MEDICAL POLICY

POLICY TITLE	**GERMLINE GENETIC TESTING FOR HEREDITARY BREAST/OVARIAN CANCER SYNDROME AND OTHER HIGH-RISK CANCERS (FORMERLY 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:	**1/1/2025**

I. POLICY

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

Germline genetic testing for high-penetrance breast cancer susceptibility genes (specifically BRCA1, BRCA2, CDH1, PALB2, PTEN, STK11, and TP53) may be considered **medically necessary** under any of the following circumstances:

- Individuals with any blood relative with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene; or
- A pathogenic/likely pathogenic variant identified on tumor genomic testing that has clinical implications if also identified in the germline; or
- To aid in systemic therapy and surgical decision-making; or
- Individuals meeting the criteria below but with previous limited testing (e.g., single gene analysis, testing without deletion duplication analysis, or testing prior to 2006); or
- Individuals with a personal history of breast cancer and 1 or more of the following:
    - Diagnosed at age ≤50 years; or
    - Ashkenazi Jewish ancestry; or
    - Breast cancer in individuals who are assigned male at birth; or
    - Triple-negative breast cancer; or
    - Multiple primary breast cancers (synchronous or metachronous); or
    - Lobular breast cancer with personal or family history of diffuse gastric cancer; or

    - Diagnosed at any age with:
        - ≥1 close blood relative with:
            - Breast cancer diagnosed at age ≤50 years; or
            - Breast cancer at any age (this criteria point only applies if the close blood relative was assigned male at birth); or
            - Ovarian cancer; or
            - Prostate cancer with metastatic, or high- or very-high-risk group (see Policy Guidelines); or
            - Pancreatic cancer; or
        - ≥ 3 diagnoses of breast and/or prostate cancer (any grade) on the same side of the family including the individual with breast cancer; or

- Individuals affected with breast cancer (not meeting testing criteria listed above) or individual unaffected with breast cancer AND
    - The individual has a first- or second-degree blood relative meeting any of the criteria listed above (except unaffected individuals whose relatives meet criteria only for systemic therapy decision-making);
- Individuals affected or unaffected with breast cancer who otherwise do not meet the criteria above but have a probability of >5% of a BRCA 1/2 P/LP variant based on prior probability models (e.g., Tyrer-Cuzick, BRCAPro, CanRisk).

Germline genetic testing for ovarian cancer susceptibility genes (specifically ATM, BRCA1, BRCA2, BRIP1, Lynch syndrome genes [MLH1, MSH2, MSH6, EPCAM], PALB2, RAD51C, and RAD51D) may be considered **medically necessary** under any of the following circumstances:

- Individuals with any blood relative with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene; or
- A pathogenic/likely pathogenic variant identified on tumor genomic testing that has clinical implications if also identified in the germline; or
- To aid in systemic therapy and surgical decision-making; or
- Individuals meeting the criteria below but with previous limited testing (e.g., single gene analysis, testing without deletion duplication analysis, or testing prior to 2006); or
- Personal history of epithelial ovarian cancer (including fallopian tube cancer or peritoneal cancer) at any age; or

- Individuals unaffected with ovarian cancer with a first- or second-degree blood relative with epithelial ovarian cancer (including fallopian tube cancer or peritoneal cancer) at any age; or
- Individuals unaffected with ovarian cancer who otherwise does not meet the criteria above but have a probability >5% of a BRCA 1/2 P/LP variant based on prior probability models (e.g. Tyrer-Cuzick, BRCAPro, CanRisk).

Germline genetic testing for pancreatic cancer susceptibility genes (specifically ATM, BRCA1, BRCA2, CDKN2A, Lynch syndrome genes [MLH1, MSH2, MSH6, EPCAM], PALB2, STK11, and TP53) may be considered **medically necessary** under any of the following circumstances:

- Individuals with any blood relative with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene; or
- A pathogenic/likely pathogenic variant identified on tumor genomic testing that has clinical implications if also identified in the germline; or
- To aid in systemic therapy and surgical decision-making; or
- Individuals meeting the criteria below but with previous limited testing (e.g., single gene analysis, testing without deletion duplication analysis, or testing prior to 2006); or
- Individuals that have been diagnosed with exocrine pancreatic cancer; or
- Individuals unaffected with pancreatic cancer with a first-degree relative who was diagnosed with exocrine pancreatic cancer; or
- Individuals that have been diagnosed with neuroendocrine pancreatic tumors (i.e., gastrinoma).

Germline genetic testing for prostate cancer susceptibility genes (specifically ATM, BRCA1, BRCA2, CHEK2, and HOXB13) may be considered **medically necessary** under any of the following circumstances:

- Individuals with any blood relative with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene; or
- A pathogenic/likely pathogenic variant identified on tumor genomic testing that has clinical implications if also identified in the germline; or
- To aid in systemic therapy and surgical decision-making; or
- Individuals meeting the criteria below but with previous limited testing (e.g., single gene analysis, testing without deletion duplication analysis, or testing prior to 2006); or

- Individuals with a personal history of metastatic, or high- or very-high-risk group prostate cancer at any age; or
- Individuals with a personal history of prostate cancer at any age with ≥1 close blood relative with:
    - Breast cancer diagnosed ≤50; or
    - Triple-negative breast cancer at any age; or
    - Breast cancer at any age (this criteria point only applies if the close blood relative was assigned male at birth); or
    - Ovarian cancer at any age; or
    - Pancreatic cancer at any age; or
    - Metastatic, high- or very-high-risk group prostate cancer at any age; or
- Individuals with a personal history of prostate cancer and ≥3 close blood relatives with prostate cancer (any grade) and/or breast cancer on the same side of the family including the individual with prostate cancer; or
- Individuals with a personal history of prostate cancer and Ashkenazi Jewish ancestry; or
- Individuals affected with prostate cancer (not meeting testing criteria listed above) or individuals unaffected with prostate cancer AND
    - The individual has a first-degree blood relative meeting any of the criteria listed above (except unaffected individuals whose relatives meet criteria only for systemic therapy decision-making)

Germline genetic testing in minors for variants for hereditary breast ovarian cancer syndrome and other high-risk cancers is considered **not medically necessary** (see Policy Guidelines). There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

Testing for germline variants, including but not limited to NBN and BARD1 variants, for hereditary breast/ovarian cancer syndrome and other high-risk cancers are considered **investigational.** There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

Germline genetic testing for variants in cancer-affected individuals or of cancer-unaffected individuals with a family history of cancer when criteria above are not met is considered **investigational**. There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

POLICY TITLE	GERMLINE GENETIC TESTING FOR HEREDITARY BREAST/OVARIAN CANCER SYNDROME AND OTHER HIGH-RISK CANCERS (FORMERLY GERMLINE GENETIC TESTING FOR HEREDITARY BREAST/OVARIAN CANCER SYNDROME AND OTHER HIGH-RISK CANCERS (BRCA1, BRCA2, PALB2))
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RNA testing alone or in conjunction with DNA analysis is considered **investigational**. There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

The National Comprehensive Cancer Network (NCCN) is a nonprofit alliance of cancer centers throughout the United States. NCCN develops the Clinical Practice Guidelines in Oncology which are recommendations aimed to help health care professionals diagnose, treat, and manage patients with cancer. Guidelines evolve continuously as new treatments and diagnostics emerge and may be used by Capital Blue Cross when determining medical necessity according to this policy.

Policy Guidelines

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

- First-degree relatives: parents, siblings, and children;
- Second-degree relatives: grandparents, aunts, uncles, nieces, nephew, grandchildren, and half-siblings;
- Third-degree relatives: great-grandparents, great-aunts, great-uncles, great-grandchildren, first cousins, and half aunts and uncles.

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 specifically identified in each section. Recommended strategies are listed below.

- In individuals with a known familial variant, targeted testing for the specific variant is recommended.
- In individuals with unknown familial variant:

- To identify clinically significant variants, National Comprehensive Cancer Network (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 variants (e.g., prostate cancer, pancreatic cancer, melanoma).
- If no familial variant can be identified, 2 possible testing strategies are:
  - Full sequencing 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 testing; see Comprehensive Variant Analysis below) may be performed as is recommended by NCCN.
    - Comprehensive testing can detect 92.5% of *BRCA*1 or *BRCA2* variants.

- Testing for variants 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
  - If patient is of known Ashkenazi Jewish descent, 1 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 included non-Ashkenazi ethnicity (or if other BRCA1/2 testing criteria are met), comprehensive genetic testing should be considered.

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 patients with familial breast

cancer who had negative variant 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. When testing for founder mutations is negative, comprehensive variant analysis should then be performed.

Testing Unaffected Individuals

In unaffected family members of potential 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 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 variant is not ruled out.

Testing Minors

The American Academy of Pediatrics states that “predictive genetic testing for adult-onset conditions generally should be deferred unless an intervention initiated in childhood may reduce morbidity or mortality. An exception might be made for families for whom diagnostic uncertainty poses a significant psychosocial burden, particularly when an adolescent and his or her parents concur in their interest in predictive testing”.

The National Society of Genetic Counselors “encourages deferring predictive genetic testing of minors for adult-onset conditions when results will not impact childhood medical management or significantly benefit the child. Predictive testing should optimally be deferred until the individual has the capacity to weigh the associated risks, benefits, and limitations of this information, taking his/her circumstances, preferences, and beliefs into account to preserve his/her autonomy and right to an open future”.

Prostate Cancer

Individuals with high penetrant variants have an increased risk of prostate cancer, and individuals with known high penetrant variants may, therefore, consider more aggressive screening approaches for prostate cancer.

Genetic Counseling

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

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 2.325 Genetic Cancer Susceptibility Panels Using Next Generation Sequencing
MP 2.326 General Approach to Genetic Testing
MP 2.384 Germline Genetic Testing for Hereditary Diffuse Gastric Cancer (CDH1, CTNNA1)
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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Hereditary Breast and Ovarian Cancer Syndrome

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.

The National Cancer Institute estimated there would be 297,790 new cases of female breast cancer (FBC) and 2,800 cases of male breast cancer (MBC) diagnosed in 2023, with an expected 43,170 deaths due to FBC and 530 deaths due to MBC. Although non-Hispanic, white women are more likely to be diagnosed with breast cancer than non-Hispanic Black, Asian/Pacific Islander, American Indian/Alaska Native and Hispanic women, non-Hispanic Black women have the highest risk of breast cancer mortality. Breast cancers can be classified as sporadic, familial, or hereditary. Most breast cancers are sporadic (70% to 75%), occurring in women without a family history of the disease. Familial cancers (15% to 25%) aggregate within families but lack clearly discernable patterns of inheritance and are likely polygenic. Hereditary cancers have discernable inheritance patterns, often occur at younger ages, may be bilateral, and comprise between 5% and 10% of breast cancers. Most inherited autosomal dominant breast cancer can be attributed to the BRCA1 and BRCA2 variants. For women who inherit a pathogenic BRCA1 and BRCA2 variants, 45% to 72% will develop breast cancer by 70-80 years of age; risk in men with BRCA1 and BRCA2 variants is much lower (1% and 7%, respectively). Pathogenic variants in other highly penetrant genes (e.g., TP53, CDH1, PTEN, STK11) contribute to a smaller number of cancer cases. CHEK2 and ATM are believed to be moderately penetrant and BARD1 has alternatively been described as moderate, low/moderate, and low penetrance.

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.

CHEK2 Gene

The *CHEK2* (checkpoint kinase 2) gene is activated in response to DNA double-strand breakage and plays a role in cell-cycle control, DNA repair, and apoptosis.

In 2002, a single recurrent truncating mutation in the *CHEK2* gene (c.1100delC) was first reported as a cause of breast cancer, and studies have since confirmed this. The incidence of *CHEK2* variants varies widely among populations. It is most prevalent in Eastern and Northern Europe, where the population frequency of the c.1100delC allele ranges from 0.5% to 1.4%; the allele is less frequent in North America and virtually absent in Spain and India. When compared with non-Hispanic, white individuals, prevalence appears to be lower in Black (odds ratio [OR] 0.17; 95% CI, 0.07 to 0.33), Asian (OR 0.14; 95% CI, 0.04 to 0.34), and Hispanic (OR 0.36; 95% CI, 0.18 to 0.62) individuals.

Although most data for truncating *CHEK2* variants are limited to the c.1100delC allele, 3 other founder variants of *CHEK2* (IVS2+1G>A, del5395, I157T) have been associated with breast cancer in Eastern Europe. Both IVS2+1G>A and del5395 are protein-truncating variants, and I157T is a missense variant. The truncating variants are associated with breast cancer in the Slavic populations of Poland, Belarus, Russia, and the Czech Republic. The I157T variant has a wider geographic distribution and has been reported to be associated with breast cancer in Poland, Finland, Germany, and Belarus.

ATM Gene

ATM (ataxia-telangiectasia mutated), located on chromosome 11q22.3, is associated with the autosomal recessive condition ataxia-telangiectasia. This condition is characterized by progressive cerebellar ataxia with onset between the ages of 1 and 4 years, telangiectasias of the conjunctivae, oculomotor apraxia, immune defects, and cancer predisposition. Female *ATM* heterozygotes carriers have a risk of breast cancer about twice as high as that of the general population; however, they do not appear to have an elevated ovarian cancer risk.

BARD1 Gene

The *BARD1* (BRCA1-associated RING [Really Interesting New Gene] domain) gene is located on chromosome 2 (sequence 2q34-q35). *BARD1* encodes a protein which interacts with the N-terminal region of *BRCA1*, and *BARD1* and *BRCA1* can form a heterodimer by their N-terminal

RING finger domains which form a stable complex. *BARD1* variants have been associated with an increased risk of estrogen-receptor (ER) negative breast cancer, triple-negative breast cancer, and with breast cancer at a younger age (under age 50 years) in some studies, but do not appear to increase risk of ovarian cancer.

RNA Testing

A counseling dilemma is posed by the finding of a variant of uncertain significance (VUS). VUS is a variation in a genetic sequence for which the association with disease risk is unclear. The genetic alteration may actually represent a benign polymorphism unrelated to an increased cancer risk or it may indicate an increased cancer risk. While a VUS should not be used to guide clinical management, additional testing can be considered to help reclassify the variant. One of the most currently used methods is RNA analytics. RNA testing can be performed after single gene or panel testing to help reclassify VUS. Increasingly, paired DNA and RNA testing are being performed at the same time to identify patients with or at risk for hereditary cancer who might otherwise be missed and decrease VUS in real-time.

IV. RATIONALE

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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 HBOC syndrome and ovarian cancer or other high-risk cancers considering systemic therapy options who receive genetic testing for a *BRCA1* or *BRCA2* variant, the evidence includes several randomized controlled trials (RCT) and single-arm trials. Relevant outcomes are OS, disease-specific survival, test validity, and quality of life. The numerous placebo-controlled RCTs of poly (adenosine diphosphate–ribose) polymerase (PARP) inhibitor drugs have consistently demonstrated that, in individuals with ovarian cancer and a germline *BRCA* variant, treatment with PARP inhibitor drugs significantly improve progression-free survival time. In individuals with *BRCA*-mutated metastatic castration-resistant prostate cancer, a single-arm clinical trial of rucaparib demonstrated a benefit on a surrogate outcome of objective response rate and evaluation of its effects on progression-free survival is pending completion of the ongoing randomized, standard care-controlled confirmatory TRITON3 trial (NCT02975934). Rates of overall Grade 3 or 4 adverse events ranged from 25.5% to 63.2% across PARP inhibitor drugs. The evidence is sufficient to determine that the technology results in an 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.

For individuals with HBOC Syndrome or other high-risk cancers and individuals with a risk of HBOC Syndrome or other-high risk cancers who receive genetic testing for CDH1, PTEN, STK11, TP53, ATM, BRIP1, Lynch syndrome genes [MLH1, MSH2, MSH6, EPCAM], RAD51C,

RAD51D, CDKN2A, CHEK2, and HOXB13, the evidence includes societal guidance from NCCN. Due to their recommendation for testing in Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic, the evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who receive RNA based genetic testing, there is limited data available. Larger, well-designed prospective studies are needed which demonstrate the clinical utility of RNA analysis alone or paired with DNA analysis to aid in the classification of VUS or to otherwise detect, diagnose or manage cancer. Differences in how RNA analysis is interpreted between laboratories can lead to discrepancies in variant classification. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

V. DEFINITIONS

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NA

VI. BENEFIT VARIATIONS

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The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations should be based in all cases on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. A member's health benefit plan governs which services are covered, which are excluded, which are subject to benefit limits, and which require preauthorization. There are different benefit plan designs in each product administered by Capital Blue Cross. Members and providers should consult the member's health benefit plan for information or contact Capital Blue Cross for benefit information.

VII. DISCLAIMER

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Capital Blue Cross' medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. If a provider or a member has a question concerning the application of this medical policy to a specific member's plan of benefits, please contact Capital Blue Cross' Provider Services or Member Services. Capital Blue Cross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

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

Non-covered:

Procedure Codes:								
0102U	0103U	0131U	0132U	0134U	0135U	0136U	0137U	0138U
0474U								

Covered when medically necessary:

Procedure Codes:								
81162	81163	81164	81165	81166	81167	81212	81215	81216
81217	81307	81308	81406	81408	81432	81479	0129U	

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

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

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

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
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
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
Q85.81	PTEN hamartoma tumor syndrome
Q85.82	Other Cowden syndrome
Z15.01	Genetic susceptibility to malignant neoplasm of breast
Z15.02	Genetic susceptibility to malignant neoplasm of ovary
Z17.0	Estrogen receptor positive status [ER+]
Z17.1	Estrogen receptor negative status [ER-]
Z80.0	Family history of malignant neoplasm of digestive organs
Z80.3	Family history of malignant neoplasm of breast

Z80.41	Family history of malignant neoplasm of ovary
Z80.42	Family history of malignant neoplasm of prostate
Z80.49	Family history of malignant neoplasm of other genital organs
Z80.8	Family history of malignant neoplasm of other organs or systems
Z85.07	Personal history of malignant neoplasm of pancreas
Z85.3	Personal history of malignant neoplasm of breast
Z85.43	Personal history of malignant neoplasm of ovary
Z85.46	Personal history of malignant neoplasm of prostate

IX. REFERENCES

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X. POLICY HISTORY

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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 7/1/2024.
	12/10/2024 Administrative Update. Deletion of code 81433 effective 1/1/2025

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