference, prior treatments, and the molecular characteristics of the tumor such as the presence of driver mutations. One purpose of biomarker testing of 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 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, *PIK3CA*, Ki-67, *RET*, or *BRAF* testing using tissue biopsy.

Comparators

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

Outcomes

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

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

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

The overall response rate (ORR) may be used as a surrogate endpoint reasonably likely to predict clinical benefit in 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),⁵⁶ or Response Assessment in Neuro-Oncology criteria,⁵⁷ 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 (*BRCA1/2*, *PIK3CA*, for pembrolizumab, *ESR1*, for selection of dostarlimab-gxly, Ki-67, *RET*, *BRAF*) and by recommended therapy.

REVIEW OF EVIDENCE

Testing for *PIK3CA* Variants and *BRCA* Variants

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

KI-67 TESTING

FDA Companion Diagnostic Test

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

RANDOMIZED CONTROLLED TRIAL

Abemaciclib

Efficacy of abemaciclib was evaluated in the multicenter, randomized, open-label monarchE (NCT03155997) trial reported by Johnston et al (2021).²⁵ Adult men and women with hormone receptor (HR) -positive, HER2-negative, node-positive, early breast cancer with clinical and pathological features consistent with a high risk of recurrence were enrolled and randomized to receive either 2 years of abemaciclib plus physician's choice of standard endocrine therapy (n=2808) or endocrine therapy (ET) alone (n=2829). The primary efficacy outcome was invasive disease-free survival (IDFS). At the preplanned interim efficacy analysis, abemaciclib plus endocrine therapy demonstrated superior IDFS compared to endocrine therapy alone (hazard ratio [HR], 0.75; 95% confidence interval [CI], 0.60 to 0.93; p=.01), with 2-year IDFS rates of 92.2% versus 88.75%, respectively. Ki-67 index $\geq 20\%$ was reported for 1262 (44.9%) and 1233 (43.6%) patients treated with abemaciclib plus endocrine therapy and endocrine therapy alone, respectively. In a secondary pre-planned efficacy analysis of patients with high risk of recurrence and retrospectively confirmed Ki-67 score of at least 20% (n=2003), the study also demonstrated a statistically significant improvement in the primary efficacy outcome of IDFS (HR 0.626; 95% CI, 0.488-0.803; p=.0042). For patients receiving abemaciclib plus tamoxifen or an aromatase

inhibitor, IDFS at 36 months was 86.1% (95% CI, 82.8% to 88.8%) compared to 79.0% at 36 months (95% CI, 75.3% to 82.3%) in patients receiving only tamoxifen or an aromatase inhibitor. At the time of IDFS, overall survival data was immature and not reported.

Efficacy of abemaciclib in the intention-to-treat (ITT) population at median follow-up 19 months showed continued benefit in IDFS (HR=0.71, 95% CI 0.58-0.87; nominal $p < .001$) with an absolute improvement of 3.0% in the 2-year IDFS rates (abemaciclib + ET: 92.3% versus ET alone: 89.3%), and benefit in distant relapse-free survival (DRFS) (HR=0.69, 95% CI 0.55 to 0.86; nominal $p < .001$) with absolute difference of 3.0% at 2 years (abemaciclib + ET: 93.8% versus ET alone: 90.8%).⁵⁸ At 27 months, the benefit of abemaciclib held (IDFS HR=0.70, 95% CI 0.59 to 0.82; nominal $p < .0001$ and DRFS HR=0.69, 95% CI 0.57 to 0.83; nominal $p < .0001$). When assessing Ki-67-high and -low populations, abemaciclib + ET showed an IDFS benefit regardless of the Ki-67 index and for all follow-up time periods assessed. The 3-year IDFS rates in the control arm suggested that patients with Ki-67-high tumors had a higher risk of developing an IDFS event than those with Ki-67-low tumors (79.0% versus 87.2%, respectively), thus indicating the prognostic value of Ki-67. While Ki-67 was prognostic, the abemaciclib benefit was observed regardless of Ki-67 status. The data for IDFS among patients with 1 to 3 positive axillary lymph nodes, tumor size less than 5cm, grade less than 3, and high Ki-67 index (over 20%) remained immature.

An interim analysis of overall survival, a secondary outcome in monarchE, was published in a letter to the editor by Harbeck et al in February 2022.⁵⁹ 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 $\geq 20\%$) overall survival was 4.1% (42/1017) in the abemaciclib + ET and 5.4% (53/986) in the ET alone groups (HR, 0.77, 95% CI 0.51 to 1.15). An updated interim analysis was published in 2023.²⁶ With median follow-up of 42 months, median IDFS had not been reached in either group, and previously-identified IDFS (HR=0.664; 95% CI, 0.578 to 0.762) and DRFS benefits (HR=0.659; 95% CI, 0.567 to 0.767) appeared to be sustained. Subgroup analysis indicated similar IDFS and DRFS benefit with the addition of abemaciclib regardless of Ki-67 status. Overall survival data remained immature and did not indicate a difference between groups. The monarchE trial is ongoing with an estimated study completion date of June 2029.

Section Summary: Ki-67 Testing

Among patients with HR-positive, HER2-negative, node-positive, early breast cancer with clinical and pathological features consistent with a high risk of recurrence (N=5637), abemaciclib plus endocrine therapy demonstrated superior invasive disease-free survival compared to endocrine therapy alone (HR=0.75; $p = .01$). For the cohort of patients with Ki-67 score of at least 20% (n=2003 [35.5%]), secondary analysis of invasive disease-free survival was also superior for the group receiving abemaciclib (HR=0.626; $p = .0042$). However, multiple subsequent analyses with additional follow-up showed the abemaciclib benefit was observed regardless of Ki-67 status. There was no clear benefit of abemaciclib on overall survival in either the ITT population or the FDA-indicated population based on interim results. Further study is necessary to confirm whether an improved overall survival benefit is observed among patients with Ki-67 positive status.

RETTESTING

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).⁵¹ LIBRETTO-001 included adult patients with solid tumors with a life expectancy of at least 3 months and with disease progression on or after previous systemic therapies or who had no satisfactory therapeutic options (Table 2). *RET* alteration status was determined by local molecular testing performed in a certified laboratory with the use of next-generation sequencing, fluorescence in situ hybridization (FISH), or PCR assay.⁶⁰ Of the 45 patients included in the trial, 4% (2/45) had primary breast cancer; 4 patients were excluded from efficacy analyses though none of these were breast cancer patients. The primary outcome was overall response rate (complete or partial response) assessed according to independent review using Response Evaluation Criteria in Solid Tumours (RECIST) criteria, version 1.1. In the total population, overall response was 43.9% (95% CI 28.5 to 60.3) and the median duration of response was 24.5 months. In the 2 breast cancer patients, the response rate was 100% (95% CI 15.8 to 100) and the median duration of response was 17.3 months. Harms of treatment were reported for the total cohort; 3 patients had serious, treatment-related adverse events, and elevated liver enzymes (AST and ALT) were the most common grade 3 or higher adverse events (Table 3). LIBRETTO-001 is ongoing, and continued selpercatinib approval in this population is subject to the results of confirmatory trials.

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

Study	Countries	Sites	Dates	Design	Participants	Intervention	Outcomes
Subbiah et al (2022) ⁵¹ , LIBRETTO-001 (NCT03157128)	Denmark, France, Germany, Israel, Japan, Singapore, Switzerland, USA	30	Dec 2017-Aug 2021	Nonrandomized, open-label phase 1/2	N=45 (n=2 with breast cancer) RET fusion-positive, tumor-agnostic adults with evaluable disease per RECIST (v. 1.1), ECOG performance status 0-2, life expectancy ≥3 months <ul style="list-style-type: none"> • Mean age 53 years 	Selpercatinib 20-240 mg/day	Primary: overall response (complete or primary) Secondary: time to response, progression-free survival, overall survival

Study	Countries	Sites	Dates	Design	Participants	Intervention	Outcomes
					<ul style="list-style-type: none"> 51% female 69% white, 24% Asian, 4% Black, 2% other race/ethnicity 		

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

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

Study	Overall Response (95% CI)	Duration of Response (95% CI)	PFS ^a (95% CI)	OS ^a (95% CI)	Treatment-related adverse events ^a
Subbiah et al (2022) ⁵¹ , 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; CI: confidence interval; OS: overall survival; PFS: progression-free survival.

Section Summary: *RET* Testing

The phase 1/2 LIBRETTO-001 trial of selpercatinib in individuals with *RET* fusion-positive solid tumors reported an overall response rate of 43.9% in the total population and 100% in the breast cancer population (n=2). Corresponding median duration of response was 24.5 months and 17.3 months. There is currently no FDA-approved companion diagnostic test for *RET* fusion-positive solid tumors, and continued selpercatinib approval in this population is subject to the results of confirmatory trials.

BRAF TESTING

FDA Companion Diagnostic Test

There is currently no FDA approved companion diagnostic test for *BRAFV600e* positive solid tumors other than melanoma and non-small cell lung cancer for dabrafenib plus trametinib.

NONRANDOMIZED TRIALS

Dabrafenib plus Trametinib

Dabrafenib plus trametinib combination therapy received FDA approval in 2022 for treatment of patients with unresectable or metastatic solid tumors with *BRAFV600E* mutation who have progressed following prior treatment and have no satisfactory alternative treatment options.⁶¹ 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).⁶² NCI-MATCH Subprotocol H and BRF117019 were conducted in adults with various solid tumors (N=131); CTMT212X2101 was conducted in a glioma pediatric population and is not further discussed in this policy.

Study characteristics of NCI-MATCH and BRF117019 are summarized in Table 4. Both trials were uncontrolled, single-arm trials. Of note, none of the patients in either trial had breast cancer. Study results are summarized in Table 5. The primary outcome in both trials was overall response, a composite outcome that includes complete and partial response. Overall response ranged from 31% to 69%, and complete response was rare. The median duration of response (range 9 to 27.5 months), progression-free survival (range 4.5 to 14 months) and overall survival (range 14 to 28.6 months) ranged widely and appeared to be dependent on tumor type. Serious and grade 3 or worse adverse events were common, occurring in up to 63% of study participants.

Table 4. Dabrafenib plus Trametinib in Patients with *BRAFV600E* Mutation Solid Tumors - Study Characteristics

Study	Countries	Sites	Date s	Desig n	Participants	Interventio n	Outcome s
Salama et al (2020) ⁶³ , NCI MATCH Subprotocol H (NCT02465060)	USA	Unclear for Subprotoco l H	Aug 2015-Feb 2018	Open-label, single-arm, basket trial	N=35 (none with breast cancer) <i>BRAFV600E</i> mutated solid tumors, lymphoma or multiple myeloma with disease progression on at least 1 standard therapy and measurable disease	Dabrafenib 150 mg 2x/day and trametinib 2 mg/day	Primary: ORR Secondary : PFS, OS, safety

Study	Countries	Sites	Dates	Design	Participants	Intervention	Outcomes
					according to standard practice for the tumor type <ul style="list-style-type: none"> • Median age 59 years • 62% female • 93% white, 1% Black, 1% mixed race, 1% NR 		
Subbiah et al (2020) ⁶⁴ , 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) <i>BRAF</i> V600E mutated biliary tract cancer that was unresectable, metastatic, locally advanced, or recurrent with no other standard treatment options available <ul style="list-style-type: none"> • 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) ⁶⁵ , BRF117019	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	Dabrafenib 150 mg 2x/day and	Primary: ORR Secondary : PFS,

Study	Countries	Sites	Dates	Design	Participants	Intervention	Outcomes
(NCT02034110)	France, Germany, Italy, Japan, the Netherlands, Norway, South Korea, Spain, Sweden, USA)			phase 2 basket trial	low-grade glioma) <i>BRAFV600E</i> mutated high- or low-grade glioma High-grade glioma: <ul style="list-style-type: none"> • Mean age 42 years • 49% female • 76% white, 13% Asian, 4% Black, 2% American Indian or Alaska Native, 4% NR Low-grade glioma: <ul style="list-style-type: none"> • Mean age 33 years • 69% female • 77% white, 33% Asian 	trametinib 2 mg/day	duration of response, OS, safety

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

Table 5. Dabrafenib plus Trametinib in Patients with *BRAFV600E* 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) ⁶³ , 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) ⁶⁴ , 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) ⁶⁵ , BRF117019 (NCT02034110)	N=45 high-grade glioma cohort N=13 low-grade glioma cohort	N=45 high-grade glioma cohort N=13 low-grade glioma cohort	N=45 high-grade glioma cohort N=13 low-grade glioma cohort	N=45 high-grade glioma cohort N=13 low-grade glioma cohort	N=58
Targeted therapy with dabrafenib + trametinib	High-grade cohort: 31% (18 to 47; 7% had complete response) Low-grade cohort: 69% (39 to 91; 8% had complete response)	High-grade cohort: median 13.6 months (4.6 to 43.4) Low-grade cohort: median 27.5 months (3.8 to 39.5)	High-grade cohort: median 4.5 months (1.8 to 7.4) Low-grade cohort: median 14.0 months (4.7 to 46.9)	High-grade cohort: median 17.6 months (9.5 to 45.2) Low-grade cohort: median NR	Serious treatment-related adverse events: 12% (7/45)

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

In addition to the results reported in Table 5, the FDA reported pooled efficacy data from the 2 trials, finding an objective response rate of 41% (95% CI, 33% to 50%).⁶¹ Response varied

according to tumor type, ranging from 0% (for various adenocarcinomas and gastrointestinal stromal tumors) to 80% (for serous ovarian cancer).⁶²

Section Summary: *BRAF* Testing

The phase NCI Match and BRF117019 trials of dabrafenib plus trametinib combination therapy in individuals with *BRAF* mutated solid tumors reported overall response rates ranging from 31% to 69%, largely driven by partial responders; complete response was rare. Duration of response, PFS, and overall survival ranged widely and appeared to be dependent on tumor type. Serious and grade 3 or worse adverse events were common, occurring in up to 63% of study participants. No breast cancer patients were included in either trial. There is currently no FDA-approved companion diagnostic test for *BRAF* mutated solid tumors other than melanoma and non-small cell lung cancer, and continued dabrafenib plus trametinib approval in this population is subject to the results of confirmatory trials.

Circulating Tumor DNA Testing to Select Targeted Treatment

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

CIRCULATING TUMOR CELL TESTING TO SELECT TARGETED TREATMENT

Clinical Context and Test Purpose

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

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

Populations

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

Interventions

The test being considered is CTC testing.

The primary reason for CTCs would be to aid in decision-making about alternative treatment. CTC testing has been proposed as a method to guide the choice between chemotherapy and endocrine therapy as first-line treatment, or to change early to an alternative chemotherapy regimen in 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.^{66,67}

CLINICAL UTILITY

Randomized Controlled Trials

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

Smerage et al (2014) reported on the results of an RCT of patients with metastatic breast cancer and persistently increased CTC levels to test whether changing chemotherapy after 1 cycle of first-line therapy could improve overall survival.⁶⁸. Level of CTCs were enumerated using the CellSearch system. Five or more CTCs per 7.5 mL whole blood was considered an increased level, and it served as the cut point for separation of favorable versus unfavorable prognosis. Patients who did not have increased CTC levels at baseline remained on initial therapy until progression (arm A), patients with initially increased CTC levels that decreased after 21 days of therapy remained on initial therapy (arm B), and patients with persistently increased CTC levels after 21 days of therapy were randomized to continue initial therapy (arm C1) or change to an alternative chemotherapy (arm C2). There were 595 eligible and evaluable patients, 276 (46%) of whom did not have increased CTC levels (arm A). Of patients with initially increased CTC levels, 31 (10%) were not retested, 165 were assigned to arm B, and 123 were randomized to arms C1 or C2. There was no difference in median overall survival between arms C1 (10.7 months) and C2 (12.5 months; $p=.98$). CTC levels were strongly prognostic, with a median overall survival for arms A, B, and C (C1 and C2 combined) of 35 months, 23 months, and 13 months, respectively ($p<.001$). While the trial showed the prognostic significance of CTCs in patients with metastatic breast cancer, changing to an alternative chemotherapeutic regimen did not improve outcomes in patients whose CTCs were not reduced after 1 cycle of first-line chemotherapy.

More recently, Bidard et al (2021) reported on a noninferiority trial comparing CTC-driven versus clinician driven first-line therapy choice in patients with metastatic breast cancer.⁶⁹ Median PFS

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

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

Study	Countries	Sites	Dates	Participants	Interventions		Endpoints
					Active	Comparator	
Smerage et al (2014); ⁶⁸ NCT00382018			Oct 2006-Mar 2012	Women with histologically confirmed breast cancer and clinical and/or radiographic evidence of metastatic disease Persistent increased CTCs following 1 cycle of chemotherapy	Changing chemotherapy after 1 cycle of first-line chemotherapy (n=59)	Continued initial therapy (n=64)	OS, PFS
Bidard et al (2021) ⁶⁹ ,	France	17	Feb 2012-Jul 2016	778 women with hormone-receptor positive, HER2-negative metastatic breast	CTC-driven treatment choice (n=391)	Clinician-driven treatment choice (n=387)	PFS, OS, rate of treatment changes, AEs

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

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

Study	OS	PFS
Smerage et al (2014) ⁶⁸ ,		
N analyzed		
CTC-Directed Treatment	12.5 months	4.6 months
Standard care	10.7 months	3.5 months

Study	OS	PFS
HR (95% CI)	1.00 (0.69 to 1.47)	0.92 (0.64 to 1.32)
p	.98	.64
Bidard et al (2021) ⁶⁹ ,		
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.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 platinum; 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 8 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 8. National Comprehensive Cancer Network Guidelines on Biomarker Testing for Targeted Treatment of Breast Cancer

Biomarker	Breast Cancer Subtype	FDA Approved Agents	Testing Recommendation	Targeted Therapy Category of Evidence	Targeted Therapy Category of Preference
<i>BRCA1/2</i> mutations	Any	Olaparib Talazoparib	Patients with recurrent or metastatic breast cancer should be assessed for <i>BRCA1/2</i> mutations with germline sequencing to identify candidates for PARP inhibitor therapy. While olaparib and talazoparib are FDA-indicated in HER2-negative disease, NCCN supports use in any breast cancer subtype associated with a germline <i>BRCA1</i> or <i>BRCA2</i> mutation.	1	Preferred
<i>PIK3CA</i>	HR-positive/HER2-negative	Alpelisib + fulvestrant	For HR-positive/HER2-negative breast cancer, assess for <i>PIK3CA</i> mutations with tumor or liquid biopsy to identify candidates for alpelisib plus fulvestrant. <i>PIK3CA</i> 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
<i>ESR1</i> mutation	HR-positive/HER2-negative	Elacestrant	For postmenopausal females or adult males with ER-positive, HER2-negative, <i>ESR1</i> -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)	Triple negative	Pembrolizumab + chemotherapy	For triple-negative breast cancer, assess PD-L1 expression using 22C3 antibody via	1	Preferred first-line therapy

Biomarker	Breast Cancer Subtype	FDA Approved Agents	Testing Recommendation	Targeted Therapy Category of Evidence	Targeted Therapy Category of Preference
positive score ≥ 10)		y (albumin-bound paclitaxel, or gemcitabine and carboplatin)	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.		
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
<i>RET</i> -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.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 9.

Table 9. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT03145961 ^a	c-TRAK TN: A Randomised Trial Utilising ctDNA Mutation Tracking to Detect Minimal Residual Disease and Trigger Intervention in Patients With Moderate and High Risk Early Stage Triple Negative Breast Cancer	208	Mar 2024
NCT02965755 ^a	Individualized Molecular Analyses Guide Efforts in Breast Cancer - Personalized Molecular Profiling in Cancer Treatment at Johns Hopkins (IMAGE-II)	200	Jul 2024
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
NCT04591431	The Rome Trial - From Histology to Target: the Road to Personalize Target Therapy and Immunotherapy	384	Jun 2025
NCT02693535 ^a	Targeted Agent and Profiling Utilization Registry (TAPUR) Study	3791	Dec 2025
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
NCT04526587	The Roswell Park Ciclib Study: A Prospective Study of Biomarkers and Clinical Features of Advanced/Metastatic Breast Cancer Treated With CDK4/6 Inhibitors	400	Jul 2025
NCT02306096	SCAN-B: The Sweden Cancerome Analysis Network - Breast Initiative	20000	Aug 2031
Unpublished			
NCT04098640	Molecular Profiling Using FoundationOne CDx in Young (<50 Years of Age) Patients With Metastatic Breast Cancer (ML41263)	200	Jul 2021

NCT: national clinical trial.

^a Denotes industry-sponsored or cosponsored trial.

CODING

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

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

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

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

CPT/HCPCS	
	copy number amplifications, and gene rearrangements (PLA for Guardant360® CDx)
0338U	Oncology (solid tumor), circulating tumor cell selection, identification, morphological characterization, detection and enumeration based on differential EpCAM, cytokeratins 8, 18, and 19, and CD45 protein biomarkers, and quantification of HER2 protein biomarker-expressing cells, peripheral blood. CellSearch® HER2 Circulating Tumor Cell
81162	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis (i.e., detection of large gene rearrangements)
81163	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis
81164	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (i.e., detection of large gene rearrangements)
81165	BRCA1 (BRCA1, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis
81166	BRCA1 (BRCA1, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (i.e., detection of large gene rearrangements)
81167	BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (i.e., detection of large gene rearrangements)
81212	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; 185delAG, 5385insC, 6174delT variants
81215	BRCA1 (BRCA1, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; known familial variant
81216	BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis
81217	BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; known familial variant
81301	Microsatellite instability analysis (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) of markers for mismatch repair deficiency (e.g., BAT25, BAT26), includes comparison of neoplastic and normal tissue, if performed
81309	PIK3CA (phosphatidylinositol-4, 5-biphosphate 3-kinase, catalytic subunit alpha) (e.g., colorectal and breast cancer) gene analysis, targeted sequence analysis (e.g., exons 7, 9, 20)
81445	Solid organ neoplasm, genomic sequence analysis panel, 5-50 genes, interrogation for sequence variants and copy number variants or rearrangements, if performed; DNA analysis or combined DNA and RNA analysis
81455	Solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes, interrogation for sequence variants and copy number variants or rearrangements,

CPT/HCPCS	
	or isoform expression or mRNA expression levels, if performed; DNA analysis or combined DNA and RNA analysis
88360	Morphometric analysis, tumor immunohistochemistry (e.g., Her-2/neu, estrogen receptor/progesterone receptor), quantitative or semiquantitative, per specimen, each single antibody stain procedure; manual
88361	Morphometric analysis, tumor immunohistochemistry (e.g., Her-2/neu, estrogen receptor/progesterone receptor), quantitative or semiquantitative, per specimen, each single antibody stain procedure; using computer-assisted technology
81479	Unlisted molecular pathology procedure

REVISIONS	
03-10-2022	Policy added to the bcbsks.com web site.
10-28-2022	Updated Coding Section <ul style="list-style-type: none"> ▪ Added 0338U (effective 10-01-2022)
05-25-2023	Updated Description Section
	Updated Policy Section <ul style="list-style-type: none"> ▪ Removed Section: <ol style="list-style-type: none"> C. <i>NTRK Gene Fusion Testing</i> <ol style="list-style-type: none"> 1. Analysis of NTRK gene fusions may be considered medically necessary to predict treatment response to entrectinib (Rozlytrek) or larotrectinib (Vitrakvi) in patients with locally advanced or metastatic breast cancer that has progressed following standard treatment and who have no alternative treatment option (see Policy Guidelines). 2. Analysis of NTRK gene fusions in patients with breast cancer is considered experimental / investigational in all other situations. ▪ Added Sections: <ol style="list-style-type: none"> F. <i>RET Testing</i> <ol style="list-style-type: none"> 1. RET testing to predict treatment response to selpercatinib (Retevmo) in individuals with breast cancer is considered experimental / investigational. G. <i>BRAF Testing</i> <ol style="list-style-type: none"> 1. BRAF testing to predict treatment response to dabrafenib (Tafinlar) plus trametinib (Mekinist) in individuals with breast cancer is considered experimental / investigational.
	Updated Policy Guideline Section <ul style="list-style-type: none"> ▪ Added: <ol style="list-style-type: none"> B. Testing for individual genes (not gene panels) associated with FDA-approved therapeutics (i.e., as companion diagnostic tests) for therapies with National Comprehensive Cancer Network (NCCN) recommendations of 2A or higher are not subject to extensive evidence review. Note that while the FDA approval of companion diagnostic tests for genes might include tests that are conducted as panels, the FDA approval is for specific genes (such as driver mutations) and not for all of the genes on the test panel. C. For guidance on testing criteria between policy updates, refer to the FDA's List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools) (https://www.fda.gov/medical-devices/in-vitro)

REVISIONS	
	<p>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.</p> <p>Updated Rationale Section</p> <p>Updated Coding Section</p> <ul style="list-style-type: none"> ▪ Updated nomenclature for 81445 and 81455 ▪ Added 0242U, 81456, 81162, 81163, 81164, 81165, 81166, 81167, 81212, 81215, 81216, 81217 ▪ Removed 81191, 81192, 81193, 81194 ▪ Removed ICD-10 Codes <p>Updated References Section</p>
01-23-2024	<p>Updated Title to: "Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Breast Cancer (BRCA1, BRCA2, PIK3CA, Ki-67, RET, BRAF, ESR1)"</p> <p>Updated Description Section</p> <p>Updated Policy Section</p> <ul style="list-style-type: none"> ▪ Removed Section B, C, and G <ul style="list-style-type: none"> B. "PD-L1 Testing <ol style="list-style-type: none"> 1. PD-L1 testing may be considered medically necessary to predict treatment response to pembrolizumab (Keytruda) in individuals with hormone receptor-negative/HER2-negative (triple negative) recurrent or metastatic breast cancer. 2. PD-L1 testing in individuals with breast cancer is considered experimental/ investigational in all other situations, including to predict treatment response to atezolizumab (Tecentriq). C. MSI-H/dMMR Testing <ol style="list-style-type: none"> 1. MSI-H/dMMR testing may be considered medically necessary to predict treatment response to pembrolizumab (Keytruda) in individuals with unresectable or metastatic breast cancer that has progressed following standard treatment and who have no alternative treatment option (see Policy Guidelines). 2. MSI-H/dMMR testing in individuals with breast cancer is considered experimental/ investigational in all other situations, including to predict treatment response to dostarlimab-gxly (Jemperli). G. Tumor Mutational Burden Testing <ol style="list-style-type: none"> 1. Tumor mutational burden testing to predict response to immunotherapy in individuals with breast cancer is considered experimental/ investigational." ▪ Added Section F2 <ol style="list-style-type: none"> 2. "ESR1 testing using Guardant360 CDx may be considered medically necessary to predict treatment response to elacestrant (Orserdu) in individuals with estrogen receptor-positive, HER2-negative advanced or metastatic breast cancer with disease progression following at least 1 line of endocrine therapy (see Policy Guidelines)." <p>Updated Rationale Section</p> <p>Updated Coding Section</p> <ul style="list-style-type: none"> ▪ Updated nomenclature for 81445 and 81455 (eff. 01-01-2024)

REVISIONS	
	▪ Removed 81456
	Updated References Section

REFERENCES

1. Nelson HD, Pappas M, Cantor A, et al. Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA-Related Cancer in Women: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. *JAMA*. Aug 20 2019; 322(7): 666-685. PMID 31429902
2. Hemel D, Domchek SM. Breast cancer predisposition syndromes. *Hematol Oncol Clin North Am*. Oct 2010; 24(5): 799-814. PMID 20816575
3. Yoshida R. Hereditary breast and ovarian cancer (HBOC): review of its molecular characteristics, screening, treatment, and prognosis. *Breast Cancer*. Nov 2021; 28(6): 1167-1180. PMID 32862296
4. Winchester DP. Breast cancer in young women. *Surg Clin North Am*. Apr 1996; 76(2): 279-87. PMID 8610264
5. Frank TS, Deffenbaugh AM, Reid JE, et al. Clinical characteristics of individuals with germline mutations in BRCA1 and BRCA2: analysis of 10,000 individuals. *J Clin Oncol*. Mar 15 2002; 20(6): 1480-90. PMID 11896095
6. Langston AA, Malone KE, Thompson JD, et al. BRCA1 mutations in a population-based sample of young women with breast cancer. *N Engl J Med*. Jan 18 1996; 334(3): 137-42. PMID 8531967
7. Malone KE, Daling JR, Thompson JD, et al. BRCA1 mutations and breast cancer in the general population: analyses in women before age 35 years and in women before age 45 years with first-degree family history. *JAMA*. Mar 25 1998; 279(12): 922-9. PMID 9544766
8. Ford D, Easton DF, Stratton M, et al. Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. The Breast Cancer Linkage Consortium. *Am J Hum Genet*. Mar 1998; 62(3): 676-89. PMID 9497246
9. Gershoni-Baruch R, Patael Y, Dagan A, et al. Association of the I1307K APC mutation with hereditary and sporadic breast/ovarian cancer: more questions than answers. *Br J Cancer*. Jul 2000; 83(2): 153-5. PMID 10901363
10. Warner E, Foulkes W, Goodwin P, et al. Prevalence and penetrance of BRCA1 and BRCA2 gene mutations in unselected Ashkenazi Jewish women with breast cancer. *J Natl Cancer Inst*. Jul 21 1999; 91(14): 1241-7. PMID 10413426
11. Hartge P, Struewing JP, Wacholder S, et al. The prevalence of common BRCA1 and BRCA2 mutations among Ashkenazi Jews. *Am J Hum Genet*. Apr 1999; 64(4): 963-70. PMID 10090881
12. Hodgson SV, Heap E, Cameron J, et al. Risk factors for detecting germline BRCA1 and BRCA2 founder mutations in Ashkenazi Jewish women with breast or ovarian cancer. *J Med Genet*. May 1999; 36(5): 369-73. PMID 10353781
13. de Ruijter TC, Veeck J, de Hoon JP, et al. Characteristics of triple-negative breast cancer. *J Cancer Res Clin Oncol*. Feb 2011; 137(2): 183-92. PMID 21069385
14. Young SR, Pilarski RT, Donenberg T, et al. The prevalence of BRCA1 mutations among young women with triple-negative breast cancer. *BMC Cancer*. Mar 19 2009; 9: 86. PMID 19298662

15. Gonzalez-Angulo AM, Timms KM, Liu S, et al. Incidence and outcome of BRCA mutations in unselected patients with triple receptor-negative breast cancer. *Clin Cancer Res*. Mar 01 2011; 17(5): 1082-9. PMID 21233401
16. Karakas B, Bachman KE, Park BH. Mutation of the PIK3CA oncogene in human cancers. *Br J Cancer*. Feb 27 2006; 94(4): 455-9. PMID 16449998
17. Davey MG, Hynes SO, Kerin MJ, et al. Ki-67 as a Prognostic Biomarker in Invasive Breast Cancer. *Cancers (Basel)*. Sep 03 2021; 13(17). PMID 34503265
18. Regua AT, Najjar M, Lo HW. RET signaling pathway and RET inhibitors in human cancer. *Front Oncol*. 2022; 12: 932353. PMID 35957881
19. Santoro M, Moccia M, Federico G, et al. RET Gene Fusions in Malignancies of the Thyroid and Other Tissues. *Genes (Basel)*. Apr 15 2020; 11(4). PMID 32326537
20. Wang L, Lu Q, Jiang K, et al. BRAF V600E Mutation in Triple-Negative Breast Cancer: A Case Report and Literature Review. *Oncol Res Treat*. 2022; 45(1-2): 54-61. PMID 34818649
21. Albanell J, Elvin JA, Suh J, et al. BRAF Genetic Alterations in Breast Cancer. *Ann Oncol*. October 1 2016; 27(Suppl 6): v170.
22. Toy W, Shen Y, Won H, et al. ESR1 ligand-binding domain mutations in hormone-resistant breast cancer. *Nat Genet*. Dec 2013; 45(12): 1439-45. PMID 24185512
23. Jeselsohn R, Yelensky R, Buchwalter G, et al. Emergence of constitutively active estrogen receptor- α mutations in pretreated advanced estrogen receptor-positive breast cancer. *Clin Cancer Res*. Apr 01 2014; 20(7): 1757-1767. PMID 24398047
24. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Breast Cancer. V4.2023.
https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed October 25, 2023.
25. Johnston SRD, Harbeck N, Hegg R, et al. Abemaciclib Combined With Endocrine Therapy for the Adjuvant Treatment of HR+, HER2-, Node-Positive, High-Risk, Early Breast Cancer (monarchE). *J Clin Oncol*. Dec 01 2020; 38(34): 3987-3998. PMID 32954927
26. Johnston SRD, Toi M, O'Shaughnessy J, et al. Abemaciclib plus endocrine therapy for hormone receptor-positive, HER2-negative, node-positive, high-risk early breast cancer (monarchE): results from a preplanned interim analysis of a randomised, open-label, phase 3 trial. *Lancet Oncol*. Jan 2023; 24(1): 77-90. PMID 36493792
27. Goetz MP, Toi M, Campone M, et al. MONARCH 3: Abemaciclib As Initial Therapy for Advanced Breast Cancer. *J Clin Oncol*. Nov 10 2017; 35(32): 3638-3646. PMID 28968163
28. Sledge GW, Toi M, Neven P, et al. MONARCH 2: Abemaciclib in Combination With Fulvestrant in Women With HR+/HER2- Advanced Breast Cancer Who Had Progressed While Receiving Endocrine Therapy. *J Clin Oncol*. Sep 01 2017; 35(25): 2875-2884. PMID 28580882
29. Sledge GW, Toi M, Neven P, et al. The Effect of Abemaciclib Plus Fulvestrant on Overall Survival in Hormone Receptor-Positive, ERBB2-Negative Breast Cancer That Progressed on Endocrine Therapy-MONARCH 2: A Randomized Clinical Trial. *JAMA Oncol*. Jan 01 2020; 6(1): 116-124. PMID 31563959
30. Dickler MN, Tolaney SM, Rugo HS, et al. MONARCH 1, A Phase II Study of Abemaciclib, a CDK4 and CDK6 Inhibitor, as a Single Agent, in Patients with Refractory HR + /HER2 - Metastatic Breast Cancer. *Clin Cancer Res*. Sep 01 2017; 23(17): 5218-5224. PMID 28533223

31. Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med*. Nov 08 2012; 367(19): 1783-91. PMID 23020162
32. von Minckwitz G, Huang CS, Mano MS, et al. Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer. *N Engl J Med*. Feb 14 2019; 380(7): 617-628. PMID 30516102
33. André 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
34. Subbiah V, Kreitman RJ, Wainberg ZA, et al. Dabrafenib plus trametinib in *BRAFV600E*-mutated rare cancers: the phase 2 ROAR trial. *Nat Med*. May 2023; 29(5): 1103-1112. PMID 37059834
35. Tafenlar (dabrafenib) package insert. Novartis; 2023. Accessed October 25, 2023.
36. Jemperli (dostarlimab) package insert. GlaxoSmithKline; 2023. Accessed October 25, 2023
37. Bidard FC, Kaklamani VG, Neven P, et al. Elacestrant (oral selective estrogen receptor degrader) Versus Standard Endocrine Therapy for Estrogen Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: Results From the Randomized Phase III EMERALD Trial. *J Clin Oncol*. Oct 01 2022; 40(28): 3246-3256. PMID 35584336
38. 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
39. Hurvitz SA, Hegg R, Chung WP, et al. Trastuzumab deruxtecan versus trastuzumab emtansine in patients with HER2-positive metastatic breast cancer: updated results from DESTINY-Breast03, a randomised, open-label, phase 3 trial. *Lancet*. Jan 14 2023; 401(10371): 105-117. PMID 36495879
40. Modi S, Jacot W, Yamashita T, et al. Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer. *N Engl J Med*. Jul 07 2022; 387(1): 9-20. PMID 35665782
41. 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
42. Tutt ANJ, Garber JE, Kaufman B, et al. Adjuvant Olaparib for Patients with *BRCA1* - or *BRCA2* -Mutated Breast Cancer. *N Engl J Med*. Jun 24 2021; 384(25): 2394-2405. PMID 34081848
43. Robson M, Im SA, Senkus E, et al. Olaparib for Metastatic Breast Cancer in Patients with a Germline *BRCA* Mutation. *N Engl J Med*. Aug 10 2017; 377(6): 523-533. PMID 28578601
44. Schmid P, Cortes J, Dent R, et al. Event-free Survival with Pembrolizumab in Early Triple-Negative Breast Cancer. *N Engl J Med*. Feb 10 2022; 386(6): 556-567. PMID 35139274
45. Cortes J, Rugo HS, Cescon DW, et al. Pembrolizumab plus Chemotherapy in Advanced Triple-Negative Breast Cancer. *N Engl J Med*. Jul 21 2022; 387(3): 217-226. PMID 35857659
46. 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

47. 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
48. Swain SM, Miles D, Kim SB, et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA): end-of-study results from a double-blind, randomised, placebo-controlled, phase 3 study. *Lancet Oncol.* Apr 2020; 21(4): 519-530. PMID 32171426
49. Gianni L, Pienkowski T, Im YH, et al. 5-year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (NeoSphere): a multicentre, open-label, phase 2 randomised trial. *Lancet Oncol.* Jun 2016; 17(6): 791-800. PMID 27179402
50. Piccart M, Procter M, Fumagalli D, et al. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer in the APHINITY Trial: 6 Years' Follow-Up. *J Clin Oncol.* May 01 2021; 39(13): 1448-1457. PMID 33539215
51. Subbiah V, Wolf J, Konda B, et al. Tumour-agnostic efficacy and safety of selpercatinib in patients with RET fusion-positive solid tumours other than lung or thyroid tumours (LIBRETTO-001): a phase 1/2, open-label, basket trial. *Lancet Oncol.* Oct 2022; 23(10): 1261-1273. PMID 36108661
52. Litton JK, Rugo HS, Ettl J, et al. Talazoparib in Patients with Advanced Breast Cancer and a Germline BRCA Mutation. *N Engl J Med.* Aug 23 2018; 379(8): 753-763. PMID 30110579
53. Slamon D, Eiermann W, Robert N, et al. Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med.* Oct 06 2011; 365(14): 1273-83. PMID 21991949
54. U.S. Food & Drug Administration. Drugs@FDA: FDA-Approved Drugs. <https://www.accessdata.fda.gov/scripts/cder/daf/>. Accessed October 25, 2023
55. U.S. 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 October 26, 2023
56. 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
57. 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
58. Harbeck N, Rastogi P, Martin M, et al. Adjuvant abemaciclib combined with endocrine therapy for high-risk early breast cancer: updated efficacy and Ki-67 analysis from the monarchE study. *Ann Oncol.* Dec 2021; 32(12): 1571-1581. PMID 34656740
59. Harbeck N, Rastogi P, Shahir A, et al. Letter to the Editor for 'Adjuvant abemaciclib combined with endocrine therapy for high-risk early breast cancer: updated efficacy and Ki-67 analysis from the monarchE study'. *Ann Oncol.* Feb 2022; 33(2): 227-228. PMID 34756989
60. Drilon A, Oxnard GR, Tan DSW, et al. Efficacy of Selpercatinib in RET Fusion-Positive Non-Small-Cell Lung Cancer. *N Engl J Med.* Aug 27 2020; 383(9): 813-824. PMID 32846060

61. U.S. Food and Drug Administration. FDA Grants Accelerated Approval to Dabrafenib in Combination with Trametinib for Unresectable or Metastatic Solid Tumors with BRAF V600E Mutation. June 23, 2022. Accessed October 24, 2023.
62. Mekinist (trametinib) package insert. Novartis; 2023. Accessed October 26, 2023
63. Salama AKS, Li S, Macrae ER, et al. Dabrafenib and Trametinib in Patients With Tumors With BRAF V600E Mutations: Results of the NCI-MATCH Trial Subprotocol H. *J Clin Oncol*. Nov 20 2020; 38(33): 3895-3904. PMID 32758030
64. Subbiah V, Lassen U, Élez E, et al. Dabrafenib plus trametinib in patients with BRAF V600E -mutated biliary tract cancer (ROAR): a phase 2, open-label, single-arm, multicentre basket trial. *Lancet Oncol*. Sep 2020; 21(9): 1234-1243. PMID 32818466
65. Wen PY, Stein A, van den Bent M, et al. Dabrafenib plus trametinib in patients with BRAF V600E -mutant low-grade and high-grade glioma (ROAR): a multicentre, open-label, single-arm, phase 2, basket trial. *Lancet Oncol*. Jan 2022; 23(1): 53-64. PMID 34838156
66. 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
67. Lu YJ, Wang P, Wang X, et al. The significant prognostic value of circulating tumor cells in triple-negative breast cancer: a meta-analysis. *Oncotarget*. Jun 14 2016; 7(24): 37361-37369. PMID 27008698
68. 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
69. 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*. Jan 01 2021; 7(1): 34-41. PMID 33151266
70. Henry NL, Somerfield MR, Dayao Z, et al. Biomarkers for Systemic Therapy in Metastatic Breast Cancer: ASCO Guideline Update. *J Clin Oncol*. Sep 20 2022; 40(27): 3205-3221. PMID 35759724
71. Burstein HJ, DeMichele A, Somerfield MR, et al. Testing for ESR1 Mutations to Guide Therapy for Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Metastatic Breast Cancer: ASCO Guideline Rapid Recommendation Update. *J Clin Oncol*. Jun 20 2023; 41(18): 3423-3425. PMID 37196213
72. Centers for Medicare and Medicaid Services (CMS). Decision Memo: Next Generation Sequencing (NGS) for Medicare Beneficiaries with Advanced Cancer [CAG-00450R]. January 2020; <https://www.cms.gov/medicare-coverage-database/view/ncacal-decision-memo.aspx?proposed=N&NCAId=296>. Accessed October 26, 2023

OTHER REFERENCES

1. Blue Cross and Blue Shield of Kansas Pathology Liaison Committee, July 2022.
2. Blue Cross and Blue Shield of Kansas Oncology Liaison Committee, June 2022, July 2023.