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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 and Immunotherapy in Breast Cancer
2.04.155 - Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Prostate Cancer (BRCA1/2, Homologous Recombination Repair Gene Alterations, Microsatellite Instability/Mismatch Repair, Tumor Mutational Burden)
2.04.156 - Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Ovarian Cancer (BRCA1, BRCA2, Homologous Recombination Deficiency, Tumor Mutational Burden, Microsatellite Instability/Mismatch Repair)
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

Description

Hereditary breast and ovarian cancer syndrome describe 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.

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/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 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 ≤60 years with:
        - Triple-negative breast cancer (see Policy Guidelines)
    - Diagnosed at any age with:
        - ≥1 close blood relative with:
            - Breast cancer diagnosed ≤50 years; or
            - Ovarian carcinoma; or
            - Metastatic or intraductal/cribriform prostate cancer, or high-risk group or very-high-risk group (see Policy Guidelines) prostate cancer; or
            - Pancreatic cancer; or
        - ≥ 3 total diagnoses of breast cancer in individual and/or close blood relatives; or
        - Ashkenazi Jewish ancestry
    - Diagnosed at any age with male breast cancer
- Personal history of epithelial ovarian carcinoma (including fallopian tube cancer or peritoneal cancer) at any age
- Personal history of exocrine pancreatic cancer at any age

- Personal history of metastatic or intraductal/cribriform histology prostate cancer at any age; or high-risk group or very-high-risk group prostate cancer at any age
- Personal history of prostate cancer at any age with:
    - ≥1 close blood relative with ovarian carcinoma, pancreatic cancer, or metastatic or intraductal/cribriform prostate cancer at any age, or breast cancer ≤50 years; or
    - ≥2 close blood relatives with breast or prostate cancer (any grade) at any age; or
    - Ashkenazi Jewish ancestry
- Personal history of cancer and a mutation 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 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 ovarian cancer syndrome but not meeting above criteria, or cancer unrelated to hereditary breast 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 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.3.2023). 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).

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.
- 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
    - 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 included 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 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

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.

BENEFIT APPLICATION

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

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient's existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

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 technology (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 RRs or 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 relative risk 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.

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.

National Comprehensive Cancer Network

Breast Cancer and Ovarian Cancer

Current National Comprehensive Cancer Network (NCCN) (v.3.2023) 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.[85,] 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 appropriate affected family member is available for testing."

The recommendations are for testing high penetrance breast cancer susceptibility genes, specifically *BRCA1*, *BRCA2*, *CDH1*, *PALB2*, *PTEN,* 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 multi-gene 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.2.2023) 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).[86,]

Pancreatic Adenocarcinoma and Pancreatic Neuroendocrine Tumors

Current NCCN guidelines for pancreatic adenocarcinoma (v.2.2023) 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."[87,]

The NCCN guidelines for genetic and familial high-risk assessment of breast, ovarian, and pancreatic cancers (v.3.2023) includes that germline testing is clinically indicated for individuals with neuroendocrine pancreatic cancers per the NCCN guidelines on neuroendocrine and adrenal tumors.[88,] The NCCN guidelines for neuroendocrine and adrenal tumors (v.2.2022) 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."

Prostate Cancer

The current NCCN guidelines for prostate cancer are version 1.2023.[89,] 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.[90,] 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.[91,] The statement included 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 recommended 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 2021) published a Practice Bulletin on hereditary breast and ovarian cancer syndrome.[92,] 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)[93,] 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 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.

REFERENCES

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, Kluźniak 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-Grska I, Grski 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. Mller 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. 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, Mller 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. 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
67. Erkko H, Dowty JG, Nikkil J, et al. Penetrance analysis of the PALB2 c.1592delT founder mutation. Clin Cancer Res. Jul 15 2008; 14(14): 4667-71. PMID 18628482
68. Heikkinen T, Krkkinen 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
69. 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
70. 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(1): 111. PMID 26283626
71. 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
72. 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
73. 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
74. 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
75. 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
76. 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
77. National Cancer Institute, Surveillance Epidemiology and End Results Program. Cancer Stat Facts: Female Breast Cancer. n.d.; https://seer.cancer.gov/statfacts/html/breast.html. Accessed June 20, 2023.
78. 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
79. 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
80. 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
81. 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
82. 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
83. 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
84. 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
85. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High Risk Assessment: Breast, Ovarian, and Pancreatic. Version 3.2023. https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf. Accessed June 17, 2023.
86. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Ovarian Cancer. Version 2.2023. https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf. Accessed June 18, 2023.
87. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Pancreatic Adenocarcinoma. Version 2.2023. https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf. Accessed June 19, 2023.
88. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology: Neuroendocrine andAdrenal Tumors Version 2.2022
89. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer. Version 1.2023. https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed June 20, 2023.
90. The American Society of Breast Surgeons. Consensus Guidelines on Genetic Testing for Hereditary Breast Cancer. 2019. https://www.breastsurgeons.org/docs/statements/Consensus-Guideline-on-Genetic-Testing-for-Hereditary-Breast-Cancer.pdf. Accessed June 16, 2023
91. 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
92. Practice Bulletin No. 182 Summary: Hereditary Breast and Ovarian Cancer Syndrome. Obstet Gynecol. Sep 2017; 130(3): 657-659. PMID 28832475
93. 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

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.