MEDICAL POLICY

POLICY TITLE	**GERMLINE GENETIC TESTING FOR HEREDITARY BREAST/OVARIAN CANCER SYNDROME AND OTHER HIGH-RISK CANCERS (BRCA1, BRCA2, PALB2)**
POLICY NUMBER	**MP 2.211**

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**

POLICY

Genetic testing should be performed in a setting that has suitably trained health care providers who can give appropriate pre- and post-test counseling and that has access to a Clinical Laboratory Improvement Amendments-licensed laboratory that offers comprehensive variant analysis (see Policy Guidelines section: Comprehensive Variant Analysis).

Individuals With Cancer or With a Personal History of Cancer

Genetic testing for *BRCA1*, *BRCA2,* and *PALB2* variants in cancer-affected individuals may be considered **medically necessary** under any of the following circumstances:

- Individuals with any close blood relative with a known *BRCA1*, *BRCA2*, or *PALB2* pathogenic/likely pathogenic variant (see Policy Guidelines for definitions and for testing strategy).
- Individuals meeting the criteria below but with previous limited testing (*e.g.*, single gene and/or absent deletion duplication analysis)
- Personal history of breast cancer and 1 or more of the following:
    - Diagnosed at age ≤45 years; or
    - Diagnosed at age 46 to 50 years with:
        - An additional breast cancer primary at any age; or
        - ≥1 close relative (see Policy Guidelines) with breast, ovarian, pancreatic, or prostate cancer at any age; or
        - An unknown or limited family history
    - Diagnosed at age ≤60 years with:
        - Triple-negative breast cancer (see Policy Guidelines)
    - Diagnosed at any age with:
        - ≥1 close blood relative with:
            - Breast cancer diagnosed at age ≤50 years; or
            - Ovarian carcinoma; or
            - Metastatic or intraductal/cribriform prostate cancer, or high-risk group or very-high-risk group (see Policy Guidelines) prostate cancer; or
            - Pancreatic cancer; or

        - ≥3 total diagnoses of breast cancer in individual and/or close blood relatives; or
        - Ashkenazi Jewish ancestry
    - Diagnosed at any age with male breast cancer
- Personal history of epithelial ovarian carcinoma (including fallopian tube cancer or peritoneal cancer) at any age
- Personal history of exocrine pancreatic cancer at any age
- Personal history of metastatic or intraductal/cribriform histology prostate cancer at any age; or high-risk group or very-high-risk group prostate cancer at any age
- Personal history of prostate cancer at any age with:
    - ≥1 close blood relative with ovarian carcinoma, pancreatic cancer, or metastatic or intraductal/cribriform prostate cancer at any age, or breast cancer at age ≤50 years; or
    - ≥2 close blood relatives with breast or prostate cancer (any grade) at any age; or
    - Ashkenazi Jewish ancestry
- Personal history of a *BRCA1*, *BRCA2*, or *PALB2* pathogenic/likely pathogenic variant identified on tumor genomic testing that has clinical implications if also identified in the germline.

Individuals Without Cancer or With Other Personal History of Cancer

(See Policy Guidelines section: Testing Unaffected Individuals.)

Genetic testing for *BRCA1, BRCA2,* and *PALB2* variants of cancer-unaffected individuals and individuals with cancer but not meeting the above criteria (including individuals with cancers unrelated to hereditary breast and ovarian cancer syndrome) may be considered **medically necessary** under any of the following circumstances:

- An individual with or without cancer and not meeting the above criteria but who has a 1st- or 2nd-degree blood relative meeting any criterion listed above for Patients with Cancer (except individuals who meet criteria only for systemic therapy decision-making). If the individual with cancer has pancreatic cancer or prostate cancer (metastatic or intraductal/cribriform or high-risk group or very-high-risk group) then only first-degree relatives should be offered testing unless there are other family history indications for testing.
- An individual with any type of cancer (cancer related to hereditary breast and ovarian cancer syndrome but not meeting above criteria, or cancer unrelated to hereditary breast and ovarian cancer syndrome) or unaffected individual who otherwise does not meet the criteria above but has a probability >5% of a *BRCA1/2* or *PALB2* pathogenic variant based on prior probability models (e.g., Tyrer-Cuzick, BRCAPro, Pennll).

Genetic testing for *BRCA*1 and *BRCA2* variants of cancer-affected individuals or cancer-unaffected individuals with a family history of cancer when criteria above are not met is considered **investigational**.

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Testing for *PALB2* variants in individuals who do not meet the criteria outlined above is considered **investigational**.

Genetic testing in minors for *BRCA1, BRCA2,* and *PALB2* variants for hereditary breast and ovarian cancer syndrome is considered **investigational** (see Policy Guidelines).

Policy Guidelines

There are differences in the position statements above and the National Comprehensive Cancer Network (NCCN) guideline on Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic (v.3.2024). Not all of the NCCN criteria are clearly separated for determining hereditary breast and ovarian cancer syndrome versus for guiding therapy. Testing for *BRCA1, BRCA2,* and/or *PALB2* outside of the above criteria, such as testing all individuals with triple negative breast cancer or testing all individuals diagnosed with breast cancer under the age of 50 years, may be indicated for guiding cancer therapies. Genetic testing for *BRCA1* and *BRCA2* variants in breast cancer-, pancreatic cancer-, prostate cancer-, or ovarian cancer-affected individuals who are considering systemic therapy is addressed separately in **MP 2.392**, **MP 2.393**, **MP 2.394**, and **MP 2.395** respectively. Genetic testing for *PALB2* variants in pancreatic cancer-affected individuals is also addressed in **MP 2.392**. Additionally, conflicting criteria reflect that some of the NCCN criteria are based on limited or no evidence; the lower level of evidence might be needed when determining coverage of testing mandated by state biomarker legislation.

Current U.S. Preventive Services Task Force guidelines recommend screening women with a personal or family history of breast, ovarian, tubal, or peritoneal cancer or who have an ancestry associated with *BRCA1/2* gene mutation. Women with a positive result on the risk assessment tool should receive genetic counseling and, if indicated after counseling, genetic testing (B recommendation).

Recommended screening tools designed to identify a family history that may be associated with an increased risk for potentially harmful variants in *BRCA1* or *BRCA2* are:

- Ontario Family History Assessment Tool (FHAT)
- Manchester Scoring System
- Referral Screening Tool (RST)
- Pedigree Assessment Tool (PAT)
- Family History Screen (FHS-7)
- International Breast Cancer Intervention Study instrument (Tyrer-Cuziak)
- Brief versions of the BRCAPRO

Close Relatives

Close relatives are blood related family members including 1st-, 2nd-, and 3rd-degree relatives on the same side of the family (maternal or paternal).

- 1st-degree relatives are parents, siblings, and children.
- 2nd-degree relatives are grandparents, aunts, uncles, nieces, nephews, grandchildren, and half-siblings.
- 3rd-degree relatives are great-grandparents, great-aunts, great-uncles, great-grandchildren, and first cousins.

Prostate Cancer Risk Groups

Risk groups for prostate cancer in this policy include high-risk groups and very-high-risk groups.

High-risk group: no very-high-risk features and are T3a (American Joint Committee on Cancer staging T3a = tumor has extended outside of the prostate but has not spread to the seminal vesicles); OR Grade Group 4 or 5; OR prostate specific antigen of 20 ng/mL or greater.

Very-high-risk group: T3b-T4 (tumor invades seminal vesicle(s); or tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall); OR Primary Gleason Pattern 5; OR 2 or 3 high-risk features; OR greater than 4 cores with Grade Group 4 or 5.

Recommended Testing Strategies

Individuals who meet criteria for genetic testing as outlined in the policy statements above should be tested for variants in *BRCA1, BRCA2,* and *PALB2*. Recommended strategies are listed below.

- In individuals with a known familial *BRCA* or *PALB2* variant, targeted testing for the specific variant is recommended.
- In individuals with unknown familial *BRCA* or *PALB2* variant:
    - To identify clinically significant variants, NCCN advises testing a relative who has early-onset disease, bilateral disease, or multiple primaries, because that individual has the highest likelihood of obtaining a positive test result. Unless the affected individual is a member of an ethnic group for which particular founder pathogenic or likely pathogenic variants are known, comprehensive genetic testing (i.e., full sequencing of the genes and detection of large gene rearrangements) should be performed.
    - If no living family member with breast or ovarian cancer exists, NCCN suggests testing first- or second-degree family members affected with cancer thought to be related to deleterious *BRCA1* or *BRCA2* variants (e.g., prostate cancer, pancreatic cancer, melanoma).
    - If no familial variant can be identified, 2 possible testing strategies are:
- Full sequencing of *BRCA1* and *BRCA2* followed by testing for large genomic rearrangements (deletions, duplications) only if sequencing detects no variant (negative result).

    - More than 90% of *BRCA* variants will be detected by full sequencing.
- Alternatively, simultaneous full sequencing and testing for large genomic rearrangements (also known as comprehensive *BRCA* testing; see Comprehensive Variant Analysis below) may be performed as is recommended by NCCN.
    - Comprehensive testing can detect 92.5% of *BRCA1* or *BRCA2* variants.
- Testing for *BRCA1*, *BRCA2*, and *PALB2* through panel testing over serial testing might be preferred for efficiency. Multi-gene panels often include genes of moderate or low penetrance, and genes with limited evidence on which to base management decisions. When considering a gene panel, NCCN recommends use of "tailored panels that are disease-focused and include clinically actionable cancer susceptibility genes".
- Ashkenazi Jewish descent
    - In individuals of known Ashkenazi Jewish descent, one approach is to test for the 3 known founder mutations (185delAG and 5182insC in *BRCA1*; 6174delT in *BRCA2*) first; if testing is negative for founder mutations and if the individual's ancestry also includes non-Ashkenazi ethnicity (or if other *BRCA1/2* testing criteria are met), comprehensive genetic testing should be considered.

Testing strategy may also include testing individuals not meeting the above criteria who are adopted and have limited medical information on biological family members, individuals with small family structure, and individuals with presumed paternal transmission.

Comprehensive Variant Analysis

Comprehensive variant analysis currently includes sequencing the coding regions and intron and exon splice sites, as well as testing to detect large deletions and rearrangements that can be missed with sequence analysis alone. In addition, before August 2006, testing for large deletions and rearrangements was not performed, thus some individuals with familial breast cancer who had negative *BRCA* testing before this time may consider repeat testing for the rearrangements (see Policy section for criteria).

High-Risk Ethnic Groups

Testing of eligible individuals who belong to ethnic populations in which there are well-characterized founder mutations should begin with tests specifically for these variants. For example, founder mutations account for approximately three-quarters of the *BRCA* variants found in Ashkenazi Jewish populations (see Rationale section). When testing for founder mutations is negative, a comprehensive variant analysis should then be performed.

Testing Unaffected Individuals

In unaffected family members of potential *BRCA* or *PALB2* variant families, most test results will be negative and uninformative. Therefore, it is strongly recommended that an *affected* family member be tested first whenever possible to adequately interpret the test. Should a *BRCA* or *PALB2* variant be found in an affected family member(s), DNA from an *unaffected* family member can be tested specifically for the same variant of the affected

family member without having to sequence the entire gene. Interpreting test results for an unaffected family member without knowing the genetic status of the family may be possible in the case of a positive result for an established disease-associated variant but leads to difficulties in interpreting negative test results (uninformative negative) or variants of uncertain significance because the possibility of a causative *BRCA or PALB2* variant is not ruled out.

Testing for known variants of *BRCA* or *PALB2* genes in an unaffected reproductive partner may be indicated as carrier screening for rare autosomal recessive conditions.

Confirmatory Testing

Consideration might be given at the local level for confirmatory germline testing of a *BRCA* or *PALB2* pathogenic/likely pathogenic variant found on tumor genomic analyses, direct-to-consumer testing, or research testing.

Testing Minors

The use of genetic testing for *BRCA1, BRCA2,* or *PALB2* variants for identifying hereditary breast and ovarian cancer syndrome has limited or no clinical utility in minors, because there is no change in management for minors as a result of knowledge of the presence or absence of a deleterious variant. In addition, there are potential harms related to stigmatization and discrimination. See policy MP 2.362 regarding testing of *BRCA1*, *BRCA2,* and *PALB2* for Fanconi anemia. See policies **2.392**, **2.393**, **2.394**, and **2.395** regarding genetic testing to guide targeted therapy.

Prostate Cancer

Individuals with *BRCA* or *PALB2* variants have an increased risk of prostate cancer, and individuals with known *BRCA* or *PALB2* variants may, therefore, consider more aggressive screening approaches for prostate cancer.

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 PG1. Nomenclature to Report on Variants Found in DNA

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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 PG2. 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.

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.

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Cross-References:

MP 2.255 Genetic Testing for *PTEN* Hamartoma Tumor Syndrome
MP 2.259 Expanded Molecular Panel Testing of Cancers to Identify Targeted Therapies
MP 2.267 Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy)
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 2.326 General Approach to Genetic Testing
MP 2.377 Molecular Testing for Germline Variants Associated with Ovarian Cancer (*BRIP1, RAD51C, RAD51D, NBN*)
MP 2.384 Germline Genetic Testing for Hereditary Diffuse Gastric Cancer (*CDH1, CTNNA1*)
MP 2.392 Germline Genetic Testing for Pancreatic Cancer Susceptibility Genes (*ATM, BRCA1, BRCA2, CDKN2A, EPCAM, MLH1, MSH2, MSH6, PALB2, PMS2, STK11, and TP53*)
MP 2.393 Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Breast Cancer (*BRCA1, BRCA2, PIK3CA, Ki-67, RET, BRAF, ESR1, NTRK*)
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

PRODUCT VARIATIONS

This policy is only applicable to certain programs and products administered by Capital Blue Cross and subject to benefit variations. 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

DESCRIPTION/BACKGROUND

Hereditary Breast and Ovarian Cancer Syndrome

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Several genetic syndromes with an autosomal dominant pattern of inheritance that features breast cancer have been identified. Of these, hereditary breast and ovarian cancer (HBOC) syndrome 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, Capital 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.

Evidence suggests that genetic services are not equitably applied. Chapman-Davis et al (2021) found that non-Hispanic Whites and Asians were more likely to be referred for genetic services based solely on family history than were non-Hispanic Blacks and Hispanics. In addition, non-Hispanic Black patients and Hispanic patients were more likely to have advanced cancer when referred for genetic services than non-Hispanic Whites and Asians.

Clinical Features Suggestive of BRCA Variant

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 years. 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 to 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.

As in the general population, a family history of breast or ovarian cancer, particularly of early age onset, is a significant risk factor for a *BRCA* variant in ethnic populations characterized by founder mutations. For example, in unaffected individuals of Ashkenazi Jewish descent, 12% to

31% will have a *BRCA* variant depending on the extent and nature of the family history. Several other studies have documented the significant influence of family history.

In patients with "triple-negative" breast cancer (i.e., negative for expression of estrogen, progesterone, and overexpression of human epidermal growth factor receptor 2 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. In 200 randomly selected patients with triple-negative breast cancer from a tertiary care center, Kandel et al (2006) reported there was a greater than 3-fold increase in the expected rate of *BRCA* variants. *BRCA1* variants were found in 39.1% of patients and *BRCA2* variants in 8.7%. 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*).

PALB2 Gene

The *PALB2* gene (partner and localizer of *BRCA2*) encodes for a protein first described in 2006. The gene is located at 16p12.2 [Short (p) arm of chromosome 16 at position 12.2.] and has 13 exons. PALB2 protein assists *BRCA2* in DNA repair and tumor suppression. Heterozygous pathogenic *PALB2* variants increase the risk of developing breast and pancreatic cancers; homozygous variants are found in Fanconi anemia. Fanconi anemia is a rare disorder, primarily affecting children, that causes bone marrow failure. Affected individuals also carry a risk of cancers including leukemia. Most pathogenic *PALB2* variants are truncating frameshift or stop codons and are found throughout the gene. Pathogenic *PALB2* variants are uncommon in unselected populations and prevalence varies by ethnicity and family history. For example, Antoniou et al (2014) assumed a prevalence of 8 per 10,000 in the general population when modeling breast cancer risks. Variants are more prevalent in ethnic populations where founder mutations have persisted (e.g., Finns, French Canadians, Poles), while infrequently found in others (e.g., Ashkenazi Jews). In women with a family history of breast cancer, the prevalence of pathogenic *PALB2* variants ranges between 0.9% and 3.9%, or substantially higher than in an unselected general population. Depending on population prevalence, *PALB2* may be responsible for as much as 2.4% of hereditary breast cancers; and in populations with founder mutations cause 0.5% to 1% of all breast cancers.

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. Genetic tests reviewed in this evidence review are available under the auspices 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 (FDA) has chosen not to require any regulatory review of this test.

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RATIONALE

SUMMARY OF EVIDENCE

For individuals who have cancer or a personal or family cancer history and meet criteria suggesting a risk of HBOC syndrome who receive genetic testing for a *BRCA1* or *BRCA2* variant, the evidence includes a TEC Assessment and studies of variant prevalence and cancer risk. Relevant outcomes are overall survival, disease-specific survival, test validity, and quality of life. The accuracy of variant testing has been shown to be high. Studies of lifetime risk of cancer for carriers of a *BRCA* variant have shown a risk as high as 85%. Knowledge of *BRCA* variant status in individuals at risk of a *BRCA* variant may impact health care decisions to reduce risk, including intensive surveillance, chemoprevention, and/or prophylactic intervention. In individuals with *BRCA1* or *BRCA2* variants, prophylactic mastectomy and oophorectomy have been found to significantly increase disease-specific survival and overall survival. Knowledge of *BRCA* variant status in individuals diagnosed with breast cancer may impact treatment decisions. A randomized controlled trial has reported that patients with human epidermal growth factor receptor 2-negative metastatic breast cancer and a *BRCA* variant experienced significantly longer progression-free survival with a targeted therapy vs standard therapy. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have other high-risk cancers (e.g., cancers of the fallopian tube, pancreas, and prostate) who receive genetic testing for a *BRCA1* or *BRCA2* variant, the evidence includes studies of variant prevalence and cancer risk. Relevant outcomes are overall survival, disease-specific survival, test validity, and quality of life. The accuracy of variant testing has been shown to be high. Knowledge of *BRCA* variant status in individuals with other high-risk cancers can inform decisions regarding genetic counseling, chemotherapy, and enrollment in clinical trials. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals with a risk of HBOC syndrome who receive genetic testing for a *PALB2* variant, the evidence includes studies of clinical validity and studies of breast cancer risk, including a meta-analysis. Relevant outcomes are OS, disease-specific survival, and test validity. Evidence supporting clinical validity was obtained from numerous studies reporting relative risks (RRs) or odds ratios (ORs). Study designs included family segregation, kin-cohort, family-based case-control, and population-based case-control. The number of pathogenic variants identified in studies varied from 1 (founder mutations) to 48. The RR for breast cancer associated with a *PALB2* variant ranged from 2.3 to 13.4, with the 2 family-based studies reporting the lowest values. Evidence of preventive interventions in women with *PALB2* variants is indirect, relying on studies of high-risk women and *BRCA* carriers. These interventions include screening with magnetic resonance imaging, chemoprevention, and risk-reducing mastectomy. Given the penetrance of *PALB2* variants, the outcomes following bilateral and contralateral risk-reducing mastectomy examined in women with a family history consistent with hereditary breast cancer (including *BRCA1* and *BRCA2* carriers) can be applied to women with *PALB2* variants, with the

benefit-to-risk balance affected by penetrance. In women at high-risk of hereditary breast cancer who would consider risk-reducing interventions, identifying a *PALB2* variant provides a more precise estimated risk of developing breast cancer compared with family history alone and can offer women a more accurate understanding of benefits and potential harms of any intervention. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

DEFINITIONS

NA

DISCLAIMER

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.

CODING INFORMATION

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.

Non-covered:

Procedure Codes:								
0102U	0103U	0129U	0134U	0137U	0138U	0474U	81432	

Covered when medically necessary:

Procedure Codes:								
81162	81163	81164	81165	81166	81167	81212	81215	81216
81217	81307	81308	81479					

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ICD-10-CM Diagnosis Code	Description
C25.0	Malignant neoplasm of head of pancreas
C25.1	Malignant neoplasm of body of pancreas
C25.2	Malignant neoplasm of tail of pancreas
C25.3	Malignant neoplasm of pancreatic duct
C25.4	Malignant neoplasm of endocrine pancreas
C25.7	Malignant neoplasm of other parts of pancreas
C25.8	Malignant neoplasm of overlapping sites of pancreas
C25.9	Malignant neoplasm of pancreas, unspecified
C48.0	Malignant neoplasm of retroperitoneum
C48.1	Malignant neoplasm of specified parts of peritoneum
C48.2	Malignant neoplasm of peritoneum, unspecified
C48.8	Malignant neoplasm of overlapping sites of retroperitoneum
C50.011	Malignant neoplasm of nipple and areola, right female breast
C50.012	Malignant neoplasm of nipple and areola, left female breast
C50.019	Malignant neoplasm of nipple and areola, unspecified female breast
C50.021	Malignant neoplasm of nipple and areola, right male breast
C50.022	Malignant neoplasm of nipple and areola, left male breast
C50.029	Malignant neoplasm of nipple and areola, unspecified male breast
C50.111	Malignant neoplasm of central portion of right female breast
C50.112	Malignant neoplasm of central portion of left female breast
C50.119	Malignant neoplasm of central portion of unspecified female breast
C50.121	Malignant neoplasm of central portion of right male breast
C50.122	Malignant neoplasm of central portion of left male breast
C50.129	Malignant neoplasm of central portion of unspecified male breast
C50.211	Malignant neoplasm of upper-inner quadrant of right female breast
C50.212	Malignant neoplasm of upper-inner quadrant of left female breast
C50.221	Malignant neoplasm of upper-inner quadrant of right male breast
C50.222	Malignant neoplasm of upper-inner quadrant of left male breast
C50.229	Malignant neoplasm of upper-inner quadrant of unspecified male breast
C50.311	Malignant neoplasm of lower-inner quadrant of right female breast
C50.312	Malignant neoplasm of lower-inner quadrant of left female breast
C50.319	Malignant neoplasm of lower-inner quadrant of unspecified female breast
C50.321	Malignant neoplasm of lower-inner quadrant of right male breast
C50.322	Malignant neoplasm of lower-inner quadrant of left male breast
C50.329	Malignant neoplasm of lower-inner quadrant of unspecified male breast
C50.411	Malignant neoplasm of upper-outer quadrant of right female breast
C50.412	Malignant neoplasm of upper-outer quadrant of left female breast
C50.419	Malignant neoplasm of upper-outer quadrant of unspecified female breast
C50.421	Malignant neoplasm of upper-outer quadrant of right male breast

POLICY TITLE	GERMLINE GENETIC TESTING FOR HEREDITARY BREAST/OVARIAN CANCER SYNDROME AND OTHER HIGH-RISK CANCERS (BRCA1, BRCA2, PALB2)
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C50.422	Malignant neoplasm of upper-outer quadrant of left male breast
C50.429	Malignant neoplasm of upper-outer quadrant of unspecified male breast
C50.511	Malignant neoplasm of lower-outer quadrant of right female breast
C50.512	Malignant neoplasm of lower-outer quadrant of left female breast
C50.519	Malignant neoplasm of lower-outer quadrant of unspecified female breast
C50.521	Malignant neoplasm of lower-outer quadrant of right male breast
C50.522	Malignant neoplasm of lower-outer quadrant of left male breast
C50.529	Malignant neoplasm of lower-outer quadrant of unspecified male breast
C50.611	Malignant neoplasm of axillary tail of right female breast
C50.612	Malignant neoplasm of axillary tail of left female breast
C50.619	Malignant neoplasm of axillary tail of unspecified female breast
C50.621	Malignant neoplasm of axillary tail of right male breast
C50.622	Malignant neoplasm of axillary tail of left male breast
C50.629	Malignant neoplasm of axillary tail of unspecified male breast
C50.811	Malignant neoplasm of overlapping sites of right female breast
C50.812	Malignant neoplasm of overlapping sites of left female breast
C50.819	Malignant neoplasm of overlapping sites of unspecified female breast
C50.821	Malignant neoplasm of overlapping sites of right male breast
C50.822	Malignant neoplasm of overlapping sites of left male breast
C50.829	Malignant neoplasm of overlapping sites of unspecified male breast
C50.911	Malignant neoplasm of unspecified site of right female breast
C50.912	Malignant neoplasm of unspecified site of left female breast
C50.919	Malignant neoplasm of unspecified site of unspecified female breast
C50.921	Malignant neoplasm of unspecified site of right male breast
C50.922	Malignant neoplasm of unspecified site of left male breast
C50.929	Malignant neoplasm of unspecified site of unspecified male 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
C56.1	Malignant neoplasm of right ovary
C56.2	Malignant neoplasm of left ovary
C56.3	Malignant neoplasm of bilateral ovaries
C56.9	Malignant neoplasm of unspecified ovary
C57.00	Malignant neoplasm of unspecified fallopian tube
C57.01	Malignant neoplasm of right fallopian tube
C57.02	Malignant neoplasm of left fallopian tube
C57.8	Malignant neoplasm of overlapping sites of female genital organs
C61	Malignant neoplasm prostate
C79.60	Secondary malignant neoplasm of unspecified ovary
C79.61	Secondary malignant neoplasm of right ovary
C79.62	Secondary malignant neoplasm of left ovary
C79.63	Secondary malignant neoplasm of bilateral ovaries

POLICY TITLE	GERMLINE GENETIC TESTING FOR HEREDITARY BREAST/OVARIAN CANCER SYNDROME AND OTHER HIGH-RISK CANCERS (BRCA1, BRCA2, PALB2)
POLICY NUMBER	MP 2.211

C79.81	Secondary malignant neoplasm of breast
D05.01	Lobular carcinoma in situ of right breast
D05.02	Lobular carcinoma in situ of left breast
D05.10	Intraductal carcinoma in situ of unspecified breast
D05.11	Intraductal carcinoma in situ of right breast
D05.12	Intraductal carcinoma in situ of left breast
D05.80	Other specified type of carcinoma in situ of unspecified breast
D05.81	Other specified type of carcinoma in situ of right breast
D05.82	Other specified type of carcinoma in situ of left breast
D05.91	Unspecified type of carcinoma in situ of right breast
D05.92	Unspecified type of carcinoma in situ of left breast
Z15.01	Genetic susceptibility to malignant neoplasm of breast
Z15.02	Genetic susceptibility to malignant neoplasm of ovary
Z15.05	Genetic susceptibility to malignant neoplasm of fallopian tube(s)
Z80.3	Family history of malignant neoplasm of breast
Z80.41	Family history of malignant neoplasm of ovary
Z80.44	Family history of malignant neoplasm of fallopian tube(s)
Z80.49	Family history of malignant neoplasm of other genital organs
Z80.8	Family history of malignant neoplasm of other organs or systems
Z85.3	Personal history of malignant neoplasm of breast
Z85.43	Personal history of malignant neoplasm of ovary
Z85.4A	Personal history of malignant neoplasm of fallopian tube(s)
Z86.00A	Personal history of in-situ neoplasm of the fallopian tube(s)

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POLICY HISTORY

MP 2.211	**03/06/2020 Consensus Review**. Policy statement unchanged. References, policy guidelines and regulatory status updated. Coding reviewed.
	07/01/2020 Administrative Update. New code 0172U added.
	05/14/2021 Consensus Review. Added NCCN statement. Updated Policy Guidelines and References. No changes to coding.
	09/07/2021 Administrative Update. New codes C56.3 and C79.63 added. Effective 10/01/2021
	10/28/2022 Minor Review. Updated criteria to align with NCCN version 1.2023. Testing of minors is now NMN. RNA testing is INV. Updated background, rationale, and references. Updated coding table: added several procedure codes to both the MN and non-covered tables. Removed 0172U as it is for somatic testing (can be found in MP 2.326). Title update to accommodate PALB2 testing.
	12/21/2023 Minor Review. Created sections for breast cancer, ovarian cancer, pancreatic cancer, and prostate cancer. Criteria created for each section to align with NCCN. Policy now allows for more than BRCA1/2 and PALB2 testing. Each section specifies the variants that can be tested for if criteria met. 0129U moved to MN coding table. Codes 81408, 0135U, and 0136U were added to this policy.
	06/07/2024 Administrative Update. Addition of new code 0474U. Effective date 07/01/2024.
	12/10/2024 Administrative Update. Deletion of code 81433 effective 01/01/2025
	01/10/2025 Minor Review. Title change; policy now only includes BRCA1, BRCA2, and PALB2 variants. Updated policy statements, policy guidelines,

POLICY TITLE	GERMLINE GENETIC TESTING FOR HEREDITARY BREAST/OVARIAN CANCER SYNDROME AND OTHER HIGH-RISK CANCERS (BRCA1, BRCA2, PALB2)
POLICY NUMBER	MP 2.211

	background, and rationale. Updated coding table to align with modified criteria statements.
	06/11/2025 Administrative Update. Removing the Benefit Variations Section and updating the Disclaimer.
	09/02/2025 Administrative Update Addition of new ICD10 codes effective 10/01/2025
	11/13/2025 Consensus Review. Updated references. Removed procedure codes 0131U, 0132U & 0135U as they are no longer effective 01/01/2026.
	03/05/2026 Retirement Review. EviCore delegation