MEDICAL POLICY

POLICY TITLE	**GERMLINE AND SOMATIC BIOMARKER TESTING (INCLUDING LIQUID BIOPSY) FOR TARGETED TREATMENT IN BREAST CANCER (BRCA1, BRCA2, PIK3CA, KI-67, RET, BRAF, ESR1, NTRK)**
POLICY NUMBER	**MP 2.393**

CLINICAL BENEFIT	☐ MINIMIZE SAFETY RISK OR CONCERN. ☒ MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. ☐ ASSURE APPROPRIATE LEVEL OF CARE. ☐ ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. ☒ ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. ☐ ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective Date:	**RETIRED 7/1/2026**

I. POLICY

BRCA1 and BRCA2 Testing

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).

Genetic testing of *BRCA1* or *BRCA2* germline or somatic variants in individuals with breast cancer for guiding therapy is considered **investigational** in all other situations. The evidence is insufficient to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

PIK3CA Testing

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

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

PIK3CA testing of tissue in individuals with breast cancer is considered **investigational** in all other situations. The evidence is insufficient to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

Ki-67 Testing

Ki-67 testing to predict treatment response to abemaciclib (Verzenio) in individuals with breast cancer is considered **investigational**. The evidence is insufficient to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

RET Testing

RET testing to predict treatment response to selpercatinib (Retevmo) in individuals with breast cancer is considered **investigational**. The evidence is insufficient to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

BRAF Testing

BRAF testing to predict treatment response to dabrafenib (Tafinlar) plus trametinib (Mekinist) in individuals with breast cancer is considered **investigational**. The evidence is insufficient to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

Circulating Tumor DNA Testing (Liquid Biopsy)

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

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

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

Circulating tumor DNA testing in individuals with breast cancer is considered **investigational** in all other situations. The evidence is insufficient to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

Circulating Tumor Cell Testing

Analysis of circulating tumor cells to select treatment in individuals with breast cancer is considered **investigational**. The evidence is insufficient to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

NTRK Gene Fusion Testing

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

NTRK gene fusion testing in individuals with breast cancer is considered **investigational** in all other situations. The evidence is insufficient to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

Other

Testing for other variants may become available between policy updates.

Policy Guidelines

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

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

This policy does not address HER2 testing. Agents targeted against HER2 with approved companion diagnostic tests include monoclonal antibodies (margetuximab, pertuzumab, trastuzumab) and antibody-drug conjugates (ado-trastuzumab emtansine, fam-trastuzumab deruxtecan), which are not true targeted therapies.

For expanded panel testing, see **MP 2.259**.

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

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

Breast Cancer Risk Groups

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

- Patients with triple-negative breast cancer who were treated with adjuvant chemotherapy were required to have axillary node-positive disease or an invasive primary tumor measuring at least 2 cm on pathological analysis. Patients treated with neoadjuvant chemotherapy were required to have not achieved pathological complete response.

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

Table PG1. CPS+EG Score[a,b]

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

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

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[a] Adapted from Tung et al (2021; PMID 34343058).
[b] Add points for clinical stage, pathologic stage, ER status, and nuclear grade to yield a sum between 0 and 6.

Paired Genetic Testing

Testing for genetic changes in tumor tissue assesses somatic changes. However, most somatic testing involves a paired blood analysis in order to distinguish whether findings in tumor tissue are acquired somatic changes or inherited germline changes. As such, simultaneous sequencing of tumor and normal tissue can recognize potential secondary germline changes that may identify risk for other cancers as well as identify risk for relatives. Thus, some laboratories offer concurrent full germline and somatic testing or paired tumor sequencing and germline sequencing, through large panels of germline and somatic variants. For paired panel testing involving germline components, see evidence review 2.04.93 - Genetic Cancer Susceptibility Panels Using Next Generation Sequencing. For paired panel testing involving somatic components, see evidence review 2.04.115 - Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies**.**

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 PG1). 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 PG2 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	Change in DNA sequence with uncertain effects on disease
Benign	Benign change in the DNA sequence

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

Cross-References:

MP 2.211 Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers (*BRCA1, BRCA2, PALB2*)
MP 2.246 Genetic Testing for Familial Cutaneous Malignant Melanoma
MP 2.274 Genetic Testing for Li-Fraumeni Syndrome
MP 2.279 Germline Genetic Testing for Gene Variants Associated with Breast Cancer in Individuals at High Breast Cancer Risk (*CHEK2, ATM, BARD1*)
MP 2.325 Genetic Cancer Susceptibility Panels Using Next-Generation Sequencing
MP 2.377 Molecular Testing for Germline Variants Associated with Ovarian Cancer (*BRIP1, RAD51C, RAD51D, NBN)*

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POLICY NUMBER	MP 2.393

MP 2.392 Germline Genetic Testing for Pancreatic Susceptibility Genes (*ATM, BRCA1, BRCA2, CDKN2A, EPCAM, MLH1, MSH2, MSH6, PALB2, PMS2, STK11,* and *TP53*)
MP 2.394 Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Prostate Cancer (*BRCA1/2*, Homologous Recombination Repair Gene Alterations, *NTRK* Gene Fusion)
MP 2.395 Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Ovarian Cancer (*BRCA1, BRCA2*, Homologous Recombination Deficiency, *NTRK*)
MP 5.013 Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes

II. PRODUCT VARIATIONS

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This policy is only applicable to certain programs and products administered by Capital Blue Cross and subject to benefit variations as discussed in Section VI. Please see additional information below

FEP PPO - Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at: https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies .

III. DESCRIPTION/BACKGROUND

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BRCA Variant Testing

The prevalence of *BRCA* variants is approximately 0.2% to 0.3% in the general population. The prevalence may be much higher for particular ethnic groups with characterized founder mutations (e.g., 2.5% [1/40] in the Ashkenazi Jewish population). Family history of breast and ovarian cancer is an important risk factor for the *BRCA* variant; additionally, age and ethnicity could be independent risk factors.

Several genetic syndromes with an autosomal dominant pattern of inheritance that feature breast cancer have been identified. Of these, hereditary breast and ovarian cancer (HBOC) and some cases of hereditary site-specific breast cancer have in common causative variants in *BRCA* (breast cancer susceptibility) genes. Families suspected of having HBOC syndrome are characterized by an increased susceptibility to breast cancer occurring at a young age, bilateral breast cancer, male breast cancer, ovarian cancer at any age, as well as cancer of the fallopian tube and primary peritoneal cancer. Other cancers, such as prostate cancer, pancreatic cancer, gastrointestinal cancers, melanoma, and laryngeal cancer, occur more frequently in HBOC families. Hereditary site-specific breast cancer families are characterized by

early-onset breast cancer with or without male cases, but without ovarian cancer. For this evidence review, BCBSA refers collectively to both as hereditary breast and/or ovarian cancer.

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

Young age of onset of breast cancer, even in the absence of family history, is a risk factor for *BRCA1* variants. Winchester (1996) estimated that hereditary breast cancers account for 36% to 85% of patients diagnosed before age 30. 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). In cancer-prone families, the mean age of breast cancer diagnosis among women carrying *BRCA1* or *BRCA2* variants is in the 40s. 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. 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. 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.

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. 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. 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*).

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.

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.

Rearranged During Transfection

The REarranged during Transfection (RET) proto-oncogene encodes a receptor tyrosine kinase growth factor. 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.

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. BRAF mutations occur in approximately 1% of breast cancer cases.

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.

Circulating Tumor DNA

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

Circulating Tumor Cells

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

Neurotrophic Receptor Tyrosine Kinase (*NTRK*) Gene Fusion Testing

The presence of *NTRK* gene fusion can be detected by multiple methods including next-generation sequencing, reverse transcription-polymerase chain reaction, fluorescence in situ hybridization and immunohistochemistry. Next-generation sequencing provides the most comprehensive view of a large number of genes and may identify *NTRK* gene fusions as well as

other actionable alterations, with minimal tissue needed. The fluorescence in situ hybridization using break-apart probes can detect gene rearrangements in DNA that may generate a fusion transcript. The immunohistochemistry techniques have generally been used in the research setting. Reverse transcription-polymerase chain reaction is designed to identify only known translocation partners and breakpoints and cannot identify novel breakpoints or novel fusion partners.

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of these tests.

Table 1 lists some of the available targeted treatments with FDA approval for breast cancer and the FDA cleared or approved companion diagnostic tests associated with each. An up-to-date list of FDA cleared or approved companion diagnostics is available at https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools.

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

Treatment	Companion Diagnostic
Abemaciclib (Verzenio)[a]	Ki-67 IHC MIB-1 pharmDx (Dako Omnis)
Alpelisib (Piqray)	FoundationOne CDx FoundationOne Liquid CDx therascreen PIK3CA RGQ PCR Kit
Dabrafenib (Tafinlar) + Trametinib (Mekinist)	No FDA approved companion diagnostic
Elacestrant (Orserdu)	Guardant360 CDx
Entrectinib (Rozlytrek)	FoundationOne CDx (Foundation Medicine, Inc.) FoundationOne Liquid CDx (Foundation Medicine, Inc.)
Larotrectinib (Vitrakvi)	FoundationOne CDx
Olaparib (Lynparza)	BRACAnalysis CDx FoundationOne CDx
Selpercatinib (Retevmo)	No FDA-approved companion diagnostic test

Talazoparib (Talzenna)	BRACAnalysis CDx
Itovebi (inavolisib)	FoundationOne CDx (Foundation Medicine, Inc.) FoundationOne Liquid CDx (Foundation Medicine, Inc.) *therascreen* PIK3CA RGQ PCR Kit (QIAGEN GmbH)

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

IV. RATIONALE

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

For individuals with hormone receptor-positive, HER2-negative advanced or metastatic breast cancer who receive *PIK3CA* gene testing to select targeted treatment, the evidence includes FDA-approved therapeutics with NCCN recommendations of 2A or higher and was not extensively evaluated. The evidence includes the pivotal studies leading to the FDA and NCCN recommendations.

For individuals with breast cancer who are being considered for abemaciclib therapy who receive Ki-67 testing, the evidence includes a randomized, controlled, open-label trial. Relevant outcomes include overall survival, disease-specific survival, test validity, quality of life, and treatment-related morbidity. Among patients with hormone receptor-positive, HER2-negative, node-positive, early breast cancer with clinical and pathological features consistent with a high risk of recurrence (n=5637), abemaciclib plus endocrine therapy demonstrated superior invasive disease-free survival compared to endocrine therapy alone (hazard ratio [HR] =0.75; p=.01). For the cohort of patients with Ki-67 score of at least 20% (n=2003 [35.5%]), secondary analysis of invasive disease-free survival was also superior for the group receiving abemaciclib (HR=0.626; p=.0042). However, additional analyses showed the abemaciclib benefit was observed regardless of Ki-67 status. There was no clear benefit of abemaciclib on overall survival in either the ITT population or the FDA-indicated population based on preliminary results that were not subject to peer review. Further study is necessary to confirm whether an improved overall survival benefit is observed among patients with Ki-67 'high' versus 'low' status. The evidence is

insufficient to determine that the technology results in an improvement in the net health outcome.

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

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

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

For individuals with metastatic breast cancer who receive circulating tumor cell (CTC) testing to guide treatment decisions, the evidence includes randomized controlled trials (RCTs), observational studies, and systematic reviews. Relevant outcomes include overall survival, disease-specific survival, test validity, quality of life, and treatment-related morbidity. Systematic reviews and meta-analyses have described an association between CTCs and poor prognosis in metastatic breast cancer, but evidence that CTC-driven treatment improves health outcomes is lacking. One RCT found no improvement in overall survival or progression-free survival (PFS) with CTC-driven treatment (early switching to a different chemotherapy regimen) compared to

continuing initial therapy. A second RCT found that CTC-driven first-line therapy was noninferior to clinician-driven therapy in previously untreated patients with metastatic breast cancer (hazard ratio for PFS 0.94; 95% confidence interval 0.81 to 1.09). The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with recurrent unresectable (local or regional) or stage IV breast cancer who receive *NTRK* gene fusion testing to guide treatment decisions, the evidence includes FDA-approved therapeutics with National Comprehensive Cancer Network (NCCN) recommendations of 2A or higher and was not extensively evaluated. The evidence includes the pivotal studies leading to the FDA and National Comprehensive Cancer Network (NCCN) recommendations.

V. DEFINITIONS/BACKGROUND

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N/A

VI. DISCLAIMER

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Capital Blue Cross' medical policies are used to determine coverage for specific medical technologies, procedures, equipment, and services. These medical policies do not constitute medical advice and are subject to change as required by law or applicable clinical evidence from independent treatment guidelines. Treating providers are solely responsible for medical advice and treatment of members. These polices are not a guarantee of coverage or payment. Payment of claims is subject to a determination regarding the member's benefit program and eligibility on the date of service, and a determination that the services are medically necessary and appropriate. Final processing of a claim is based upon the terms of contract that applies to the members' benefit program, including benefit limitations and exclusions. If a provider or a member has a question concerning this medical policy, please contact Capital Blue Cross' Provider Services or Member Services.

VII. CODING INFORMATION

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Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement. The codes need to be in numerical order.

Investigational; therefore, not covered:

Procedure Codes							
0048U	0211U	0338U	81210	81404	81405	81406	81445
81455	81479*						

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*Could be used for Ki-67 testing or another gene variant without a specific code

Covered when medically necessary:

Procedure Codes							
0037U	0155U	0177U	0239U	0242U	81162	81163	81164
81165	81166	81167	81191	81192	81193	81194	81212
81215	81216	81217	81309				

ICD-10-CM Diagnosis Code	Description
C50.011-C50.929	Malignant neoplasm of the breast code range
C50.A	Malignant inflammatory neoplasm of breast
C50.A0	Malignant inflammatory neoplasm of unspecified breast
C50.A1	Malignant inflammatory neoplasm of right breast
C50.A2	Malignant inflammatory neoplasm of left breast
C79.81	Secondary malignant neoplasm of breast

VIII. REFERENCES

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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(Supp 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. *TRK Fusion Cancer (Testing). https://trkcancer.com/testing. Accessed November 12, 2024.*
25. *National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Breast Cancer. V5.2024. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed October 15, 2024.*
26. *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*
27. *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*
28. *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*
29. *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*
30. *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*
31. *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*
32. *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*
33. *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*
34. *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*
35. *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*
36. *Tafinlar (dabrafenib) package insert. Novartis; 2024. Accessed October 15, 2024.*

37. *Jemperli (dostarlimab) package insert. GlaxoSmithKline; 2024. Accessed October 15, 2024*
38. *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*
39. *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*
40. *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*
41. *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*
42. *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*
43. *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*
44. *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*
45. *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*
46. *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*
47. *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*
48. *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*
49. *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

50. *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*
51. *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*
52. *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*
53. *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*
54. *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*
55. *Turner NC, Im SA, Saura C, et al. Inavolisib-Based Therapy in PIK3CA -Mutated Advanced Breast Cancer. N Engl J Med. Oct 31 2024; 391(17): 1584-1596. PMID 39476340*
56. *U.S. Food & Drug Administration. Drugs@FDA: FDA-Approved Drugs. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed October 15, 2024.*
57. *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 16, 2024.*
58. *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*
59. *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*
60. *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*
61. *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*

62. *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*
63. *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.*
64. *Mekinist (trametinib) package insert. Novartis; 2024. Accessed October 16, 2024.*
65. *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*
66. *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*
67. *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*
68. *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*
69. *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*
70. *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*
71. *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*
72. *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*
73. *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*
74. *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 16, 2024.*

POLICY TITLE	GERMLINE AND SOMATIC BIOMARKER TESTING (INCLUDING LIQUID BIOPSY) FOR TARGETED TREATMENT IN BREAST CANCER (BRCA1, BRCA2, PIK3CA, KI-67, RET, BRAF, ESR1, NTRK)
POLICY NUMBER	MP 2.393

IX. POLICY HISTORY

TOP

MP 2.393	**01/17/2025 Major Review**. New policy adoption.
	06/24/2025 Administrative Update. Removed Benefit Variations Section and updated Disclaimer.
	09/03/2025 Administrative Update. New ICD10 codes added as part of the new code review process for 10/01/2025
	03/03/2026 Retirement Review. Indications to be managed by the vendor Evicore.

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