BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

FEP 2.04.02 Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers (BRCA1, BRCA2, PALB2)

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Related Policies:

2.04.126 - Germline Genetic Testing for Gene Variants Associated With Breast Cancer in Individuals at High Breast Cancer Risk (CHEK2, ATM, and BARD1)
2.04.128 - Genetic Testing for Fanconi Anemia
2.04.148 - Germline Genetic Testing for Pancreatic Cancer Susceptibility Genes (ATM, BRCA1, BRCA2, CDKN2A, EPCAM, MLH1, MSH2, MSH6, PALB2, PMS2, STK11, and TP53)
2.04.151 - Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Breast Cancer (BRCA1, BRCA2, PIK3CA, Ki-67, RET, BRAF, ESR1, NTRK)
2.04.155 - Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Prostate Cancer (BRCA1/2, Homologous Recombination Repair Gene Alterations, NTRK Gene Fusion)
2.04.156 - Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Ovarian Cancer (BRCA1, BRCA2, Homologous Recombination Deficiency, NTRK)
2.04.157 - Somatic Biomarker Testing for Immune Checkpoint Inhibitor Therapy (BRAF, MSI/MMR, PD-L1, TMB)
2.04.93 - Genetic Cancer Susceptibility Panels Using Next Generation Sequencing

Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers (BRCA1, BRCA2, PALB2)

Description

Hereditary breast and ovarian cancer syndrome describes the familial cancer syndromes related to variants in the *BRCA* genes (*BRCA1* located on chromosome 17q21, *BRCA2* located on chromosome 13q12-13). The *PALB2* gene is located at 16p12.2 and has 13 exons. PALB2 protein assists *BRCA2* in DNA repair and tumor suppression. Families with hereditary breast and ovarian cancer syndrome have an increased susceptibility to the following types of cancer: breast cancer occurring at a young age, bilateral breast cancer, male breast cancer, ovarian cancer (at any age), cancer of the fallopian tube, primary peritoneal cancer, prostate cancer, pancreatic cancer, gastrointestinal cancers, melanoma, and laryngeal cancer.

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OBJECTIVE

The objective of this evidence review is to determine whether germline genetic testing for *BRCA1*, *BRCA2*, or *PALB2* variants improves the net health outcomes in individuals with cancer or who have a personal or family history of cancer, which might suggest hereditary breast and ovarian cancer syndrome or other high-risk cancers.

POLICY STATEMENT

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

Individuals With Cancer or With a Personal History of Cancer

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

- Individuals with any close blood relative with a known *BRCA1*, *BRCA2*, or *PALB2* pathogenic/likely pathogenic variant (see Policy Guidelines for definitions and for testing strategy).
- Individuals meeting the criteria below but with previous limited testing (*eg*, single gene and/or absent deletion duplication analysis)
- Personal history of breast cancer and 1 or more of the following:
    - Diagnosed at age ≤45 years; or
    - Diagnosed at age 46 to 50 years with:
        - An additional breast cancer primary at any age; or
        - ≥1 close relative (see Policy Guidelines) with breast, ovarian, pancreatic, or prostate cancer at any age; or
        - An unknown or limited family history
    - Diagnosed at age ≤60 years with:
        - Triple-negative breast cancer (see Policy Guidelines)
    - Diagnosed at any age with:
        - ≥1 close blood relative with:
            - Breast cancer diagnosed at age ≤50 years; or
            - Ovarian carcinoma; or
            - Metastatic or intraductal/cribriform prostate cancer, or high-risk group or very-high-risk group (see Policy Guidelines) prostate cancer; or
            - Pancreatic cancer; or
        - ≥3 total diagnoses of breast cancer in individual and/or close blood relatives; or
        - Ashkenazi Jewish ancestry
    - Diagnosed at any age with male breast cancer
- Personal history of epithelial ovarian carcinoma (including fallopian tube cancer or peritoneal cancer) at any age

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

Individuals Without Cancer or With Other Personal History of Cancer

(See Policy Guidelines section: Testing Unaffected Individuals.)

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

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

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

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

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

POLICY GUIDELINES

Plans may need to alter local coverage medical policy to conform to state law regarding coverage of biomarker testing.

There are differences in the position statements above and the National Comprehensive Cancer Network (NCCN) guideline on Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic (v.3.2025). Not all of the NCCN criteria are clearly separated for determining hereditary breast and ovarian cancer syndrome versus for guiding therapy. Testing for *BRCA1, BRCA2,* and/or *PALB2* outside of the above criteria, such as testing all individuals with triple negative breast cancer or testing all individuals diagnosed with breast cancer under the age of 50 years, may be indicated for guiding cancer therapies. Genetic testing for *BRCA1* and *BRCA2* variants in breast cancer-, pancreatic cancer-, prostate cancer-, or ovarian cancer-affected individuals who are considering systemic therapy is addressed separately in evidence reviews 2.04.151, 2.04.148, 2.04.155, and 2.04.156, respectively. Genetic testing for *PALB2* variants in pancreatic cancer-affected individuals is also addressed in 2.04.148. Additionally, conflicting criteria reflect that some of the NCCN criteria are based on limited or no evidence; the lower level of evidence might be needed when determining coverage of testing mandated by state biomarker legislation.

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

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

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

Close Relatives

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

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

Prostate Cancer Risk Groups

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

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

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

Recommended Testing Strategies

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

- In individuals with a known familial *BRCA* or *PALB2* variant, targeted testing for the specific variant is recommended.
- In individuals with unknown familial *BRCA* or *PALB2* variant:
    - To identify clinically significant variants, NCCN advises testing a relative who has early-onset disease, bilateral disease, or multiple primaries, because that individual has the highest likelihood of obtaining a positive test result. Unless the affected individual is a member of an ethnic group for which particular founder pathogenic or likely pathogenic variants are known, comprehensive genetic testing (ie, 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 (eg, prostate cancer, pancreatic cancer, melanoma).
    - If no familial variant can be identified, 2 possible testing strategies are:
- Full sequencing of *BRCA1* and *BRCA2* followed by testing for large genomic rearrangements (deletions, duplications) only if sequencing detects no variant (negative result).
    - More than 90% of *BRCA* variants will be detected by full sequencing.

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

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

Comprehensive Variant Analysis

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

High-Risk Ethnic Groups

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

Testing Unaffected Individuals

In unaffected family members of potential *BRCA* or *PALB2* variant families, most test results will be negative and uninformative. Therefore, it is strongly recommended that an *affected* family member be tested first whenever possible to adequately interpret the test. Should a *BRCA* or *PALB2* variant be found in an affected family member(s), DNA from an *unaffected* family member can be tested specifically for the same variant of the affected family member without having to sequence the entire gene. Interpreting test results for an unaffected family member without knowing the genetic status of the family may be possible in the case of a positive result for an established disease-associated variant but leads to difficulties in interpreting negative test results (uninformative negative) or variants of uncertain significance because the possibility of a causative *BRCA or PALB2* variant is not ruled out.

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

Confirmatory Testing

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

Testing Minors

The use of genetic testing for *BRCA1, BRCA2,* or *PALB2* variants for identifying hereditary breast and ovarian cancer syndrome has limited or no clinical utility in minors, because there is no change in management for minors as a result of knowledge of the presence or absence of a deleterious variant. In addition, there are potential harms related to stigmatization and discrimination. See policy 2.04.128 regarding testing of *BRCA1*, *BRCA2,* and *PALB2* for Fanconi anemia. See policies 2.04.148, 2.04.151, 2.04.155, and 2.04.156 regarding genetic testing to guide targeted therapy.

Prostate Cancer

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

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology- "pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"- to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

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

Table PG2. American College of Medical Genetics and Genomics and the Association for Molecular Pathology Standards and Guidelines for Variant Classification

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

Genetic Counseling

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

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BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

State or federal mandates (eg, Federal Employee Program) may dictate that certain U.S. Food and Drug Administration–approved devices, drugs, or biologics may not be considered investigational, and thus these devices may be assessed only by their medical necessity.

FDA REGULATORY STATUS

Some Plans may have contract or benefit exclusions for genetic testing, or have state mandates for biomarker testing coverage.

Under the Patient Protection and Affordable Care Act, preventive services with a U.S. Preventive Services Task Force recommendation grade of A or B will be covered with no cost-sharing requirements. Plans that have been grandfathered are exceptions to this rule and are not subject to this coverage mandate.

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

RATIONALE

Summary of Evidence

For individuals who have cancer or a personal or family cancer history and meet criteria suggesting a risk of hereditary breast and ovarian cancer (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 (OS), disease-specific survival, test validity, and quality of life (QOL). 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 OS. Knowledge of *BRCA* variant status in individuals diagnosed with breast cancer may impact treatment decisions. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have other high-risk cancers (eg, cancers of the fallopian tube, pancreas, prostate) who receive genetic testing for a *BRCA1* or *BRCA2* variant, the evidence includes studies of variant prevalence and cancer risk. Relevant outcomes are OS, disease-specific survival, test validity, and QOL. 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 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.

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SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Society of Clinical Oncology

In 2024, the American Society of Clinical Oncology (ASCO) published a guideline on germline testing in patients with breast cancer.[88,] The guideline recommends *BRCA1* and *BRCA2* testing for all patients with breast cancer who are younger than 65 years of age, and some patients over age 65 years (including those who are eligible for poly-ADP ribose polymerase [PARP] inhibitor therapy). Patients with a history of breast cancer may also be candidates for *BRCA1* and *BRCA2* testing if it would help determine their personal and family risk. Testing for other high-penetrance genes (ie, *PALB2*, *TP53*, *PTEN*, *STK11*, and *CDH1*) may be appropriate for some patients.

In 2024, ASCO also published a guideline on germline genetic testing in patients with cancer. Genes with a strong testing recommendation are those that confer a higher cancer risk or are highly actionable. For breast cancer, the more strongly recommended genes for testing and inclusion in multigene panels are: *BRCA1*, *BRCA2*, *PALB2*, *CDH1*, *PTEN*, *STK11*, and *TP53*. Of these, *CDH1*, *PTEN*, *STK11*, and *TP53* are associated with specific syndromes and can be excluded from testing if personal or family history do not suggest an increased risk of the syndrome.[89,] For epithelial ovarian cancer, the more strongly recommended genes are: *BRCA1*, *BRCA2*, *BRIP1*, *EPCAM*, *MLH1*, *MSH2*, *MSH6*, *PALB2*, *PMS2*, *RAD51C*, and *RAD51D*. Testing for *BRCA1* and *BRCA2* is also strongly recommended for pancreatic adenocarcinoma and prostate cancer, and testing for *PALB2* is strongly recommended for pancreatic adenocarcinoma. The authors note that including *BRCA1*, *BRCA2*, and Lynch syndrome genes (ie, *MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM*) in multigene panels for any patient with cancer is reasonable due to their importance and prevalence.

National Comprehensive Cancer Network

Breast Cancer and Ovarian Cancer

Current National Comprehensive Cancer Network (NCCN) (v.3.2025) guidelines on the genetic and familial high-risk assessment of breast, ovarian, and pancreatic cancers include criteria for identifying individuals who should be referred for further risk assessment and separate criteria for genetic testing.[90,] Patients who satisfy any of the testing criteria listed in CRIT-1 through CRIT-4 should undergo "further personalized risk assessment, genetic counseling, and often genetic testing and management.” For these criteria, both invasive and in situ breast cancers were included. Maternal and paternal sides of the family should be considered independently for familial patterns of cancer. Testing of unaffected individuals should be considered "when no affected family member is available for testing.”

The recommendations are for testing high penetrance breast cancer susceptibility genes, specifically *BRCA1*, *BRCA2*, *CDH1*, *PALB2*, *PTEN, STK11*, and *TP53*. Use of "tailored panels that are disease-focused and include clinically actionable cancer susceptibility genes is preferred over large panels that include genes of uncertain clinical relevance".

The panel does not endorse population based testing, stating instead that the panel, "continues to endorse a risk-stratified approach" and does not "endorse universal testing of all patients with breast cancer due to limitations of this approach, such as low specificity, shortages in trained genetics health professionals to provide appropriate pre- and post-test genetic counseling, and lack of evidence to support risk management for genes included in many multigene panels."

BRCA1 and *BRCA2* somatic only variants are uncommon. The NCCN recommends if a somatic variant is identified through tumor profiling, then *BRCA1* and *BRCA2* germline testing is recommended.

Additionally, the NCCN ovarian cancer guidelines (v.2.2025) recommend tumor molecular testing for persistent/recurrent disease (OV-6) and describe in multiple algorithms that testing should include at least *BRCA1/2,* homologous recombination, microsatellite instability, tumor mutational burden, and neurotrophic tyrosine receptor kinase, (OV-6, OV-7, OV-B Principles of Pathology, OV-C Principles of Systemic Therapy).[91,]

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Pancreatic Adenocarcinoma and Pancreatic Neuroendocrine Tumors

Current NCCN guidelines for pancreatic adenocarcinoma (v.2.2025) refers to the NCCN guidelines on genetic/familial high-risk assessment of breast, ovarian, and pancreatic cancers detailed above, and state: "The panel recommends germline testing in any patient with confirmed pancreatic cancer and in those in whom there is a clinical suspicion for inherited susceptibility." The panel recommends "using comprehensive gene panels for hereditary cancer syndromes."[92,]

The NCCN guidelines for genetic and familial high-risk assessment of breast, ovarian, and pancreatic cancers (v.3.2025) states that germline testing is clinically indicated for individuals with neuroendocrine pancreatic cancers per the NCCN guidelines on neuroendocrine and adrenal tumors. [90,] The NCCN guidelines for neuroendocrine and adrenal tumors (v.2.2025) states, "consider genetic risk evaluation and genetic testing: In a patient with duodenal/pancreatic neuroendocrine tumor at any age", noting, "studies of unselected patients with pancreatic neuroendocrine tumors have identified germline variants in 16%-17% of cases. However, these studies involved relatively small cohorts of patients."[93,]

Prostate Cancer

The current NCCN guidelines for prostate cancer are version 2.2025.[94,] The Principles of Genetics and Molecular/Biomarker Analysis section (PROS-C) provides appropriate scenarios for germline genetic testing in individuals with a personal history of prostate cancer.

American Society of Breast Surgeons

A consensus guideline on genetic testing for hereditary breast cancer was updated in February 2019.[95,] The guideline states that genetic testing should be made available to all patients with a personal history of breast cancer and that such testing should include *BRCA1/BRCA2* and *PALB2*, with other genes as appropriate for the clinical scenario and patient family history. Furthermore, patients who had previous genetic testing may benefit from updated testing. Finally, genetic testing should be made available to patients without a personal history of breast cancer when they meet NCCN guideline criteria. The guidelines also note that variants of uncertain significance are not clinically actionable.

Society of Gynecologic Oncology

In 2015, the Society of Gynecologic Oncology (SGO) published an evidence-based consensus statement on risk assessment for inherited gynecologic cancer.[96,] The statement includes criteria for recommending genetic assessment (counseling with or without testing) to patients who may be genetically predisposed to breast or ovarian cancer. Overall, the SGO and the NCCN recommendations are very similar; the main differences are the exclusion of women with breast cancer onset at age 50 years or younger who have 1 or more first-, second-, or third-degree relatives with breast cancer at any age; women with breast cancer or history of breast cancer who have a first-, second-, or third-degree male relative with breast cancer; and men with a personal history of breast cancer. Additionally, SGO recommends genetic assessment for unaffected women who have a male relative with breast cancer. Moreover, SGO indicated that some patients who do not satisfy criteria may still benefit from genetic assessment (eg, few female relatives, hysterectomy, or oophorectomy at a young age in multiple family members, or adoption in the lineage).

American College of Obstetricians and Gynecologists

The American College of Obstetricians and Gynecologists (2017, reaffirmed 2024) published a Practice Bulletin on hereditary breast and ovarian cancer syndrome.[97,] The following recommendation was based primarily on consensus and expert opinion (level C): "Genetic testing is recommended when the results of a detailed risk assessment that is performed as part of genetic counseling suggest the presence of an inherited cancer syndrome for which specific genes have been identified and when the results of testing are likely to influence medical management."

U.S. Preventive Services Task Force

Current U.S. Preventative Services Task Force (USPSTF) recommendations (2019, update in progress)[98,] for genetic testing of *BRCA1* and *BRCA2* variants in women state:

"The USPSTF recommends that primary care clinicians assess women with a personal or family history of breast, ovarian, tubal, or peritoneal cancer or who have an ancestry associated with *BRCA1/2* gene mutation with an appropriate brief familial risk assessment tool. Women with a positive result on the risk assessment tool should receive genetic counseling and, if indicated after counseling, genetic testing (B recommendation). The USPSTF

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recommends against routine risk assessment, genetic counseling, or genetic testing for women whose personal or family history or ancestry is not associated with potentially harmful *BRCA1/2* gene mutations. (D recommendation)"

Recommended screening tools included the Ontario Family History Assessment Tool, Manchester Scoring System, Referral Screening Tool, Pedigree Assessment Tool, 7-Question Family History Screening Tool, International Breast Cancer Intervention Study instrument (Tyrer-Cuziak), and brief versions of the BRCAPRO.

Medicare National Coverage

There are no national coverage determinations. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
December 2020	New Policy	Genetic testing for a BRCA1 or BRCA2 variant is medically necessary for individuals who meet policy criteria: (1) cancer or a personal or family cancer history suggesting a risk of hereditary breast and ovarian cancer (HBOC) syndrome; (2) have other high-risk cancers (eg, cancers of the fallopian tube, pancreas, prostate); (3) HBOC Syndrome or other high-risk cancers considering systemic therapy options.
March 2021	Replace policy	Policy updated with editing/formatting changes; NCCN guideline for Prostate Cancer added to references. No change to policy statements.
March 2022	Replace policy	Policy updated with literature review through October 1, 2021; references added. Policy statement regarding genetic testing for systemic therapy options updated to include individuals with high-risk, early stage breast cancer. Other minor edits made to policy statements and policy guidelines to reflect current NCCN guidelines.
September 2022	Replace policy	Policy updated with literature review through June 22, 2022; references added. Policy revised to add PALB2 PICO previously found in Policy 2.04.126. Title changed to "Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers (BRCA1, BRCA2, PALB2)." Policy statements updated to include PALB2 information.
December 2022	Replace policy	Policy revised to remove content on use of BRCA1 and BRCA2 testing in prostate and ovarian cancer-affected individuals considering systemic therapy. This content is addressed separately in evidence reviews 2.04.155 and 2.04.156.
December 2023	Replace policy	Policy updated with literature review through June 19, 2023; no references added. Policy statements unchanged.
December 2024	Replace policy	Policy updated with literature review through June 12, 2024; references added. Policy statement about personal history of genetic mutations revised.
December 2025	Replace policy	Policy updated with literature review through June 20, 2025; references added. Policy statements unchanged.

The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.