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

Effective Date:	4/1/2023

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).

Members With Cancer or With a Personal History of Cancer

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

- Members with any blood relative with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene; or
- Members meeting the criteria below but with previous limited testing (eg, single gene analysis, testing without deletion duplication analysis, or testing prior to 2006); or
- Members 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 members 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
    - Unknown or limited family history (i.e. adoption or fewer than 2 female first- or second- degree relatives having lived beyond age 45 in either lineage); or
    - Diagnosed at any age with:
        - ≥1 close blood relative with:
            - Breast cancer diagnosed at age ≤50 years; or
            - Breast cancer in relative assigned male at birth; or
            - Ovarian cancer; or
            - Metastatic, high- or very-high-risk group prostate cancer (see Policy Guidelines); or
            - Pancreatic cancer; or

    - ≥ 3 total diagnoses of breast cancer in member and/or close blood relatives; or
    - ≥ 2 close blood relatives with either breast or prostate cancer (any grade); or

- Personal history of epithelial ovarian cancer (including fallopian tube cancer or peritoneal cancer) at any age; or
- Personal history of exocrine pancreatic cancer at any age; or
- Personal history of metastatic, high- or very-high-risk group prostate cancer at any age; or
- 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 in relative 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
    - ≥2 close blood relatives with breast or prostate cancer (any grade) at any age; or
    - Ashkenazi Jewish ancestry; or
- Personal history of cancer and a mutation identified on tumor genomic testing that has clinical implications if also identified in the germline; or
- Personal history of cancer and to aid in systemic therapy and surgical decision-making (e.g., PARP-inhibitors for ovarian cancer, prostate cancer, pancreatic cancer, and metastatic HER2-negative breast cancer, platinum therapy for prostate cancer and pancreatic cancer, and risk-reducing surgery).

Members Without Cancer or With Other Personal History of Cancer

(See Policy Guidelines section: Testing Unaffected Individuals.)

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

- The unaffected member has any blood relative with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene; or

- The affected or unaffected member has a 1st- or 2nd-degree blood relative meeting any criterion listed above for Members With Cancer (except unaffected members whose relatives meet criteria only for systemic therapy decision-making).
    - If the blood relative has pancreatic cancer or prostate cancer, only members who are first-degree relatives should be offered testing unless there are other family history indications for testing.
- The affected or unaffected member has a probability >5% of a *BRCA1/2* or *PALB2* pathogenic variant based on prior probability models (*eg*, Tyrer-Cuzick, BRCAPro, CanRisk, Penn II).

Germline genetic testing in minors for BRCA1, BRCA2, and PALB2 variants for hereditary breast ovarian cancer syndrome 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.

Germline genetic testing for *BRCA*1, *BRCA2, and PALB2* 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.

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

Members 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 members with a known familial *BRCA or PALB2* variant, targeted testing for the specific variant is recommended.
- In members with unknown familial *BRCA or PALB2* 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 *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 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 *BRCA*1 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
    - 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 *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. When testing for founder mutations is negative, 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 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

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

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.

Cross-references:

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, and BARD1)
MP 2.325 Genetic Cancer Susceptibility Panels Using Next Generation Sequencing
MP 2.326 General Approach to Genetic Testing

II. PRODUCT VARIATIONS

Top

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

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III. DESCRIPTION/BACKGROUND

Top

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.

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 (ie, 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 (eg, Finns, French Canadians, Poles), while infrequently found in others (eg, 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.

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.

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 this test.

U.S. Food and Drug Administration Approved Companion Diagnostics

FDA has approved various companion diagnostics to identify patients with *BRCA* mutations who may benefit from treatment with a targeted therapy *(ie,* PARP inhibitor drugs). FDA product codes: PQP, PJG

For example, FDA has approved BRACAnalysis CDx ® to detect germline *BRCA1* and *BRCA2* variants to identify patients with breast or ovarian cancer who may be considered for treatment with various PARP inhibitor drugs.

In addition to the various individual variant tests which are the focus of this policy, numerous other multigene panel tests exist that include *BRCA1/2* among other genes. For example, FoundationOne CDx™ (F1CDx) is an FDA approved companion diagnostic for use of olaparib and rucaparib in accordance with their respective FDA labels in women with ovarian cancer with variants in somatic *BRCA1/2*. F1CDx is FDA approved to assess somatic *BRCA1/2* and other homologous recombination pathway genes (eg, *ATM, BRIP1, CHEK2, FANCA, FANCL, FANCM, NBN, RAD51C, RAD51D, and RAD54L* as well as microsatellite instability (MSI) and DNA mismatch repair genes (*MLH1, MSH2, MSH6, PMS2*). FoundationOne CDx is also FDA approved for determining somatic homologous recombination deficiency based on genomic loss of heterozygosity (LOH) and *BRCA* mutant status. Also, FoundationOne Liquid CDx is FDA approved for detection of somatic *BRCA1* and *BRCA2* alterations in individuals with prostate cancer considering treatment with rucaparib. However, further discussion of these multigene panel tests are outside of the scope of this review, but can be found in MP 2.259 and MP 2.267.

Poly (Adenosine Diphosphate–Ribose) Polymerase (PARP) Inhibitors

Poly (adenosine diphosphate–ribose) polymerase (PARP) inhibitors drugs are oral targeted therapies used to treat certain types of cancers that have damaged DNA repair pathways (*eg, BRCA* mutation).

IV. RATIONALE

TOP

SUMMARY OF EVIDENCE

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

Top

NA

VI. BENEFIT VARIATIONS

Top

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

Top

Capital Blue Cross's 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.

VIII. CODING INFORMATION

Top

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	0131U	0132U	0134U	0137U	0138U	

Covered when medically necessary:

Procedure Codes:								
81162	81163	81164	81165	81166	81167	81212	81215	81216
81217	81307	81308	81406	81432	81433	81479		

ICD-10-CM Diagnosis Code	Description
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
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
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
C57.01	Malignant neoplasm of right fallopian tube
C57.02	Malignant neoplasm of left fallopian tube

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
Z15.01	Genetic susceptibility to malignant neoplasm of breast
Z15.02	Genetic susceptibility to malignant neoplasm of ovary
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
Z80.8	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

Top

1. *Chapman-Davis E, Zhou ZN, Fields JC, et al. Racial and Ethnic Disparities in Genetic Testing at a Hereditary Breast and Ovarian Cancer Center. J Gen Intern Med. Jan 2021; 36(1): 35-42. PMID 32720237*
2. *Winchester DP. Breast cancer in young women. Surg Clin North Am. Apr 1996; 76(2): 279-87. PMID 8610264*
3. *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*
4. *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*
5. *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

6. *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*
7. *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*
8. *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*
9. *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*
10. *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*
11. *Moslehi R, Chu W, Karlan B, et al. BRCA1 and BRCA2 mutation analysis of 208 Ashkenazi Jewish women with ovarian cancer. Am J Hum Genet. Apr 2000;66(4):1259-1272. PM*
12. *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*
13. *Kandel MJ, Stadler D, Masciari S, et al. Prevalence of BRCA1 mutations in triple negative breast cancer (BC) [abstract 508]. J Clin Oncol. 2006;24(18S):508.*
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. *Xia B, Sheng Q, Nakanishi K, et al. Control of BRCA2 cellular and clinical functions by a nuclear partner, PALB2. Mol Cell. Jun 23 2006; 22(6): 719-729. PMID 16793542*
17. *Antoniou AC, Casadei S, Heikkinen T, et al. Breast-cancer risk in families with mutations in PALB2. N Engl J Med. Aug 07 2014; 371(6): 497-506. PMID 25099575*
18. *Catucci I, Peterlongo P, Ciceri S, et al. PALB2 sequencing in Italian familial breast cancer cases reveals a high-risk mutation recurrent in the province of Bergamo. Genet Med. Sep 2014; 16(9): 688-94. PMID 24556926*
19. *Casadei S, Norquist BM, Walsh T, et al. Contribution of inherited mutations in the BRCA2-interacting protein PALB2 to familial breast cancer. Cancer Res. Mar 15 2011; 71(6): 2222-9. PMID 21285249*
20. *Cybulski C, Kluzniak W, Huzarski T, et al. Clinical outcomes in women with breast cancer and a PALB2 mutation: a prospective cohort analysis. Lancet Oncol. Jun 2015; 16(6): 638-44. PMID 25959805*

21. *Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). BRCA1 and BRCA2 testing to determine the risk of breast and ovarian cancer. TEC Assessments. 1997;Volume 12:Tab 4.*
22. *Zhu Y, Wu J, Zhang C, et al. BRCA mutations and survival in breast cancer: an updated systematic review and meta-analysis. Oncotarget. Oct 25 2016; 7(43): 70113-70127. PMID 27659521*
23. *Nelson HD, Fu R, Goddard K, et al. Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA- Related Cancer: Systematic Review to Update the U.S. Preventive Services Task Force Recommendation. Evidence Synthesis No. 101 (AHRQ Publication No. 12-05164-EF-1). Rockville, MD Agency for Healthcare Research and Quality; 2013.*
24. *Kuchenbaecker KB, Hopper JL, Barnes DR, et al. Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers. JAMA. Jun 20 2017; 317(23): 2402-2416. PMID 28632866*
25. *Begg CB. On the use of familial aggregation in population-based case probands for calculating penetrance. J Natl Cancer Inst. Aug 21 2002; 94(16): 1221-6. PMID 12189225*
26. *Thorlacius S, Struewing JP, Hartge P, et al. Population-based study of risk of breast cancer in carriers of BRCA2 mutation. Lancet. Oct 24 1998; 352(9137): 1337-9. PMID 9802270*
27. *King MC, Marks JH, Mandell JB. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. Science. Oct 24 2003; 302(5645): 643-6. PMID 14576434*
28. *Metcalfe K, Lynch HT, Ghadirian P, et al. Contralateral breast cancer in BRCA1 and BRCA2 mutation carriers. J Clin Oncol. Jun 15 2004; 22(12): 2328-35. PMID 15197194*
29. *Mavaddat N, Peock S, Frost D, et al. Cancer risks for BRCA1 and BRCA2 mutation carriers: results from prospective analysis of EMBRACE. J Natl Cancer Inst. Jun 05 2013; 105(11): 812-22. PMID 23628597*
30. *Trainer AH, Meiser B, Watts K, et al. Moving toward personalized medicine: treatment-focused genetic testing of women newly diagnosed with ovarian cancer. Int J Gynecol Cancer. Jul 2010; 20(5): 704-16. PMID 20973257*
31. *Zhang S, Royer R, Li S, et al. Frequencies of BRCA1 and BRCA2 mutations among 1,342 unselected patients with invasive ovarian cancer. Gynecol Oncol. May 01 2011; 121(2): 353-7. PMID 21324516*
32. *Kurian AW, Hughes, E., Handorf, E. A., et al. Breast and ovarian cancer penetrance estimates derived from germline multiple-gene sequencing results in women. Precis Oncol. 2017;1:1-12.*
33. *Langer LR, McCoy H, Kidd J, et al. Hereditary cancer testing in patients with ovarian cancer using a 25-gene panel. J Community Supportive Oncol. 2016;14(7):314-319.*
34. *Norquist BM, Harrell MI, Brady MF, et al. Inherited Mutations in Women With Ovarian Carcinoma. JAMA Oncol. Apr 2016; 2(4): 482-90. PMID 26720728*
35. *Harter P, Hauke J, Heitz F, et al. Prevalence of deleterious germline variants in risk genes including BRCA1/2 in consecutive ovarian cancer patients (AGO-TR-1). PLoS One. 2017; 12(10): e0186043. PMID 29053726*

36. *Hirst JE, Gard GB, McIllroy K, et al. High rates of occult fallopian tube cancer diagnosed at prophylactic bilateral salpingo-oophorectomy. Int J Gynecol Cancer. Jul 2009; 19(5): 826-9. PMID 19574767*
37. *Powell CB, Swisher EM, Cass I, et al. Long term follow up of BRCA1 and BRCA2 mutation carriers with unsuspected neoplasia identified at risk reducing salpingo-oophorectomy. Gynecol Oncol. May 2013; 129(2): 364-71. PMID 23391663*
38. *Hruban RH, Canto MI, Goggins M, et al. Update on familial pancreatic cancer. Adv Surg. 2010; 44: 293-311. PMID 20919528*
39. *Couch FJ, Johnson MR, Rabe KG, et al. The prevalence of BRCA2 mutations in familial pancreatic cancer. Cancer Epidemiol Biomarkers Prev. Feb 2007; 16(2): 342-6. PMID 17301269*
40. *Ferrone CR, Levine DA, Tang LH, et al. BRCA germline mutations in Jewish patients with pancreatic adenocarcinoma. J Clin Oncol. Jan 20 2009; 27(3): 433-8. PMID 19064968*
41. *Holter S, Borgida A, Dodd A, et al. Germline BRCA Mutations in a Large Clinic-Based Cohort of Patients With Pancreatic Adenocarcinoma. J Clin Oncol. Oct 01 2015; 33(28): 3124-9. PMID 25940717*
42. *Shindo K, Yu J, Suenaga M, et al. Deleterious Germline Mutations in Patients With Apparently Sporadic Pancreatic Adenocarcinoma. J Clin Oncol. Oct 20 2017; 35(30): 3382-3390. PMID 28767289*
43. *Yurgelun MB, Chittenden AB, Morales-Oyarvide V, et al. Germline cancer susceptibility gene variants, somatic second hits, and survival outcomes in patients with resected pancreatic cancer. Genet Med. Jan 2019; 21(1): 213-223. PMID 29961768*
44. *Hu C, Hart SN, Polley EC, et al. Association Between Inherited Germline Mutations in Cancer Predisposition Genes and Risk of Pancreatic Cancer. JAMA. Jun 19 2018; 319(23): 2401-2409. PMID 29922827*
45. *Edwards SM, Kote-Jarai Z, Meitz J, et al. Two percent of men with early-onset prostate cancer harbor germline mutations in the BRCA2 gene. Am J Hum Genet. Jan 2003; 72(1): 1-12. PMID 12474142*
46. *Pritchard CC, Mateo J, Walsh MF, et al. Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer. N Engl J Med. Aug 04 2016; 375(5): 443-53. PMID 27433846*
47. *Abida W, Armenia J, Gopalan A, et al. Prospective Genomic Profiling of Prostate Cancer Across Disease States Reveals Germline and Somatic Alterations That May Affect Clinical Decision Making. JCO Precis Oncol. Jul 2017; 2017. PMID 28825054*
48. *Walsh T, Casadei S, Coats KH, et al. Spectrum of mutations in BRCA1, BRCA2, CHEK2, and TP53 in families at high risk of breast cancer. JAMA. Mar 22 2006; 295(12): 1379-88. PMID 16551709*
49. *Palma MD, Domchek SM, Stopfer J, et al. The relative contribution of point mutations and genomic rearrangements in BRCA1 and BRCA2 in high-risk breast cancer families. Cancer Res. Sep 01 2008; 68(17): 7006-14. PMID 18703817*
50. *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

51. *Grann VR, Whang W, Jacobson JS, et al. Benefits and costs of screening Ashkenazi Jewish women for BRCA1 and BRCA2. J Clin Oncol. Feb 1999; 17(2): 494-500. PMID 10080590*
52. *Hartmann LC, Schaid DJ, Woods JE, et al. Efficacy of bilateral prophylactic mastectomy in women with a family history of breast cancer. N Engl J Med. Jan 14 1999; 340(2): 77-84. PMID 9887158*
53. *Menkiszak J, Rzepka-Gorska I, Gorski B, et al. Attitudes toward preventive oophorectomy among BRCA1 mutation carriers in Poland. Eur J Gynaecol Oncol. 2004; 25(1): 93-5. PMID 15053071*
54. *Moller P, Borg A, Evans DG, et al. Survival in prospectively ascertained familial breast cancer: analysis of a series stratified by tumour characteristics, BRCA mutations and oophorectomy. Int J Cancer. Oct 20 2002; 101(6): 555-9. PMID 12237897*
55. *Olopade OI, Artioli G. Efficacy of risk-reducing salpingo-oophorectomy in women with BRCA-1 and BRCA-2 mutations. Breast J. Jan-Feb 2004; 10 Suppl 1: S5-9. PMID 14984481*
56. *Rebbeck TR, Lynch HT, Neuhausen SL, et al. Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations. N Engl J Med. May 23 2002; 346(21): 1616-22. PMID 12023993*
57. *Weitzel JN, McCaffrey SM, Nedelcu R, et al. Effect of genetic cancer risk assessment on surgical decisions at breast cancer diagnosis. Arch Surg. Dec 2003; 138(12): 1323-8; discussion 1329. PMID 14662532*
58. *Finch AP, Lubinski J, Moller P, et al. Impact of oophorectomy on cancer incidence and mortality in women with a BRCA1 or BRCA2 mutation. J Clin Oncol. May 20 2014; 32(15): 1547-53. PMID 24567435*
59. *Domchek SM, Friebel TM, Singer CF, et al. Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality. JAMA. Sep 01 2010; 304(9): 967-75. PMID 20810374*
60. *Elmi M, Azin A, Elnahas A, et al. Concurrent risk-reduction surgery in patients with increased lifetime risk for breast and ovarian cancer: an analysis of the National Surgical Quality Improvement Program (NSQIP) database. Breast Cancer Res Treat. Aug 2018; 171(1): 217-223. PMID 29761322*
61. *Li X, You R, Wang X, et al. Effectiveness of Prophylactic Surgeries in BRCA1 or BRCA2 Mutation Carriers: A Meta-analysis and Systematic Review. Clin Cancer Res. Aug 01 2016; 22(15): 3971-81. PMID 26979395*
62. *Ludwig KK, Neuner J, Butler A, et al. Risk reduction and survival benefit of prophylactic surgery in BRCA mutation carriers, a systematic review. Am J Surg. Oct 2016; 212(4): 660-669. PMID 27649974*
63. *Marchetti C, De Felice F, Palaia I, et al. Risk-reducing salpingo-oophorectomy: a meta-analysis on impact on ovarian cancer risk and all cause mortality in BRCA 1 and BRCA 2 mutation carriers. BMC Womens Health. Dec 12 2014; 14: 150. PMID 25494812*

64. *Scheuer L, Kauff N, Robson M, et al. Outcome of preventive surgery and screening for breast and ovarian cancer in BRCA mutation carriers. J Clin Oncol. Mar 01 2002; 20(5): 1260-8. PMID 11870168*
65. *Mitra AV, Bancroft EK, Barbachano Y, et al. Targeted prostate cancer screening in men with mutations in BRCA1 and BRCA2 detects aggressive prostate cancer: preliminary analysis of the results of the IMPACT study. BJU Int. Jan 2011; 107(1): 28-39. PMID 20840664*
66. *Moore KN, Secord AA, Geller MA, et al. Niraparib monotherapy for late-line treatment of ovarian cancer (QUADRA): a multicentre, open-label, single-arm, phase 2 trial. Lancet Oncol. May 2019; 20(5): 636-648. PMID 30948273*
67. *Pujade-Lauraine E, Ledermann JA, Selle F, et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol. Sep 2017; 18(9): 1274-1284. PMID 28754483*
68. *Hussain M, Mateo J, Fizazi K, et al. Survival with Olaparib in Metastatic Castration-Resistant Prostate Cancer. N Engl J Med. Dec 10 2020; 383(24): 2345-2357. PMID 32955174*
69. *Mirza MR, Monk BJ, Herrstedt J, et al. Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer. N Engl J Med. Dec 01 2016; 375(22): 2154-2164. PMID 27717299*
70. *Coleman RL, Oza AM, Lorusso D, et al. Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. Oct 28 2017; 390(10106): 1949-1961. PMID 28916367*
71. *Abida W, Patnaik A, Campbell D, et al. Rucaparib in Men With Metastatic Castration-Resistant Prostate Cancer Harboring a BRCA1 or BRCA2 Gene Alteration. J Clin Oncol. Nov 10 2020; 38(32): 3763-3772. PMID 32795228*
72. *Suszynska M, Klonowska K, Jasinska AJ, et al. Large-scale meta-analysis of mutations identified in panels of breast/ovarian cancer-related genes - Providing evidence of cancer predisposition genes. Gynecol Oncol. May 2019; 153(2): 452-462. PMID 30733081*
73. *Erkko H, Dowty JG, Nikkila J, et al. Penetrance analysis of the PALB2 c.1592delT founder mutation. Clin Cancer Res. Jul 15 2008; 14(14): 4667-71. PMID 18628482*
74. *Heikkinen T, Karkkainen H, Aaltonen K, et al. The breast cancer susceptibility mutation PALB2 1592delT is associated with an aggressive tumor phenotype. Clin Cancer Res. May 01 2009; 15(9): 3214-22. PMID 19383810*
75. *Rahman N, Seal S, Thompson D, et al. PALB2, which encodes a BRCA2-interacting protein, is a breast cancer susceptibility gene. Nat Genet. Feb 2007; 39(2): 165-7. PMID 17200668*
76. *Thompson ER, Gorringe KL, Rowley SM, et al. Prevalence of PALB2 mutations in Australian familial breast cancer cases and controls. Breast Cancer Res. Aug 19 2015; 17: 111. PMID 26283626*

77. *Southey MC, Goldgar DE, Winqvist R, et al. PALB2, CHEK2 and ATM rare variants and cancer risk: data from COGS. J Med Genet. Dec 2016; 53(12): 800-811. PMID 27595995*
78. *Lu HM, Li S, Black MH, et al. Association of Breast and Ovarian Cancers With Predisposition Genes Identified by Large-Scale Sequencing. JAMA Oncol. Jan 01 2019; 5(1): 51-57. PMID 30128536*
79. *Woodward ER, van Veen EM, Forde C, et al. Clinical utility of testing for PALB2 and CHEK2 c.1100delC in breast and ovarian cancer. Genet Med. Oct 2021; 23(10): 1969-1976. PMID 34113003*
80. *Yang X, Leslie G, Doroszuk A, et al. Cancer Risks Associated With Germline PALB2 Pathogenic Variants: An International Study of 524 Families. J Clin Oncol. Mar 01 2020; 38(7): 674-685. PMID 31841383*
81. *Li N, Lim BWX, Thompson ER, et al. Investigation of monogenic causes of familial breast cancer: data from the BEACCON case-control study. NPJ Breast Cancer. Jun 11 2021; 7(1): 76. PMID 34117267*
82. *Antoniou AC, Foulkes WD, Tischkowitz M. Breast cancer risk in women with PALB2 mutations in different populations. Lancet Oncol. Aug 2015; 16(8): e375-6. PMID 26248842*
83. *National Cancer Institute, Surveillance Epidemiology and End Results Program. Cancer Stat Facts: Female Breast Cancer. n.d.; Accessed October 28, 2022.*
84. *Rosenthal ET, Evans B, Kidd J, et al. Increased Identification of Candidates for High-Risk Breast Cancer Screening Through Expanded Genetic Testing. J Am Coll Radiol. Apr 2017; 14(4): 561-568. PMID 28011157*
85. *Phi XA, Saadatmand S, De Bock GH, et al. Contribution of mammography to MRI screening in BRCA mutation carriers by BRCA status and age: individual patient data meta-analysis. Br J Cancer. Mar 15 2016; 114(6): 631-7. PMID 26908327*
86. *Phillips KA, Milne RL, Rookus MA, et al. Tamoxifen and risk of contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. J Clin Oncol. Sep 01 2013; 31(25): 3091-9. PMID 23918944*
87. *Hartmann LC, Sellers TA, Schaid DJ, et al. Efficacy of bilateral prophylactic mastectomy in BRCA1 and BRCA2 gene mutation carriers. J Natl Cancer Inst. Nov 07 2001; 93(21): 1633-7. PMID 11698567*
88. *Portschy PR, Kuntz KM, Tuttle TM. Survival outcomes after contralateral prophylactic mastectomy: a decision analysis. J Natl Cancer Inst. Aug 2014; 106(8). PMID 25031308*
89. *Schrag D, Kuntz KM, Garber JE, et al. Decision analysis--effects of prophylactic mastectomy and oophorectomy on life expectancy among women with BRCA1 or BRCA2 mutations. N Engl J Med. May 15 1997; 336(20): 1465-71. PMID 9148160*
90. *Schrag D, Kuntz KM, Garber JE, et al. Life expectancy gains from cancer prevention strategies for women with breast cancer and BRCA1 or BRCA2 mutations. JAMA. Feb 02 2000; 283(5): 617-24. PMID 10665701*
91. *National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High Risk Assessment: Breast, Ovarian, and Pancreatic. Version 1.2023. Accessed October 28, 2022.*

92. *National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Ovarian Cancer. Version 1.2022. Accessed October 28, 2022.*
93. *National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Pancreatic Adenocarcinoma. Version 1.2022. Accessed October 28, 2022.*
94. *National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer. Version 4.2022. Accessed October 28, 2022.*
95. *The American Society of Breast Surgeons. Consensus Guidelines on Genetic Testing for Hereditary Breast Cancer. 2019.. Accessed October 28, 2022.*
96. *Lancaster JM, Powell CB, Chen LM, et al. Society of Gynecologic Oncology statement on risk assessment for inherited gynecologic cancer predispositions. Gynecol Oncol. Jan 2015; 136(1): 3-7. PMID 25238946*
97. *Practice Bulletin No. 182 Summary: Hereditary Breast and Ovarian Cancer Syndrome. Obstet Gynecol. Sep 2017; 130(3): 657-659. PMID 28832475*
98. *National Institute for Health and Care Excellence (NICE). Olaparib for maintenance treatment of BRCA mutation-positive advanced ovarian, fallopian tube or peritoneal cancer after response to first-line platinum-based chemotherapy [TA598]. August 2019; Accessed October 28, 2022.*
99. *Owens DK, Davidson KW, Krist AH, et al. Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA-Related Cancer: US Preventive Services Task Force Recommendation Statement. JAMA. Aug 20 2019; 322(7): 652-665. PMID 31429903*
100. *Peshkin B and Isaacs C. Gene test interpretation: BRCA1 and BRCA2. In: UpToDate Online Journal [serial online]. Waltham, MA: UpToDate; updated June 7, 2022. Literature review current through May 2022. Accessed on October 28, 2022.*
101. *Peshkin B and Isaacs C. Genetic testing and management of individuals at risk of hereditary breast and ovarian cancer syndromes. In: UpToDate Online Journal [serial online]. Waltham, MA: UpToDate; updated May 16, 2022. Literature review current through May 2022. Accessed on October 28, 2022.*
102. *COMMITTEE ON BIOETHICS; COMMITTEE ON GENETICS, AND; AMERICAN COLLEGE OF MEDICAL GENETICS AND; GENOMICS SOCIAL; ETHICAL; LEGAL ISSUES COMMITTEE. Ethical and policy issues in genetic testing and screening of children. Pediatrics. 2013;131(3):620-622. doi:10.1542/peds.2012-3680*
103. *National Society of Genetic Counselors. Position Statement: Genetic Testing of Minors for Adult-Onset Conditions. April 12, 2018. Accessed October 28, 2022.*
104. *Karam R, Conner B, LaDuca H, et al. Assessment of diagnostic outcomes of RNA genetic testing for hereditary cancer. JAMA Netw Open. 2019; 2(10):e1913900.*
105. *Landrith T, Li B, Cass AA, et al. Splicing profile by capture RNA-seq identifies pathogenic germline variants in tumor suppressor genes. NPJ Precis Oncol. 2020; 4:4.*
106. *Nix P, Mundt E, Manley S, Coffee B, Roa B. Functional RNA Studies Are a Useful Tool in Variant Classification but Must Be Used With Caution: A Case Study of One BRCA2 Variant. JCO Precis Oncol. 2020;4:730-735. doi:10.1200/PO.20.00118*
107. *Blue Cross Blue Shield Association Medical Policy Reference Manual. 2.04.02, Genetic Testing for BRCA1 or BRCA2 for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers. February 2022.*

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

X. POLICY HISTORY

Top

MP 2.211	**03/06/2020 Consensus review**. Policy statement unchanged. References, policy guidelines and regulatory status updated. Coding reviewed.
	07/01/2020 Administrative review. 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 review. 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.

Top

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