# Medical Policy

BlueCross BlueShield Kansas
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## Title: Germline Genetic Testing for BRCA1 or BRCA2 for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers

**Pre-Determination of Services IS REQUIRED by the Member's Contract.**
**http://www.bcbsks.com/CustomerService/Forms/pdf/15-17_predeterm_request_frm.pdf**

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| *Related Policies:* | ▪ *Genetic Cancer Susceptibility Panels Using Next Generation Sequencing*<br>▪ *Risk-Reducing Mastectomy* |

| **Professional** | **Institutional** |
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| Populations | Interventions | Comparators | Outcomes |
|---|---|---|---|
| **Individuals:**<br>• With cancer or personal or family cancer history and criteria suggesting risk of hereditary breast/ovarian cancer syndrome | **Interventions of interest are:**<br>• Genetic testing for a BRCA1 or BRCA2 variant | **Comparators of interest are:**<br>• Standard of care without genetic testing | **Relevant outcomes include:**<br>• Overall survival<br>• Disease-specific survival<br>• Test validity<br>• Quality of life |
| **Individuals:**<br>• With other high-risk cancers (e.g., cancers of the fallopian tube, pancreas, prostate) | **Interventions of interest are:**<br>• Genetic testing for a BRCA1 or BRCA2 variant | **Comparators of interest are:**<br>• Standard of care without genetic testing | **Relevant outcomes include:**<br>• Overall survival<br>• Disease-specific survival<br>• Test validity<br>• Quality of life |
| **Individuals:**<br>• With cancer and criteria suggesting risk of hereditary breast/ovarian cancer syndrome or other high-risk cancers (e.g., cancers of the fallopian tube, pancreas, prostate) and considering systemic therapy (i.e., poly(adenosine diphosphate–ribose) polymerase [PARP] inhibitors for ovarian, prostate, pancreatic | **Interventions of interest are:**<br>• Genetic testing for a BRCA1 for BRCA2 variant | **Comparators of interest are:**<br>• Standard of care without genetic testing | **Relevant outcomes include:**<br>• Overall survival<br>• Disease-specific survival<br>• Test validity<br>• Quality of life |

| Populations | Interventions | Comparators | Outcomes |
|---|---|---|---|
| cancer, and metastatic or high-risk, early stage human epidermal receptor 2 [HER]-negative breast cancer or; platinum therapy for prostate cancer and pancreatic cancer) | | | |

## 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). 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 genetic testing for germline *BRCA1* or *BRCA2* 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.

## BACKGROUND

### Hereditary Breast and Ovarian Cancer Syndrome

Several genetic syndromes with an autosomal dominant pattern of inheritance that features breast cancer have been identified. Of these, HBOC and some cases of hereditary site-specific breast cancer have in common causative variants in *BRCA* (breast cancer susceptibility) genes. Families suspected of having HBOC syndrome are characterized by an increased susceptibility to breast cancer occurring at a young age, bilateral breast cancer, male breast cancer, ovarian cancer at any age, as well as cancer of the fallopian tube and primary peritoneal cancer. Other cancers, such as prostate cancer, pancreatic cancer, gastrointestinal cancers, melanoma, and laryngeal cancer, occur more frequently in HBOC families. Hereditary site-specific breast cancer families are characterized by early-onset breast cancer with or without male cases, but without ovarian cancer.

Germline variants in the *BRCA1* and *BRCA2* genes are responsible for the cancer susceptibility in most HBOC families, especially if ovarian cancer or male breast cancer are features. However, in site-specific cancer, BRCA variants are responsible only for a proportion of affected families. *BRCA* gene variants are inherited in an autosomal dominant fashion through maternal or paternal lineage. It is possible to test for abnormalities in *BRCA1* and *BRCA2* genes to identify the specific variant in cancer cases and to identify family members at increased cancer risk.

Family members without existing cancer who are found to have *BRCA* variants can consider preventive interventions for reducing risk and mortality.

### Clinical Features Suggestive of *BRCA* Variant

Young age of onset of breast cancer, even in the absence of family history, is a risk factor for *BRCA1* variants. Winchester (1996) estimated that hereditary breast cancers account for 36% to 85% of patients diagnosed before age 30.[3,] In several studies, BRCA variants were independently predicted by early age at onset, being present in 6% to 10% of breast cancer cases diagnosed at ages younger than various premenopausal age cutoffs (age range, 35-50 years).[3,4,5,6,] In cancer-prone families, the mean age of breast cancer diagnosis among women carrying *BRCA1* or *BRCA2* variants is in the 40s.[7,] In the Ashkenazi Jewish population, Frank et al (2002) reported that 13% of 248 cases with no known family history and diagnosed before 50 years of age had *BRCA* variants.[4,] In a similar study by Gershoni-Baruch et al (2000), 31% of Ashkenazi Jewish women, unselected for family history, diagnosed with breast cancer at younger than 42 years of age had *BRCA* variants.[8,] Other studies have indicated that early age of breast cancer diagnosis is a significant predictor of BRCA variants in the absence of family history in this population.[9,10,11,]

As in the general population, a family history of breast or ovarian cancer, particularly of early age onset, is a significant risk factor for a *BRCA* variant in ethnic populations characterized by founder mutations. For example, in unaffected individuals of Ashkenazi Jewish descent, 12% to 31% will have a *BRCA* variant depending on the extent and nature of the family history.[6,] Several other studies have documented the significant influence of family history.[8,9,10,11,12,]

In patients with "triple-negative" breast cancer (i.e., negative for expression of estrogen, progesterone, and overexpression of human epidermal growth factor receptor 2 receptors), there is an increased prevalence of *BRCA* variants. Pathophysiologic research has suggested that the physiologic pathway for the development of triple-negative breast cancer is similar to that for *BRCA*-associated breast cancer.[13,] In 200 randomly selected patients with triple-negative breast cancer from a tertiary care center, Kandel et al (2006) reported there was a greater than 3-fold increase in the expected rate of *BRCA* variants.[14,] *BRCA1* variants were found in 39.1% of patients and *BRCA2* variants in 8.7%. Young et al (2009) studied 54 women with high-grade, triple-negative breast cancer with no family history of breast or ovarian cancer, representing a group that previously was not recommended for *BRCA* testing.[15,] Six BRCA variants (5 *BRCA1*, 1 *BRCA2*) were found, for a variant rate of 11%. Finally, Gonzalez-Angulo et al (2011) in a study of 77 patients with triple-negative breast cancer, reported that 15 patients (19.5%) had BRCA variants (12 in *BRCA1*, 3 in *BRCA2*).[16,]

## REGULATORY STATUS

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

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

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

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

**Poly (Adenosine Diphosphate–Ribose) Polymerase (PARP) Inhibitors**
Poly (adenosine diphosphate–ribose) polymerase (PARP) inhibitors drugs are oral targeted therapies used to treat certain types of cancers that have damaged DNA repair pathways (*e.g., BRCA* mutation). Table 1 provides a list of FDA approved PARP inhibitor drugs and their *BRCA* mutation-related approved indications.

**Table 1. FDA-Approved *BRCA* Mutation-Related Indications for Poly (Adenosine Diphosphate–Ribose) Polymerase (PARP) Inhibitors**

| PARP Inhibitor | Year Approved | Indication |
|---|---|---|
| Olaparib | 2018 | Maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic *BRCA*-mutated advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic |
| | 2018 | Treatment of adult patients with deleterious or suspected deleterious germline *BRCA*- |

| PARP Inhibitor | Year Approved | Indication |
|---|---|---|
| | | mutated (*gBRCAm*) advanced ovarian cancer who have been treated with 3 or more prior lines of chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic |
| | 2018 | Treatment of adult patients with deleterious or suspected deleterious *gBRCAm*, HER2-negative metastatic breast cancer who have been treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting. Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine therapy. Select patients for therapy based on an FDA-approved companion diagnostic |
| | 2019 | Maintenance treatment of adult patients with deleterious or suspected deleterious *gBRCAm* metastatic pancreatic adenocarcinoma whose disease has not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen. Select patients for therapy based on an FDA-approved companion diagnostic |
| | 2020 | In combination with bevacizumab for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy and whose cancer is associated with homologous recombination deficiency positive status defined by either a deleterious or suspected deleterious *BRCA* mutation, and/or genomic instability. Select patients for therapy based on an |

| PARP Inhibitor | Year Approved | Indication |
|---|---|---|
| | | FDA-approved companion diagnostic |
| | 2020 | Treatment of adult patients with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC) who have progressed following prior treatment with enzalutamide or abiraterone |
| Niraparib | 2017 | For the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy |
| | 2019 | Treatment of adult patients with advanced ovarian, fallopian tube, or primary peritoneal cancer who have been treated with 3 or more prior chemotherapy regimens and whose cancer is associated with homologous recombination deficiency positive status defined by either a deleterious or suspected deleterious *BRCA* mutation, or genomic instability and who have progressed more than 6 months after response to the last platinum-based chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic |
| Rucaparib | 2019 | Treatment of patients with deleterious *BRCA* mutation-associated epithelial ovarian, fallopian tube, or primary peritoneal cancer who have been treated with 2 or more chemotherapies. Select patients for therapy based on an FDA-approved companion diagnostic |

| PARP Inhibitor | Year Approved | Indication |
|---|---|---|
| | 2020 | Treatment of adult patients with a deleterious *BRCA* mutation (germline and/or somatic)-associated metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor-directed therapy and a taxane based chemotherapy[a] |
| Talazoparib | 2018 | Treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm) HER2-negative locally advanced or metastatic breast cancer. Select patients for therapy based on an FDA-approved companion diagnostic |

[a] This indication is approved under accelerated approval based on objective response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. The ongoing FDA-required confirmatory trial is TRITON3 (NCT02975934), which is a randomized, phase 3 study evaluating rucaparib 600 mg BID vs physician's choice treatment in patients with mCRPC and a deleterious germline or somatic *BRCA1*, *BRCA2*, or *ATM* mutation and powered to measure progression-free survival as its primary outcome.
BRCA: Breast Cancer gene; FDA: U.S. Food and Drug Administration; gBRCAm: germline BRCA mutated; HER2: human epidermal growth factor receptor 2; PARP: Poly (adenosine diphosphate–ribose) polymerase

## POLICY

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

A. **Patients With Cancer or With a Personal History of Cancer**
Genetic testing for *BRCA1* and *BRCA2* variants in cancer-affected individuals may be considered **medically necessary** under any of the following circumstances:

1. Individual from a family with a known *BRCA1* or *BRCA2* variant

2. Individuals meeting the criteria below but with previous limited testing (e.g., single gene and/or absent deletion duplication analysis)

3. Personal history of breast cancer and 1 or more of the following:

    a. Diagnosed at age ≤45 years

    b. Diagnosed 46 to 50 years with:
        I. One or more 1st-, 2nd-, or 3rd-degree blood relative with breast cancer, ovarian, pancreatic, or prostate cancer at any age; **OR**
        II. An unknown or limited family history; **OR**
        III. An additional breast cancer primary at any age

    c. Diagnosed ≤60 years with:
        I. Triple negative breast cancer

    d. Diagnosed at any age with:
        I. One or more 1st-, 2nd-, or 3rd-degree blood relative with
            i. Breast cancer diagnosed at ≤50 years; **OR**
            ii. Ovarian, fallopian tube, or primary peritoneal cancer; **OR**
            iii. Metastatic or intraductal/cribriform prostate cancer, or high-risk group or very-high-risk group (see Policy Guidelines) prostate cancer; **OR**
            iv. Pancreatic cancer
        II. ≥3 total diagnoses of breast cancer at any age in patient and/or 1st-, 2nd-, or 3rd-degree blood relative
        III. Ashkenazi Jewish ancestry

    e. Diagnosed at any age with male breast cancer

4. Personal history of ovarian, fallopian tube, or primary peritoneal cancer at any age

5. Personal history of exocrine pancreatic cancer at any age

6. 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

7. Personal history of prostate cancer at any age with:
   a. One or more 1st-, 2nd-, or 3rd-degree blood relative with ovarian, fallopian tube, or primary peritoneal cancer, pancreatic cancer, or metastatic or intraductal/cribriform prostate cancer at any age or breast cancer ≤50 years; **OR**
   b. Two or more 1st-, 2nd-, or 3rd-degree blood relatives with breast or prostate cancer (any grade) at any age; **OR**
   c. Ashkenazi Jewish ancestry

8. Personal history of cancer and a mutation identified on tumor genomic testing that has clinical implications if also identified in the germline

9. Personal history of cancer and to aid in systemic therapy decision-making for PARP-inhibitors for human epidermal receptor 2 (HER2)-negative metastatic and HER2-negative early stage, high-risk breast cancer (see Policy Guidelines)

10. Personal history of cancer and to aid in systemic therapy decision-making for PARP-inhibitors for ovarian cancer, prostate cancer, and pancreatic cancer and platinum therapy for prostate cancer and pancreatic cancer.

B. **Patients Without Cancer or Without History of Cancer** (see Policy Guidelines: Testing Unaffected Individuals)

1. Genetic testing for *BRCA1* and *BRCA2* variants of cancer-unaffected individuals may be considered **medically necessary** under any of the following circumstances:
   a. Individual from a family with a known *BRCA1* or *BRCA2* variant
   b. An unaffected individual with 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.
   c. An unaffected individual who otherwise does not meet the criteria above but has a probability >5% of a *BRCA1/2* pathogenic variant based on prior probability models (*e.g.*, Tyrer-Cuzick, BRCAPro, Pennll)

C. Genetic testing for *BRCA1* and *BRCA2* variants in cancer-affected individuals or of cancer-unaffected individuals with a family history of cancer when criteria above are not met is considered **experimental / investigational**.

D. Genetic testing in minors for *BRCA1* and *BRCA2* variants is considered **experimental / investigational**.

## POLICY GUIDELINES

A. Current U.S. Preventive Services Task Force (USPSTF) 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 positive screening result on the risk assessment tool should receive genetic counseling and, if indicated after counseling, genetic testing (B Recommendation).

B. 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:
   1. Ontario Family History Assessment Tool (FHAT)
   2. Manchester Scoring System
   3. Referral Screening Tool (RST)
   4. Pedigree Assessment Tool (PAT)
   5. Family History Screen (FHS-7)
   6. International Breast Cancer Intervention Study instrument (Tyrer-Cuziak)
   7. Brief versions of the BRCAPRO

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

D. **Breast Cancer Risk Groups:** In the OlympiA trial, patients with HER2-negative early-stage breast cancer (Clinical Stage I-III) and germline *BRCA1/2* mutations treated with (neo)adjuvant chemotherapy were considered at high risk of recurrent disease when the following eligibility criteria were met for treatment with olaparib:[1,]
   1. Patients with triple-negative breast cancer who were treated with adjuvant chemotherapy were required to have axillary node-positive disease or an invasive primary tumor measuring at least 2 cm on pathological analysis. Patients treated with neoadjuvant chemotherapy were required to have not achieved pathological complete response.
   2. Patients treated with adjuvant chemotherapy for hormone receptor (HR)-positive, HER2-negative breast cancer were required to have at least 4 pathologically confirmed positive lymph nodes. Those treated with neoadjuvant chemotherapy were required to have not achieved a pathological complete response with a clinical stage, pathologic stage, estrogen receptor status, and tumor grade (CPS+EG) score of 3 or higher (Table PG1). This scoring system estimates relapse probability on the basis of clinical and pathological stage (CPS) and estrogen-receptor status and histologic grade (EG). Scores range from 0 to 6, with higher scores reflecting a worse prognosis.

**Table PG1. CPS+EG Score[a,b]**

| Stage or Feature | Points |
|---|---|
| ***Clinical Stage (AJCC Staging)*** | |
| I | 0 |
| IIA | 0 |
| IIB | 1 |
| IIIA | 1 |
| IIIB | 2 |
| IIIC | 2 |
| ***Pathologic Stage (AJCC Staging)*** | |
| 0 | 0 |
| I | 0 |
| IIA | 1 |
| IIB | 1 |
| IIIA | 1 |
| IIIB | 1 |
| IIIC | 2 |
| ***Receptor Status*** | |
| ER-negative | 1 |
| ***Nuclear Grade*** | |
| Nuclear grade 3 | 1 |

AJCC: American Joint Committee on Cancer; CPS+EG: clinical stage, pathologic stage, ER status, and tumor grade; ER: estrogen receptor.
[a] Adapted from Tung et al (2021).[2,]
[b] Add points for clinical stage, pathologic stage, ER status, and nuclear grade to yield a sum between 0 and 6.

E. **Prostate Cancer Risk Groups:** Risk groups for prostate cancer in this policy include high-risk groups and very-high-risk groups.
   1. 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.
   2. 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

F. **Recommended Testing Strategies:** Patients who meet criteria for genetic testing as outlined in the policy statements above should be tested for variants in *BRCA1* and *BRCA2*. Recommended strategies are listed below.

1. In patients with a known familial *BRCA* variant, targeted testing for the specific variant is recommended.
2. In patients with unknown familial *BRCA* variant:
    a. To identify clinically significant variants, National Comprehensive Cancer Network (NCCN) advises testing a relative who has early-onset disease, bilateral disease, multiple primaries, because that individual has the highest likelihood of obtaining a positive test result. Unless the affected individual is a member of an ethnic group for which particular founder pathogenic or likely pathogenic variants are known, comprehensive genetic testing (*i.e.,* full sequencing of the genes and detection of large gene rearrangements) should be performed
    b. If no living family member with breast or ovarian cancer exists, NCCN suggests testing first- or second-degree family members affected with cancer thought to be related to deleterious *BRCA1* or *BRCA2* variants (e.g., prostate cancer, pancreatic cancer, melanoma).
    c. If no familial variant can be identified, 2 possible testing strategies are:
        I. Full sequencing followed by testing for large genomic rearrangements (deletions/duplications) only if sequencing detects no variant (negative result).
            i. More than 90% of *BRCA* variants will be detected by full sequencing.
        II. 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.
            i. Comprehensive testing can detect 92.5% of *BRCA1* or *BRCA2* variants.
        III. If comprehensive BRCA testing is negative, testing for uncommon large genomic rearrangements (e.g., BART) may be done.
        IV. Testing for *uncommon* large rearrangements should not be done unless both sequencing and testing for *common* large rearrangements have been performed and are negative.
            i. Among patients with negative comprehensive testing, BART identified a deleterious variant (positive result) in less than 1%.
    d. Ashkenazi Jewish descent
        I. In patients of know Ashkenazi Jewish descent, one approach is to test for the 3 known founder mutations (185delAG and 5182insC in BRCA1; 6174delT in BRCA2) first.
        II. If testing is negative for founder mutations and if the individual's ancestry also included non-Ashkenazi ethnicity (of if other BRCA1/2 testing criteria are met), comprehensive genetic testing may should be considered (see Comprehensive Mutation Analysis).

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

H. **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, comprehensive variant analysis should then be performed.

I. **Testing Unaffected Individuals:** In unaffected family members of potential *BRCA* 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* 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* variant is not ruled out.

J. **Testing Minors:** The use of genetic testing for *BRCA* variants 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.

K. **Prostate Cancer:** Patients with *BRCA* variants have an increased risk of prostate cancer, and patients with known *BRCA* variants may, therefore, consider more aggressive screening approaches for prostate cancer. However, the presence of prostate cancer in an individual, or in a family, is not itself considered sufficient justification for *BRCA* testing.

L. **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 PG21). 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 PG32 shows the recommended standard terminology- "pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"- to describe variants identified that cause Mendelian disorders.

**Table PG21. 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 PG32. ACMG-AMP Standards and Guidelines for Variant Classification**

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

ACMG-AMP: American College of Medical Genetics and Genomics and the Association for Molecular Pathology.

M. **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.

**Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.**

## RATIONALE

This evidence review has been updated regularly with searches of the PubMed database. The most recent literature update was performed through October 1, 2021.

This review was informed by a TEC Assessment (1997).[17,]

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

## TESTING FOR *BRCA1* AND *BRCA2* VARIANTS IN INDIVIDUALS AT RISK FOR HEREDITARY BREAST/OVARIAN CANCER SYNDROME OR OTHER HIGH-RISK CANCERS

### Clinical Context and Test Purpose

The purpose of testing for *BRCA1* and *BRCA2* variants in individuals at high-risk for HBOC syndrome is to evaluate whether variants are present and if so, to determine the appropriate surveillance and treatment to decrease the risk of mortality from breast and/or ovarian cancer.

The question addressed in this evidence review is: Does testing for *BRCA1* and *BRCA2* variants improve the net health outcome in individuals with or suspected of having HBOC syndrome or other high-risk cancers?

The following PICO was used to select literature to inform this review.

#### *Populations*

The relevant population of interest is patients with cancer (i.e., breast cancer, epithelial ovarian, fallopian tube, primary peritoneal cancer), or patients with a personal or family history of cancer and criteria that might suggest they are at risk of HBOC syndrome.

#### *Interventions*

The intervention of interest is *BRCA1* and *BRCA2* variant testing.

For patients without a cancer diagnosis who are assessing cancer risk, results may guide potential prophylactic measures such as surveillance, chemoprevention, or prophylactic mastectomy, and/or oophorectomy.

For patients with a cancer diagnosis, results may guide treatment decisions.

Testing for *BRCA1* and *BRCA2* variants is conducted in adults when appropriate treatment and/or prophylactic treatment options are available. Variant testing is offered in a primary care setting (e.g., for people without cancer) or the specialty setting (e.g., multidisciplinary oncology care) through various test manufacturers and institutions.

***Comparators***
The following practice is currently being used to manage HBOC syndrome or other high-risk cancers: standard of care without genetic testing.

***Outcomes***
The outcomes of interest are overall survival (OS), disease-specific (breast and ovarian cancer) survival, test validity, and quality of life (QOL; e.g., anxiety).

**Study Selection Criteria**
For the evaluation of clinical validity, studies of variant prevalence and cancer risk were included. For the evaluation of clinical utility, studies that represent the intended clinical use of the technology in the intended population were included. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings.

Evidence for the 2 indications is presented together because there is overlap in the evidence base for the 2 populations: (1) patients at risk of HBOC syndrome, and (2) patients with other high-risk cancers such as cancers of the fallopian tube, pancreas, and prostate.

**Clinically Valid**
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

**REVIEW OF EVIDENCE**

**Prevalence of *BRCA* Variants and Risks of Cancer and Survival**
The prevalence of *BRCA* variants is approximately 0.1% to 0.2% in the general population. The prevalence may be much higher for particular ethnic groups with characterized founder mutations (e.g., 2.5% [1/40] in the Ashkenazi Jewish population). Family history of breast and ovarian cancer is an important risk factor for the *BRCA* variant; additionally, age and ethnicity could be independent risk factors.

**Systematic Reviews**
A systematic review published by Zhu et al (2016) found a significantly lower risk of OS in breast cancer patients with *BRCA1* (pooled hazard ratio [HR], 1.69; 95% confidence interval [CI], 1.35 to 2.12) and with *BRCA2* (pooled HR, 1.50; 95% CI, 1.02 to 2.09; p=.034).[18,] However, in patients with breast cancer, *BRCA1* and *BRCA2* were not associated with a lower breast cancer-specific survival.

Nelson et al (2013) conducted a systematic review that included meta-analytic estimates of the prevalence and penetrance of *BRCA* variants; this review was used to update the U.S. Preventive Services Task Force (USPSTF) recommendation for risk assessment, genetic counseling, and genetic testing for *BRCA*-related cancer.[19,] In high-risk women with positive test results, cumulative risks for developing breast cancer by age 70 were 46% for *BRCA1* and 50% for *BRCA2* when a single family member was tested, and 70% for *BRCA1* and 71% for *BRCA2* when multiple family members were tested; cumulative risks for developing ovarian cancer by age 70 were 41% for *BRCA1* and 17% for *BRCA2* when a single family member was

tested; and 46% for *BRCA1* and 23% for *BRCA2* when multiple family members were tested. For Ashkenazi Jewish women with positive test results, cumulative risks for developing breast or ovarian cancer by age 75 were 34% and 21%, respectively. Nelson et al (2013) included meta-analytic estimates of *BRCA* prevalence in their review for USPSTF. In unselected women, *BRCA* variant prevalence estimates were 0.2% to 0.3%; in women with breast cancer, 1.8% for *BRCA1* and 1.3% for *BRCA2*; in women with breast cancer onset at age 40 years or younger, 6%; in women from high-risk families, 13.6% for *BRCA1*, 7.9% for *BRCA2*, and 19.8% for *BRCA1* or *BRCA2*; in unselected Ashkenazi Jewish women, 2.1%; and in Ashkenazi Jewish women from high-risk families, 10.2%.

Estimates of lifetime risk of cancer for *BRCA* variant carriers (penetrance), based on studies of families with an extensive history of the disease, have been as high as 85%. For example, Kuchenbaecker et al (2017) found that the cumulative risk of breast cancer up to age 80 was 72% in *BRCA1* carriers and 69% in *BRCA2* carriers.[20,] Because other factors that influence risk may be present in families with extensive breast and ovarian cancer histories, early penetrance estimates may have been biased upward.[21,] Studies of founder mutations in ethnic populations (e.g., Ashkenazi Jewish, Polish, Icelandic populations) unselected for family history have indicated lower penetrance estimates, in the range of 40% to 60% for *BRCA1* and 25% to 40% for *BRCA2*.[9,12,22,23,] However, a genotyping study of Ashkenazi Jewish women with incident invasive breast cancer, selected regardless of family history of cancer and their family members, resulted in an 82% lifetime risk of breast cancer for carriers of any of 3 *BRCA* founder mutations (185delAG, 5382insC, 6174delT).[23,] Importantly, the risk of cancer in variant carriers from families with little history of cancer (»50% of all carriers) did not differ significantly. Lifetime risk estimates of ovarian cancer were 54% for *BRCA1* and 23% for *BRCA2* variant carriers.

**Prospective Studies**

Women with a history of breast cancer and a *BRCA* variant have a significant risk of contralateral breast cancer. In a prospective study by Metcalfe et al (2004), the 10-year risk was 29.5% for women with initial stage I or II diseases.[24,] In a prospective study, Epidemiological Study of Familial Breast Cancer, Mavaddat et al (2013) reported that the cumulative risk of contralateral breast cancer by age 70 years was 83% in the *BRCA1* variant carriers, and 62% for *BRCA2* variant carriers.[25,] These investigators also reported cumulative risks of breast cancer by age 70 in women without previous cancer (60% in *BRCA1* carriers, 55% in *BRCA2* carriers). Similarly, the cumulative risk estimates of ovarian cancer by age 70 years in women without previous ovarian cancer were 59% for *BRCA1* carriers and 17% for *BRCA2* carriers.

**_BRCA_ Variant Rates Associated With Ovarian Cancer**

Women with a personal history of ovarian cancer have an increased rate of *BRCA* variants. In a systematic review of 23 studies, Trainer et al (2010) estimated the rate of *BRCA* variants among women with ovarian cancer to be 3% to 15%.[26,] In this review, 3 U.S. studies tested for both *BRCA1* and *BRCA2*; incidences of BRCA variants were 11.3%, 15.3%, and 9.5%. In the systematic review for USPSTF by Nelson et al (2013), meta-analytic estimates of *BRCA* prevalence among women with ovarian cancer were 4.4% for *BRCA1* and 5.6% for *BRCA2*.[19,] Table 2 lists the results from several additional studies measuring the presence of *BRCA* variants among patients with ovarian cancer.[27,28,29,30,31,] One study noted that variant prevalence was higher for women in their 40s (24%) and for women with serous ovarian cancer (18%).[27,] Ethnicity was another risk factor for *BRCA*, with higher rates seen in women of Italian (43.5%), Jewish (30%), and Indo-Pakistani (29.4%) origin.[27,]

**Table 2. *BRCA* Variant Rates in Patients With Ovarian Cancer**

| Study | Population | N | *BRCA* Variant, n (%) | |
|---|---|---|---|---|
| | | | *BRCA1* | *BRCA2* |
| Harter et al (2017)[31,] | Patients with invasive ovarian cancer across 20 medical centers | 523 | 81 (15.5) | 29 (5.5) |
| Kurian et al (2017)[28,] | Patients with invasive ovarian cancer tested for hereditary cancer risk from a commercial laboratory database | 5020[a] | 255 (15.5) | 199 (5.5) |
| Langer et al (2016)[29,] | Patients with ovarian cancer tested for hereditary cancer risk from a commercial laboratory database | 3088 | 153 (4.9) | 124 (4.0) |
| Norquist et al (2016)[30,] | Patients with invasive ovarian cancer, from 2 phase 3 clinical trials and a gynecologic oncology tissue bank | 1915 | 182 (9.5) | 98 (5.1) |
| Zhang et al (2011)[27,] | Patients with invasive ovarian cancer | 1342 | 107 (8.0) | 67 (5.0) |

[a] Total N was reported as 5020, however, the percentage of *BRCA* variants as reported in article is inconsistent with 5020 as the denominator.

### *BRCA* Variant Rates Associated With Fallopian Tube Cancer

A study by Hirst et al (2009) described the high rate of occult fallopian tube cancers in at-risk women having prophylactic bilateral salpingo-oophorectomy.[32,] In this prospective series of 45 women, 4 (9%) had fallopian tube malignancies. Reviewers noted that these findings supported other studies that have demonstrated the fimbrial end of the fallopian tube as an important site of cancer in those with *BRCA1* or *BRCA2* variants.

A long-term study by Powell et al (2013; median follow-up, 7 years; range, 3-14 years) followed 32 *BRCA* variant carriers with occult malignancy (4 ovarian, 23 fallopian tube, 5 ovarian and fallopian tube) diagnosed of prophylactic salpingo-oophorectomy.[33,] Among 15 women with invasive carcinoma (median age, 50 years), 7 (47%) experienced recurrence at a median of 33 months, and OS was 73%. Among 17 women with noninvasive neoplasia (median age, 53 years), 4 (24%) received chemotherapy, none of whom experienced recurrence. One (6%) patient who did not receive chemotherapy experienced recurrence at 43 months. OS was 100%. The authors concluded that, in *BRCA* variant carriers, unsuspected invasive carcinoma has a relatively high rate of recurrence, but noninvasive neoplasms rarely recur and may not require adjuvant chemotherapy.

### *BRCA* Variant Rates Associated With Pancreatic Cancer

Unaffected individuals also may be at high-risk due to other patterns of non-breast-cancer malignancies. A personal history of pancreatic cancer is estimated to raise the risk of a *BRCA* variant by 3.5- to 10-fold over the general population.[34,] Table 3 lists the results from several studies measuring the presence of *BRCA* variants among patients with pancreatic adenocarcinoma.[35,36,37,38,39,40,] Patients with pancreatic adenocarcinoma of Jewish descent appear to have a higher prevalence of *BRCA* variants compared with the general population of patients with pancreatic adenocarcinoma.

**Table 3. *BRCA* Variant Rates in Patients With Pancreatic Cancer**

| Study | Population | N | *BRCA* Variant, n (%) | |
|---|---|---|---|---|
| | | | *BRCA1* | *BRCA2* |
| Hu et al (2018)[40,a] | Patients with pancreatic adenocarcinoma from a prospective pancreatic cancer registry | 3030 | 18 (0.6) | 59 (1.9) |
| Yurgelun et al (2018)[39,] | Patients with pancreatic adenocarcinoma from 3 medical centers | 289 | 3 (1.0) | 4 (1.4) |
| Shindoet al (2017)[38,] | Patients with pancreatic adenocarcinoma from 1 medical center | 854 | 3 (0.3) | 12 (1.4) |
| Holter et al (2015)[37,] | Patients with pancreatic adenocarcinoma from a large academic health care complex | 306 | 3 (1.0) | 11 (3.6) |
| Ferrone et al (2009)[36,] | Jewish patients with pancreatic adenocarcinoma from 1 hospital | 145 | 2 (1.3) | 6 (4.1) |
| Couch et al (2007)[35,] | Probands from high-risk families identified through pancreatic cancer clinics and a pancreatic tumor registry | 180 | | 10 (5.5) |

[a] Case-control study; rates for *BRCA1* and *BRCA2* variants in controls were 0.2 and 0.3, respectively.

### *BRCA* Variant Rates Associated With Prostate Cancer

Table 4 lists the results from several studies measuring the presence of *BRCA* variants among patients with prostate cancer.[41,42,43,]

**Table 4. *BRCA* Variant Rates in Patients With Prostate Cancer**

| Study | Population | N | *BRCA* Variant, n (%) | |
|---|---|---|---|---|
| | | | ***BRCA1*** | ***BRCA2*** |
| Abida et al (2017)[43,] | Patients with prostate cancer from 1 clinical practice | 221 | 2 (1) | 20 (9) |
| Pritchard et al (2016)[42,] | Patients with metastatic prostate cancer from 7 case series across multiple centers | 692 | 6 (0.9) | 37 (5.3) |
| Edwards et al (2003)[41,] | Patients with prostate cancer diagnosed before age 56 from 2 cancer study groups | 263 | | 6 (2.3) |

### Testing for Large *BRCA* Rearrangements

A number of studies have shown that a significant percentage of women with a strong family history of breast cancer and negative tests for BRCA variants have large genomic rearrangements (including deletions or duplications) in 1 of these genes. For example, Walsh et al (2006) reported on probands from 300 U.S. families with 4 or more cases of breast or ovarian cancer but with negative (wild-type) commercial genetic tests for *BRCA1* and *BRCA2*.[44,] These patients underwent screening with additional multiple DNA-based and RNA-based methods. Of these 300 patients, 17% carried previously undetected variants, including 35 (12%) with genomic rearrangement of *BRCA1* or *BRCA2*.

A study by Palma et al (2008) evaluated 251 patients with an estimated *BRCA* variant prevalence using the Myriad II model of at least 10%.[45,] In 136 non-Ashkenazi Jewish probands, 36 (26%) had *BRCA* point mutations and 8 (6%) had genomic rearrangements (7 in *BRCA1*, 1 in *BRCA2*). Genomic rearrangements comprised 18% of all identified *BRCA* variants. No genomic rearrangements were identified in the 115 Ashkenazi Jewish probands, but 47 (40%) had point mutations. The authors indicated that the estimated prevalence of a variant did not predict the presence of a genomic rearrangement.

**Clinically Useful**

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

**Direct Evidence**

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs). In their systematic review for the USPSTF, Nelson et al (2019) confirmed that they identified no studies that compared health outcomes for patients managed with and without *BRCA* variant testing.[46,]

Knowledge of variant status in individuals at potentially increased risk of a *BRCA* variant may impact health care decisions to reduce risk.[47,48,49,50,51,52,53,] Risk-reducing options include intensive surveillance, chemoprevention, prophylactic mastectomy, or prophylactic oophorectomy.

Prophylactic mastectomy reduces the risk of breast cancer in high-risk women (based on family history) by 90%.[48,] Prophylactic oophorectomy significantly reduces the risk of ovarian cancer by 80% or more[51,52,54,] and reduces the risk of breast cancer by approximately 50%.[52,] In women who have already had breast cancer, prophylactic oophorectomy reduces the risk of cancer relapse.[38,] Prophylactic oophorectomy or salpingo-oophorectomy in women with *BRCA1* or *BRCA2* reduced the risk of all-cause mortality by 60% to 77%.[54,55,] For patients at risk for both breast and ovarian cancer, a study by Elmi et al (2018), drawing on data from the American College of Surgeon's National Surgical Quality Improvement Program dataset, found that prophylactic mastectomy with concurrent salpingo-oophorectomy was not associated with significant additional morbidity compared with prophylactic mastectomy alone.[56,]

Systematic reviews of observational studies comparing prophylactic surgeries with observation in women who had *BRCA1* and *BRCA2* variants have demonstrated that contralateral prophylactic mastectomy in women with breast cancer is associated with significantly lower all-cause mortality while bilateral prophylactic mastectomy was not associated with all-cause mortality.[57,58,59,] Studies have indicated that the results of genotyping significantly influenced treatment choices.[49,60,53,]

In a systematic review for the USPSTF, Nelson et al (2019) assessed the efficacy of risk-reducing surgery in *BRCA*-positive women.[46,] The literature search was conducted through March 2019. A total of 13 observational studies (n=9938) provided consistent and moderate-strength evidence of the benefits of risk-reducing surgery. For high-risk women and variant carriers, bilateral mastectomy reduced breast cancer incidence by 90% to 100% and breast cancer mortality by 81% to 100%; oophorectomy or salpingo-oophorectomy reduced breast cancer incidence by 37% to 83%, ovarian cancer incidence by 69% to 100%. Some women experienced reduced

anxiety. Limitations of the studies of benefits included lack of comparison groups, variations in methodology and enrollment criteria, and heterogeneous outcome measures. Additionally, a total of 14 observational studies (n=3073) provided low-strength evidence of the harms of risk-reducing surgery. Adverse events included physical complications of the surgery, postsurgical symptoms, and changes in body image. Studies of harms shared the same limitations as the studies of benefits as noted above, with the addition that their findings were inconsistent and the sample sizes were smaller. As reviewers observed, it is still currently unknown whether *BRCA* variant testing reduces cause-specific or all-cause mortality, or if it improves the QOL. Harms associated with false-negative results or variants of uncertain significance also are unknown.

Other studies have looked at the results of prostate cancer screening in men with *BRCA* variants. The Immunotherapy for Prostate Adenocarcinoma Treatment study (2011) evaluated the results of screening in 205 men 40 to 69 years of age who were *BRCA* variant carriers and 95 control patients.[61,] At the baseline screen, biopsies were performed in 7.0% of men with a prostate-specific antigen level greater than 3.0 ng/mL, and prostate cancer was identified in 3.3%. This resulted in a positive predictive value of 47.6%, which is considerably higher than that estimated for men at normal risk. Moreover, the grade of tumor identified was intermediate in 67% of cancers and high in 11%. This differs from the expected distribution of cancer grade in average-risk men, with more than 60% expected to have low-grade cancer.

### Section Summary: Testing for *BRCA1* and *BRCA2* Variants in Individuals at Risk for HBOC Syndrome or Other High-Risk Cancers

Evidence for the clinical validity of *BRCA1* and *BRCA2* variant testing consists of multiple studies that calculated *BRCA1* and *BRCA2* variant prevalence among samples of patients with HBOC syndrome, fallopian tube cancer, pancreatic cancer, and prostate cancer.

Regarding clinical utility of *BRCA1* and *BRCA2* variant testing, current evidence has not directly evaluated management with and without genetic testing. In terms of prophylactic measures (mastectomy and oophorectomy), RCTs would be difficult to conduct. However, retrospective analyses have shown that prophylactic mastectomy and/or oophorectomy greatly reduced the risk of breast cancer (90-100%) and ovarian cancer (69%-100%).

## TESTING FOR *BRCA1* AND *BRCA2* VARIANTS TO GUIDE SYSTEMIC THERAPY DECISIONS IN INDIVIDUALS WITH HBOC SYNDROME OR OTHER HIGH-RISK CANCERS

### Clinical Context and Test Purpose

The purpose of testing for *BRCA1* and *BRCA2* variants in individuals with HBOC Syndrome or other high-risk cancers considering systemic therapy options (*i.e.,* poly(adenosine diphosphate–ribose) polymerase [PARP] inhibitors for ovarian, prostate, or pancreatic cancer and metastatic human epidermal receptor 2 [HER]-negative breast cancer; platinum therapy for prostate cancer and pancreatic cancer) is to guide treatment selection.

The question addressed in this evidence review is: Does testing for *BRCA1* and *BRCA2* variants in individuals with HBOC Syndrome or other high-risk cancers to guide systematic therapy decisions improve the net health outcome?

The following PICO was used to select literature to inform this review.

***Populations***
The relevant population of interest is individuals with HBOC Syndrome or other high-risk cancers considering systemic therapy.

***Interventions***
The test being considered is *BRCA1* and *BRCA2* variant testing.

***Comparators***
The following practice is currently being used to manage HBOC syndrome or other high-risk cancers: standard of care without genetic testing.

***Outcomes***
The outcomes of interest are overall survival (OS), disease-specific (breast and ovarian cancer) survival, test validity, and quality of life (QOL; e.g., anxiety).

**Clinically Valid**
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

**Study Selection Criteria**
For the evaluation of the clinical validity of the genetic test, studies that reported on the sensitivity and specificity and/or diagnostic yield of the test were considered.

**Clinical Validity**
Studies of the clinical validity of testing for *BRCA1* or *BRCA2* variants associated with HBOC syndrome or other high-risk cancers are previously summarized.

**Clinically Useful**
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

**Study Selection Criteria**
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

**CLINICAL UTILITY**

**Direct Evidence**
There are no direct outcome data on the clinical usefulness of testing for confirmation of a *BRCA1* or *BRCA2* variant in patients with HBOC syndrome or other high-risk cancers (*i.e.,* no studies have reported outcomes data for patients tested and not tested for a variant).

**Indirect Evidence**

A chain of indirect evidence would demonstrate that genetic testing can identify individuals with a *BRCA1* or *BRCA2* variant associated with HBOC syndrome or other high-risk cancers who would not otherwise be identified, that treatments are available for these patients that would not otherwise be given to patients with HBOC syndrome or other high-risk cancers, and that these treatments improve health outcomes.

**Review of Evidence**
Numerous clinical trials have been conducted to evaluate the effectiveness of PARP inhibitor drugs in individuals with HBOC Syndrome or other high-risk cancers confirmed to have a *BRCA1/2* mutation. Summarized below are the pivotal trials that supported the *BRCA* mutation-related U.S. Food and Drug Administration (FDA) approved indications.

***Olaparib***

***Breast Cancer***
Tutt et al (2021) published results from the phase 3 multicenter, multinational, and double-blind OlympiA RCT, which evaluated the safety and efficacy of olaparib in patients with germline *BRCA1* or *BRCA2* pathogenic or likely pathogenic variants and high-risk, human epidermal growth factor receptor 2 (*HER2*)-negative primary early-stage breast cancer after definitive local treatment and neoadjuvant or adjuvant chemotherapy.[1,] Patients with triple-negative breast cancer who were treated with adjuvant chemotherapy were required to have axillary node-positive disease or an invasive primary tumor measuring at least 2 cm on pathological analysis. Patients treated with neoadjuvant chemotherapy were required to have not achieved pathological complete response. Patients treated with adjuvant chemotherapy for hormone receptor (HR)-positive, HER2-negative breast cancer were required to have at least 4 pathologically confirmed positive lymph nodes. Those treated with neoadjuvant chemotherapy were required to have not achieved a pathological complete response with a CPS+EG score of 3 or higher. This scoring system estimates relapse probability on the basis of clinical and pathological stage (CPS) and estrogen-receptor status and histologic grade (EG). Scores range from 0 to 6, with higher scores reflecting a worse prognosis. Approximately half of patients received adjuvant chemotherapy and half neoadjuvant chemotherapy, with the majority (93.7%) receiving a combination of an anthracycline and a taxane in their regimen. Patients with triple-negative disease comprised 82.2% of the trial population. Patients were randomized 1:1 to treatment with twice daily 300 mg olaparib (n = 921) or placebo (n=915) for 52 weeks. At the prespecified interim analysis, 86% of the primary analysis target of 330 events of invasive disease or death in the intention-to-treat population were observed, with a median follow-up duration of 2.5 years (IQR, 1.5 to 3.5 y). The 3-year invasive disease-free survival was 85.9% in the olaparib group and 77.1% in the placebo group (difference, 8.8%; 95% CI, 4.5% to 13.0%). Invasive disease-free survival was significantly longer among patients receiving olaparib (HR, 0.58; 99.5% CI, 0.41 to 0.82; p <.001). Distant disease-free survival at 3 years was 87.5% in the olaparib group and 80.4% in the placebo group (difference, 7.1%; 95% CI, 3.0% to 11.1%). This outcome was significantly longer among patients assigned to receive olaparib (HR, 0.57; 99.5% CI, 0.39 to 0.83; p <.001). While fewer deaths were reported in the olaparib group (59 versus 86) with a HR of 0.68 (99% CI, 0.44 to 1.05; p =.02), the between-group difference did not cross the prespecified multiple-testing procedure boundary for significance of p <.01. Subgroup analysis of invasive disease-free survival revealed treatment effects for olaparib over placebo that were consistent with those in the overall analysis population across all stratification groups and prespecified subgroups. Serious adverse events occurred in 8.7% and 8.4% of

patients treated with olaparib and placebo, respectively. Adverse events leading to trial regimen discontinuation occurred in 9.9% and 4.2% of patients treated with olaparib and placebo, respectively.

OlympiAD is a phase 3 RCT in which patients with HER2-negative metastatic breast cancer and a germline *BRCA* variant were randomized to olaparib (n=205) or standard therapy (n=97).[62,] *BRCA1/2* mutation was detected by BRACAnalysis testing. In its initial publication, Robson et al (2017) reported that after a median follow-up of 14.5 months, patients receiving olaparib experienced significantly longer progression-free survival compared with patients receiving standard therapy (HR, 0.6; 95% CI, 0.4 to 0.8).[63,] The rate of grade 3 or higher adverse events was lower in the group receiving olaparib (37%) compared with the group receiving standard therapy (51%). However, regarding OS, in their subsequent publication, Robson et al (2019) further reported that although improvement with olaparib was not significant overall (19.3 vs 17.1 months; HR, 0.90; 95% CI, 0.66 to 1.23) there may be a benefit in the subgroup of patients who had not received chemotherapy for metastatic disease (HR, 0.51; 95% CI 0.29-0.90).[64,]

### *Ovarian Cancer*

Moore et al (2018) published results from the phase 3, international, multi-center, double-blind, placebo-controlled trial of maintenance olaparib 300 mg twice daily in 391 patients with newly diagnosed advanced high-grade serous or endometrioid ovarian cancer, primary peritoneal cancer, and/or fallopian-tube cancer with a *BRCA1/2* mutation following a complete or partial clinical response following platinum-based chemotherapy (SOLO-1).[65,] A total of 177 sites participated across 15 countries (United States, Australia, Brazil, Canada, China, France, Israel, Italy, Japan, Korea, Netherlands, Poland, New Zealand, Russian Federation, Spain, United Kingdom). Participants were enrolled between September 2013 and March 2015. The primary tumor location was the ovary in 85% of participants. The primary end point was progression-free survival, which was assessed by investigators and defined as the time from randomization to objective disease progression on imaging (according to modified Response Evaluation Criteria in Solid Tumors [RECIST], version 1.1) or death from any cause. Median follow-up was 41 months. Median progression-free survival was 13.8 months in the placebo group and not reported for the olaparib group. At 3 years, the proportions of patients free from disease progression and from death was 60% for olaparib and 27% for placebo, resulting in a 70% lower risk of disease progression or death for olaparib (HR 0.30; 95% CI, 0.23 to 0.41). Grade 3 or higher adverse events occurred in 39% of the olaparib group and 18% of the placebo group, with the most common events being anemia (22%) and neutropenia (9%).

Pujade-Lauraine et al (2017) published results from the phase 3, international, multi-center, double-blind, placebo-controlled trial of maintenance olaparib 300 mg twice daily in 295 patients with platinum-sensitive, relapsed, high-grade serous ovarian cancer or high-grade endometrioid cancer, including primary peritoneal or fallopian tube cancer, with a *BRCA1/2* mutation who had received at least 2 lines of previous chemotherapy (SOLO-2).[66,] A total of 123 sites participated across 16 countries (United States, Australia, Belgium, Brazil, Canada, France, Germany, Israel, Italy, Japan, Korea, Netherlands, Poland, Russian Federation, Spain, United Kingdom). Participants were enrolled between September 2013 and November 2014. The primary tumor location was the ovary in 85% of participants. The primary endpoint was investigator-assessed progression-free survival, defined as the time from randomization until objective radiological disease progression or death using modified RECIST version 1.1. Median follow-up was 22.1

months in the olaparib group and 22.2 months in the placebo group. Olaparib resulted in a significantly longer progression-free survival (19.1 vs 5.5 months; HR 0.30, 95% CI, 0.22 to 0.41). Grades 3 and 4 adverse events occurred in 32% and 4% of olaparib patients, respectively and 15% and 3% of the placebo group. The most common grade 3 or higher adverse event in the olaparib group was anemia (19%).

### *Prostate Cancer*

Hussain et al (2020) published results from the open-label, multicenter, phase 3 PROfound trial which randomized patients with metastatic castration-resistant prostate cancer and disease progression following prior treatment with a next-generation hormonal agent to treatment with olaparib 300 mg twice daily (n = 256) or investigator's choice of enzalutamide or abiraterone acetate plus prednisone (n = 131).[67,] Patients were divided into two cohorts based on their homologous recombination repair (HRR) gene mutation status. Specifically, patients with mutations in *BRCA1*, *BRCA2*, or *ATM* were randomized to Cohort A (n = 245) and patients with mutations in 12 other HRR pathway genes were randomized to Cohort B (n = 142). Patients with co-mutations were assigned to Cohort A. The primary efficacy outcome was radiological progression-free survival (rPFS) in Cohort A, which demonstrated a statistically significant improvement for olaparib compared to control with a median rPFS of 7.4 months versus 3.6 months (HR, 0.34; 95% CI, 0.25 to 0.47; p <.0001). Median OS was 19.1 months versus 14.7 months (HR, 0.69; 95%CI: 0.50 to 0.97; p =.0175) for olaparib compared to control. Exploratory gene-level analyses demonstrated HRs for death (olaparib versus control) among patients with an alteration in only *BRCA1* and only *BRCA2* of 0.42 (95% CI, 0.12 to 1.53) and 0.59 (95% CI, 0.37 to 0.95), respectively.

### *Niraparib*

### *Ovarian Cancer*

Mirza et al (2016) published results from the phase 3, international, multi-center, double-blind, placebo-controlled trial of 553 patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer that evaluated maintenance treatment with niraparib 300 mg once daily (NOVA).[68,] This trial was conducted by the European Network for Gynecological Oncological Trial groups and investigators across 107 sites in the United States, Canada, and Hungary. Two independent cohorts were separately evaluated on the basis of the presence or absence of a germline *BRCA* mutation (*gBRCA* cohort and non-*gBRCA* cohort), as determined on BRACAnalysis testing. Participants were enrolled between August 2013 and June 2016 and the majority had stage III or IV ovarian cancer. The *gBRCA* cohort consisted of 201 individuals (36.3%). The primary endpoint was progression-free survival. Overall median follow-up duration was 16.9 months. Progression-free survival was significantly longer in the niraparib group, regardless of the presence or absence of *gBRCA* mutations (*gBRCA* cohort: 21.0 vs 5.5 months; HR 0.27, 95% CI, 0.17 to 0.41; non-*gBRCA* cohort: 9.3 vs 3.9 months; HR 0.45, 95% CI, 0.34 to 0.61). Thrombocytopenia (33.8%), anemia (25.3%), and neutropenia (19.6%) were the most common grade 3 or higher adverse events in the niraparib group.

Moore et al (2019) published results from the phase 2, multi-center, single-arm clinical trial of niraparib monotherapy 300 mg once daily in individuals with relapsed, high-grade serous (grade 2 or 3) epithelial ovarian, fallopian tube, or primary peritoneal cancer who had been treated with 3 or more previous chemotherapy regimens (QUADRA).[65,] Between April 2015 and November 2017, this trial enrolled 463 patients across 56 sites in the United States and Canada. All

participants underwent tumor homologous recombination deficiency (HRD) testing and blood germline *BRCA*-mutated status testing and were stratified into 4 cohorts: *BRCA*-mutated, HRD-positive/non-*BRCA*-mutated, HRD-negative, and HRD-unknown. The majority of participants had ovarian cancer (79%). The *BRCA*-mutated cohort consisted of 87 (19%) participants. In the *BRCA*-mutated cohort, the primary endpoint of investigator-assessed confirmed overall response was met by 30% (95% CI, 17% to 64%) and 36% of patients with stable disease at 24 weeks had a progression-free survival ratio greater than 1.3 (9/25). In the overall population, anemia (24%) and thrombocytopenia (21%) were the most frequent grade 3 or higher adverse events. A key limitation of this trial is its lack of a control group.

### *Rucaparib*

#### *Ovarian Cancer*

Coleman et al (2017) published results from the phase 3, international, multi-center, double-blind trial of 564 patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer that compared rucaparib maintenance treatment to placebo following response to second-line or later platinum-based chemotherapy (ARIEL3).[69,] A total of 87 sites participated across 11 countries (United States, Australia, Belgium, Canada, France, Germany, Israel, Italy, New Zealand, Spain, United Kingdom). Germline mutations were identified using the BRACAnalysis CDx test. Tumor tissue samples were tested using a clinical trial assay and the FoundationFocus CDx test. Three nested cohorts were evaluated: patients with *BRCA* mutations, patient with homologous recombination deficiencies, and the intention-to-treat populations. Participants were enrolled between April 2014 and July 2016 and the majority had epithelial ovarian cancer (84%). A total of 196 (34.8%) had *BRCA1/2* mutations. The primary endpoint was progression-free survival, which was significantly longer in the rucaparib group in the *BRCA*-mutant cohort (16.6 months vs 5.4 months; HR 0.23, 95% CI, 0.16 to 0.34), the homologous recombination deficient carcinoma cohort (13.6 months vs 5.4 months; HR 0.32, 95% CI, 0.24 to 0.42), and in the intention-to-treat cohort (10.8 months vs 5.4 months; HR 0.36, 95% CI, 0.30 to 0.45). Grade 3 or higher adverse events were reported in 56% of patients in the rucaparib group compared with 15% in the placebo group. The most common of these were anemia or decreased hemoglobin concentration.

Kristeleit et al (2019) published integrated results from 2 multi-center, single-arm, open-label trials of rucaparib 600 mg twice daily (Study 10 and ARIEL2) in patients with high-grade serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer and a deleterious *BRCA1* or *BRCA2* mutation who had progressed after receiving 2 or more prior chemotherapies (including 2 or more platinum-based therapies).[70,] The majority of patients had epithelial ovarian cancer (87.3%). The efficacy population consisted of 79 patients who took at least 1 dose of rucaparib. Median treatment and follow-up durations were not reported. The primary end point was investigator-assessed, confirmed objective response rate, which was 64.6% (95% CI, 53.0% to 75.0%). Median progression-free survival was 332 days (95% CI, 255 to 391). Grade 3 or greater adverse events occurred in 63.2% of patients, which were most frequently decreased hemoglobin (24.2%), asthenia/fatigue (11.3%) and alanine/aspartate aminotransferase increased (10.8%).

#### *Prostate Cancer*

Abida et al (2020) published results from the phase 2, multi-center, single-arm clinical trial of rucaparib in patients with BRCA-mutated metastatic castration-resistant prostate cancer (mCRPC)

that supported its accelerated FDA approval in 2020 (TRITON2).[71,] This trial enrolled 115 patients who were treated with rucaparib 600 mg twice daily. For the efficacy population, median treatment duration was 8.1 months and median follow-up was 17.1 months. The primary endpoint of objective response rate, which was rated by blinded, independent radiology review, was 43.5% (95% CI, 31.0% to 56.7%). Median radiographic progression-free survival duration was 9.0 months (95% CI, 8.3 to 13.5). Anemia was the most frequent grade 3 or higher adverse event (25.2%). A key limitation of this trial is its lack of a control group. Continued approval for this indication for rucaparib may be contingent upon verification of progression-free survival in the ongoing confirmatory TRITON3 trial (NCT02975934), which is a randomized, controlled phase 3 trial evaluating rucaparib 600 mg twice daily versus physician's choice treatment in patients with mCRPC and a deleterious germline or somatic *BRCA1*, *BRCA2*, or *ATM* mutation.

### *Talazoparib*

#### *Breast Cancer*

Litton et al (2018) published results from a phase 3, randomized, open-label trial of 431 patients with advanced breast cancer and a germline *BRCA1/2* mutation that compared talazoparib 1 mg once daily to standard single-agent therapy (EMBRACA).[72,] *BRCA1/2* mutation was detected by BRACAnalysis testing. The primary endpoint was progression-free survival. Median duration of follow-up for that endpoint was 11.2 months. Progression-free survival was significantly longer in the talazoparib group (8.6 months vs 5.6 months; HR 0.54, 95% CI, 0.41 to 0.71). The rate of overall grade 3 or higher adverse events was similar for talazoparib compared with the standard care (25.5% vs 25.4%), but hematologic grade 3-4 adverse events (primarily anemia) were more frequent for talazoparib (55% vs 38%) compared with nonhematologic grade 3-4 adverse events (32% vs 38%). Based on the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30), compared to baseline, there was a significant improvement in the talazoparib group (+3.0; 95% CI, 1.2 to 4.8) and a significant decline in the standard therapy group (-5.4; 95% CI, -8.8 to -2.0). Although the trial was open-label, assessment of the primary outcome was based on blinded independent central review.

**Section Summary: Testing for *BRCA1* and *BRCA2* Variants to Guide Treatment in Individuals with HBOC Syndrome or Other High-Risk Cancers**

No studies were identified that have directly compared health outcomes in patients with HBOC syndrome or other high-risk cancers who did and did not use *BRCA1* and *BRCA2* variant testing to guide systemic treatment decisions. Evidence for the use of testing for *BRCA1* and *BRCA2* variants in individuals with HBOC Syndrome or other high-risk cancers to guide systematic therapy decisions consists of a chain of indirect studies demonstrating that genetic testing can identify individuals with a *BRCA1* or *BRCA2* variant associated with HBOC syndrome or other high-risk cancers who would not otherwise be identified, that treatments are available for these patients that would not otherwise be given to patients with HBOC syndrome or other high-risk cancers, and that these treatments improve health outcomes. The numerous placebo-controlled RCTs of PARP inhibitor drugs have consistently demonstrated that, in individuals identified by genetic testing as having a *BRCA1* or *BRCA2* variant associated with HBOC syndrome or other high-risk cancers, treatment with PARP inhibitor drugs significantly improve progression-free survival time. In individuals with ovarian cancer and a *BRCA1* or *BRCA2* mutation that were followed for a median of 17 to 36 months, treatment with a PARP inhibitor drug resulted in a 70% to 77% lower risk of disease progression or death. In individuals with a *BRCA1/2* mutation and either HER2-negative metastatic breast cancer or other

advanced breast cancer who were followed for 11-12 months, treatment with a PARP inhibitor drug resulted in a 40% to 46% lower risk of disease progression or death. In individuals with a *BRCA1/2* mutation and high-risk, early-stage breast cancer, treatment with olaparib resulted in a 9% improvement in 3-year invasive disease-free survival. In individuals with *BRCA*-mutated metastatic castration-resistant prostate cancer, the accelerated FDA approval of rucaparib was based on a phase 2, multi-center, single-arm clinical trial which demonstrated a benefit on a surrogate outcome of objective response rate. Continued approval for this indication for rucaparib may be contingent upon verification of the clinical outcome, progression-free survival in the ongoing randomized, standard care-controlled confirmatory TRITON3 trial (NCT02975934). Rates of overall Grade 3 or 4 adverse events ranged from 25.5% to 63.2% across PARP inhibitor drugs.

**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. 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 (e.g., 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 quality of life. The accuracy of variant testing has been shown to be high. Knowledge of *BRCA* variant status in individuals with other high-risk cancers can inform decisions regarding genetic counseling, chemotherapy, and enrollment in clinical trials. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with HBOC Syndrome or other high-risk cancers considering systemic therapy options who receive genetic testing for a *BRCA1* or *BRCA2* variant, the evidence includes several randomized controlled trials (RCT) and single-arm trials. Relevant outcomes are OS, disease-specific survival, test validity, and quality of life. The numerous placebo-controlled RCTs of PARP inhibitor drugs have consistently demonstrated that, in individuals with HER2-negative metastatic breast cancer, other advanced breast cancer, or ovarian cancer and a germline *BRCA* variant, treatment with PARP inhibitor drugs significantly improve progression-free survival time. In individuals with a *BRCA1/2* mutation and high-risk, early-stage breast cancer, treatment with olaparib resulted in a 9% improvement in 3-year invasive disease-free survival. In individuals with *BRCA*-mutated metastatic castration-resistant prostate cancer, a single-arm clinical trial of rucaparib demonstrated a benefit on a surrogate outcome of objective response rate and evaluation of its effects on progression-free survival is pending completion of the ongoing randomized, standard care-controlled confirmatory TRITON3 trial (NCT02975934). Rates of

overall Grade 3 or 4 adverse events ranged from 25.5% to 63.2% across PARP inhibitor drugs. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

## SUPPLEMENTAL INFORMATION

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

### Clinical Input From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

### 2010 Input

In response to requests, input was received for 3 physician specialty societies (5 reviewers) and 3 academic medical centers (5 reviewers) while this policy was under review in 2010. Those providing input were in general agreement with the Policy statements considering testing for genomic rearrangements of *BRCA1* and *BRCA2* as medically necessary and with adding fallopian tube and primary peritoneal cancer as *BRCA*-associated malignancies to assess when obtaining the family history.

### 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 NCCN (v.1.2022 ) guidelines on the genetic and familial high-risk assessment of breast and ovarian cancers include criteria for identifying individuals who should be referred for further risk assessment and separate criteria for genetic testing.[73,] 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 "only when an appropriate affected family member is unavailable for testing."

*BRCA1* and *BRCA2* somatic 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.3.2021 ) recommend tumor molecular testing prior to initiation of therapy for persistent/recurrent disease (OV-6) and describe in multiple algorithms that testing should include at least *BRCA1/2* and microsatellite instability or

DNA mismatch repair, and evaluation of homologous recombination deficiency can be considered (OV-6, OV-7, OV-B Principles of Pathology, OV-C Principles of Systemic Therapy).[74,]

**Pancreatic Adenocarcinoma**
Current NCCN guidelines for pancreatic adenocarcinoma (v.2.2021 ) refers to the NCCN guidelines on genetic/familial high-risk assessment of breast and ovarian detailed above, and state: "Germline testing is recommended for any patient with confirmed pancreatic cancer, using comprehensive gene panels for hereditary cancer syndromes."[75,]

**Prostate Cancer**
The current NCCN guidelines for prostate cancer are version 1.2022.[76,] The Principles of Genetics section (PROS-B) provides appropriate scenarios for germline genetic testing in individuals with a personal history of prostate cancer.

**American Society of Clinical Oncology et al**
The American Society of Clinical Oncology (ASCO) has released statements on genetic and genomic testing for cancer susceptibility since 1996. The ASCO (2003) recommended that cancer predisposition testing be offered when 3 factors are at play: (1) there is a personal or family history suggesting genetic cancer susceptibility, (2) the test can be adequately interpreted, and (3) results will influence medical management of the patient or family member at hereditary risk of cancer.[77,] A 2010 update of this statement recommended that "genetic tests with uncertain clinical utility, including genomic risk assessment, be administered in the context of clinical trials."[78,] A 2015 update affirmed that multigene panel testing "is sufficient for cancer risk assessment to evaluate genes of established clinical utility that are suggested by the patient's personal and/or family history."[79,]

In 2020, joint recommendations for the management of patients with breast cancer (BC) with germline mutations in breast cancer susceptibility genes were published by ASCO, the American Society for Radiation Oncology (ASTRO), and the Society of Surgical Oncology (SSO).[80,] Recommendations were developed by an expert panel based on a systematic review of the literature and a formal consensus process. Recommendations concerning *BRCA1/2* mutation carrier status included:

- "Patients with newly diagnosed BC and BRCA1/2 mutations may be considered for breast-conserving therapy (BCT), with local control of the index cancer similar to that of noncarriers...
- For women with mutations in BRCA1/2 or moderate-penetrance genes who are eligible for mastectomy, nipple-sparing mastectomy is a reasonable approach...
- Platinum agents are recommended versus taxanes to treat advanced BC in *BRCA* carriers. In the adjuvant/neoadjuvant setting, data do not support the routine addition of platinum to anthracycline- and taxane-based chemotherapy.
- Poly (ADP-ribose) polymerase (PARP) inhibitors (olaparib and talazoparib) are preferable to non platinum single-agent chemotherapy for treatment of advanced BC in BRCA1/2 carriers.
- Data are insufficient to recommend PARP inhibitor use in the early setting or in moderate-penetrance carriers."

In June 2021, the ASCO released a rapid recommendation guideline update amending the prior recommendation against PARP inhibitor use in the early disease setting on the basis of published

data from the OlympiA phase 3 RCT.[2,] The updated recommendation stated that "for patients with early-stage, HER2-negative breast cancer with high risk of recurrence and germline *BRCA1* or *BRCA2* pathogenic or likely pathogenic variants, one year of adjuvant olaparib should be offered after completion of (neo)adjuvant chemotherapy and local treatment, including radiation. For those who had surgery first, 1 year of adjuvant olaparib should be offered for patients with triple-negative breast cancer and tumor size >2 cm or any involved axillary nodes. For those with HR-positive disease, 1 year of adjuvant olaparib should be offered to those with at least four involved axillary lymph nodes. For patients who had neoadjuvant chemotherapy, 1 year of adjuvant olaparib should be offered to patients with triple-negative breast cancer and any residual cancer; for patients with HR-positive disease, 1 year of adjuvant olaparib should be offered to patients with residual disease and a clinical stage, pathologic stage, estrogen receptor, and tumor grade score (CPS+EG) ≥ 3."

**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.[81,] 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 (e.g., 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 2019) published a Practice Bulletin on hereditary breast and ovarian cancer syndrome.[82,] 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."

**National Institute for Health and Care Excellence**

In 2019, the National Institute for Health and Care Excellence published technical appraisal guidance on olaparib for maintenance treatment of *BRCA* mutation-positive advanced ovarian, fallopian tube or peritoneal cancer after response to first-line platinum-based chemotherapy (TA598).[83,] This Guidance recommended olaparib as an option for the maintenance treatment of BRCA mutation-positive, advanced (Federation of Gynecology and Obstetrics [FIGO] stages 3 and 4), high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer that has responded to first-line platinum-based chemotherapy in adults.

### U.S. Preventive Services Task Force

Current USPSTF recommendations (2019)[84,] 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.

### Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 5.

**Table 5. Summary of Key Trials**

| NCT No. | Trial Name | Planned Enrollment | Completion Date (status if beyond Completion Date) |
|---|---|---|---|
| ***Ongoing*** | | | |
| NCT02225015 | Cancer Prevention in Women With a BRCA Mutation | 300 | Jun 2019 (unknown) |
| NCT04090567 | Overcoming PARP Inhibitor Resistance in BRCA Germline Mutation Positive Advanced Breast Cancer | 60 | June 2021 (recruiting) |
| NCT02163694[a] | A Phase 3 Randomized, Placebo-Controlled Trial of Carboplatin and Paclitaxel With or Without the PARP Inhibitor Veliparib (ABT-888) in HER2 Negative Metastatic or Locally Advanced Unresectable BRCA-Associated Breast Cancer | 500 | Nov 2021 |
| NCT02975934[a] | TRITON3: A Multicenter, Randomized, Open Label Phase 3 Study of Rucaparib Versus Physician's Choice of Therapy for Patients With Metastatic Castration Resistant Prostate Cancer Associated With Homologous Recombination Deficiency | 400 | Apr 2022 (recruiting) |
| NCT04009148 | Cascade Testing in Families With Newly Diagnosed Hereditary Breast and Ovarian Cancer Syndrome | 300 | Mar 2023 |

| NCT No. | Trial Name | Planned Enrollment | Completion Date (status if beyond Completion Date) |
|---|---|---|---|
| NCT03246841 | Investigation of Tumor Spectrum, Penetrance and Clinical Utility of Germline Mutations in New Breast and Ovarian Cancer Susceptibility Genes (TUMOSPEC) | 500 | Dec 2023 |
| NCT02855944[a] | ARIEL4 (Assessment of Rucaparib In Ovarian CancEr TriaL): A Phase 3 Multicenter, Randomized Study of Rucaparib Versus Chemotherapy in Patients With Relapsed, BRCA Mutant, High Grade Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer | 345 | Jun 2024 |
| NCT02321228 | Early Salpingectomy (Tubectomy) With Delayed Oophorectomy in BRCA1/2 Gene Mutation Carriers (TUBA) | 510 | Jan 2035 |
| NCT03740165[a] | A Randomized Phase 3, Double-Blind Study of Chemotherapy With or Without Pembrolizumab Followed by Maintenance With Olaparib or Placebo for the First-Line Treatment of BRCA Non-mutated Advanced Epithelial Ovarian Cancer (EOC) (KEYLYNK-001/ENGOT-ov43) | 1284 | May 2025 |
| NCT02032823[a] | A Randomised, Double-blind, Parallel Group, Placebo-controlled Multi-centre Phase III Study to Assess the Efficacy and Safety of Olaparib Versus Placebo as Adjuvant Treatment in Patients With gBRCA1/2 Mutations and High Risk HER2 Negative Primary Breast Cancer Who Have Completed Definitive Local Treatment and Neoadjuvant or Adjuvant Chemotherapy (OlympiA) | 1836 | Nov 2028 |

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

## CODING

**The following codes for treatment and procedures applicable to this policy are included below for informational purposes. This may not be a comprehensive list of procedure codes applicable to this policy.**

**Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.**

**The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.**

| **CPT/HCPCS** | |
|---|---|
| 81162 | BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis (i.e., detection of large gene rearrangements) |
| 81163 | BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis |
| 81164 | BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (i.e., detection of large gene rearrangements) |
| 81165 | BRCA1 (BRCA1, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis |
| 81166 | BRCA1 (BRCA1, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (i.e., detection of large gene rearrangements) |
| 81167 | BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (i.e., detection of large gene rearrangements) |
| 81212 | BRCA 1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; 185delAG, 5385insC, 6174delT variants |
| 81215 | BRCA1 (BRCA1, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; known familial variant |
| 81216 | BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis |
| 81217 | BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; known familial variant |
| 81432 | panels including BRCA |
| 81433 | panels including BRCA |
| 0102U | panels including BRCA |
| 0103U | panels including BRCA |
| 0129U | Hereditary breast cancer–related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), genomic sequence analysis and deletion/duplication analysis panel (ATM, BRCA1, BRCA2, CDH1, CHEK2, PALB2, PTEN, and TP53) |

| CPT/HCPCS | |
|---|---|
| 0131U | Hereditary breast cancer–related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), targeted mRNA sequence analysis panel (13 genes) |
| 0132U | Hereditary ovarian cancer–related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), targeted mRNA sequence analysis panel (17 genes) |
| 0134U | Hereditary pan cancer (e.g., hereditary breast and ovarian cancer, hereditary endometrial cancer, hereditary colorectal cancer), targeted mRNA sequence analysis panel (18 genes) |
| 0138U | BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) mRNA sequence analysis (List separately in addition to code for primary procedure) |
| 0172U | Oncology (solid tumor as indicated by the label), somatic mutation analysis of BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) and analysis of homologous recombination deficiency pathways, DNA, formalin-fixed paraffin-embedded tissue, algorithm quantifying tumor genomic instability score |

| ICD-10 DIAGNOSES | |
|---|---|
| C25.0 | Malignant Neoplasm Of Head Of Pancreas |
| C25.1 | Malignant Neoplasm Of Body Of Pancreas |
| C25.2 | Malignant Neoplasm Of Tail Of Pancreas |
| C25.3 | Malignant Neoplasm Of Pancreatic Duct |
| C25.4 | Malignant Neoplasm Of Endocrine Pancreas |
| C25.7 | Malignant Neoplasm Of Other Parts Of Pancreas |
| C25.8 | Malignant Neoplasm Of Overlapping Sites Of Pancreas |
| C50.011 | Malignant neoplasm of nipple and areola, right female breast |
| C50.012 | Malignant neoplasm of nipple and areola, left female breast |
| C50.021 | Malignant neoplasm of nipple and areola, right male breast |
| C50.022 | Malignant neoplasm of nipple and areola, left male breast |
| C50.111 | Malignant neoplasm of central portion of right female breast |
| C50.112 | Malignant neoplasm of central portion of left female breast |
| C50.121 | Malignant neoplasm of central portion of right male breast |
| C50.122 | Malignant neoplasm of central portion of left male breast |
| C50.211 | Malignant neoplasm of upper-inner quadrant of right female breast |
| C50.212 | Malignant neoplasm of upper-inner quadrant of left female breast |
| C50.221 | Malignant neoplasm of upper-inner quadrant of right male breast |
| C50.222 | Malignant neoplasm of upper-inner quadrant of left male breast |
| C50.311 | Malignant neoplasm of lower-inner quadrant of right female breast |
| C50.312 | Malignant neoplasm of lower-inner quadrant of left female breast |
| C50.321 | Malignant neoplasm of lower-inner quadrant of right male breast |
| C50.322 | Malignant neoplasm of lower-inner quadrant of left male breast |
| C50.411 | Malignant neoplasm of upper-outer quadrant of right female breast |
| C50.412 | Malignant neoplasm of upper-outer quadrant of left female breast |
| C50.421 | Malignant neoplasm of upper-outer quadrant of right male breast |

| ICD-10 DIAGNOSES | |
|---|---|
| C50.422 | Malignant neoplasm of upper-outer quadrant of left male breast |
| C50.511 | Malignant neoplasm of lower-outer quadrant of right female breast |
| C50.512 | Malignant neoplasm of lower-outer quadrant of left female breast |
| C50.521 | Malignant neoplasm of lower-outer quadrant of right male breast |
| C50.522 | Malignant neoplasm of lower-outer quadrant of left male breast |
| C50.611 | Malignant neoplasm of axillary tail of right female breast |
| C50.612 | Malignant neoplasm of axillary tail of left female breast |
| C50.621 | Malignant neoplasm of axillary tail of right male breast |
| C50.622 | Malignant neoplasm of axillary tail of left male breast |
| C50.811 | Malignant neoplasm of overlapping sites of right female breast |
| C50.812 | Malignant neoplasm of overlapping sites of left female breast |
| C50.821 | Malignant neoplasm of overlapping sites of right male breast |
| C50.822 | Malignant neoplasm of overlapping sites of left male breast |
| C50.911 | Malignant neoplasm of unspecified site of right female breast |
| C50.912 | Malignant neoplasm of unspecified site of left female breast |
| C50.921 | Malignant neoplasm of unspecified site of right male breast |
| C50.922 | Malignant neoplasm of unspecified site of left male breast |
| C56.1 | Malignant neoplasm of right ovary |
| C56.2 | Malignant neoplasm of left ovary |
| C57.00 | Malignant Neoplasm Of Unspecified Fallopian Tube |
| C57.01 | Malignant Neoplasm Of Right Fallopian Tube |
| C57.02 | Malignant Neoplasm Of Left Fallopian Tube |
| C61 | Malignant Neoplasm Of Prostate |
| C79.61 | Secondary malignant neoplasm of right ovary |
| C79.62 | Secondary malignant neoplasm of left ovary |
| C79.81 | Secondary malignant neoplasm of breast |
| D05.01 | Lobular carcinoma in situ of right breast |
| D05.02 | Lobular carcinoma in situ of left breast |
| D05.11 | Intraductal carcinoma in situ of right breast |
| D05.12 | Intraductal carcinoma in situ of left breast |
| D05.81 | Other specified type of carcinoma in situ of right breast |
| D05.82 | Other specified type of carcinoma in situ of left breast |
| D05.91 | Unspecified type of carcinoma in situ of right breast |
| D05.92 | Unspecified type of carcinoma in situ of left breast |
| Z13.71 | Encounter For Nonprocreative Screening For Genetic Disease Carrier Status |
| Z80.3 | Family history of malignant neoplasm of breast |
| Z80.41 | Family history of malignant neoplasm of ovary |
| Z85.3 | Personal history of malignant neoplasm of breast |
| Z85.41 | Personal history of malignant neoplasm of ovary |

| REVISIONS | |
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| 01-01-2012 | In the Policy section:<br>Formatting changes to the policy language. |
| | In the Coding section:<br>Added new codes: 81211, 81212, 81213, 81214, 81215, 81216, 81217 |

| **REVISIONS** | |
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| 10-04-2012 | Updated Description section. |
| | In the Policy section:<br>▪ In Item II, removed "Further genetic testing by rearrangement analysis (BART—BRAC Analysis Rearrangement Test) is experimental / investigational (rearrangement analysis includes sequencing the coding regions and intron/extron splice sites as well as tests to detect large dilations and rearrangements that can be missed with sequence analysis only)" and inserted "Testing for genomic rearrangements of the *BRCA1* and *BRCA2* genes (BART—BRAC Analysis Rearrangement Test)may be considered medically necessary in patients who meet criteria for *BRCA* testing, whose testing for point mutations is negative and either (1) there are 3 or more family members (one lineage) affected with breast or ovarian or fallopian tube or primary peritoneal cancer or (2) who have a risk of a *BRCA* mutation of at least 10%."<br>▪ In the Policy Guidelines, added "#7 Comprehensive mutation analysis currently includes sequencing the coding regions and intron/exon splice sites, as well as tests to detect common large deletions and rearrangements (BART—BRAC Analysis Rearrangement Test) that can be missed with sequence analysis alone. However, current routine laboratory testing for genomic rearrangement is more limited than the criteria noted in the policy statement; automatic testing is specified for those with a risk of *BRCA* mutation of at least 30%. In addition, prior to August 2006, testing for large deletions and rearrangements was not performed, thus some patients with familial breast cancer who had negative *BRCA* testing prior to this time may consider repeat testing for the rearrangements (see Policy statement for criteria). These rates are calculated using the Myriad II risk model (Available online at: www.myriadtests.com)." |
| | Updated Reference section. |
| | Updated Reference section. |
| 10-26-2012 | In the Policy section:<br>▪ In the Policy Guidelines section, #7, corrected website, "www.myriadtests.com" to "www.myriadpro.com/brca-risk-calculator". |
| 01-15-2013 | In the Coding section:<br>▪ Added CPT code: 81406<br>▪ Removed CPT codes: 83890, 83891, 83892, 83893, 83894, 83896, 83912, 83913 (Effective 12-31-2012) |
| 02-26-2013 | Updated Description section. |
| | In the Policy section:<br>▪ In Item I, B, added "10. Diagnosed at any age with breast cancer or pancreatic cancer, who are not from families with high risk of *BRCA1* or *BRCA2* mutation, but are affected with one of the following:<br>o Early onset breast cancer<br>o Two breast primary cancers with the first cancer diagnosis occurring prior to age 50 years;<br>o Triple negative breast cancer (neither express estrogen receptor and progesterone receptor, nor overexposure HER2) diagnosed at younger than age 60.<br>o Two or more close blood relatives with pancreatic cancer at any age.<br>▪ In Item II, removed "and either (1) there are 3 or more family members (one lineage) affected with breast or ovarian or fallopian tube or primary peritoneal cancer or (2) who have a risk of a BRCA mutation of at least 10%." to read "Testing for genomic rearrangements of the *BRCA1* and *BRCA2* genes (BART-BRAC Analysis |

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| | Rearrangement Test) may be considered medically necessary in patients who meet criteria for BRCA testing, whose testing for point mutations is negative." |
| | Updated Rationale section. |
| | In Coding section:<br>▪ Removed HCPCS codes: S3818, S3819, S3820, S3822, S3823 |
| | Updated Reference section. |
| 07-22-2013 | In Coding section:<br>▪ Maintenance completed on coding section, correcting "V16.4" to read "V16.41". |
| 12-11-2013 | In Coding section:<br>▪ Added ICD-10 Diagnosis *(Effective October 1, 2014)* |
| 08-28-2014 | Description section updated. |
| | In Policy section:<br>▪ The following medical policy language was removed from the policy and replaced with policy language that mirrors the NCCN criteria (See policy section). This update liberalized the policy and did not restrict any portion of the policy.<br>"I. Genetic testing may be considered medically necessary under any one of the following circumstances:<br>A. Member of family with a known *BRCA1*/*BRCA2* mutation<br>B. Personal history of breast cancer plus one or more of the following:<br>1. Diagnosed at 45 years of age or younger<br>2. Diagnosed at 50 years of age or younger with:<br>a. one or more close blood relatives with breast cancer at 50 years of age or younger; and/or<br>b. one or more close blood relatives with epithelial ovarian / fallopian tube / primary peritoneal cancer<br>3. Two breast primaries when first breast cancer diagnosis occurred prior to age 50<br>4. Diagnosed at any age with two or more close blood relatives with breast and/or epithelial ovarian / fallopian tube / primary peritoneal cancer at any age<br>5. Close male blood relative with breast cancer<br>6. For an individual of ethnicity associated with deleterious mutations (e.g., founder populations of Ashkenazi Jewish, Icelandic, Swedish, Hungarian or other) no additional family history may be required<br>7. Diagnosed age < 60 years with a triple negative breast cancer [estrogen receptors (ER-), progesterone receptors (PR-), and HER2 (HER2-)]<br>8. Diagnosed age <50 years with a limited family history (see policy guidelines)<br>9. Personal history of breast and / or ovarian cancer at any age with ≥ 2 close blood relatives with pancreatic cancer at any age<br>10. Diagnosed at any age with breast cancer or pancreatic cancer, who are not from families with a high risk of *BRCA1* or *BRCA2* mutation, but are affected with one of the following:<br>▪ Early onset breast cancer<br>▪ Two breast primary cancers with the first cancer diagnosis occurring prior to age 50 years;<br>▪ Triple negative breast cancer (neither express estrogen receptor and progesterone receptor, nor overexposure HER2) diagnosed at younger than age 60.<br>▪ Two or more close blood relatives with pancreatic cancer at any age.<br>C. Personal history of epithelial ovarian / fallopian tube / primary peritoneal cancer |

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| | D. Personal history of pancreatic cancer at any age with ≥ 2 close blood relatives with breast and / or pancreatic cancer at any age breast cancer<br>E. Personal history of male breast cancer<br>F. Family history only –<br>1. Close family member meeting any of the above criteria<br>2. Third-degree blood relative with breast cancer and /or ovarian / fallopian tube/ primary peritoneal cancer with ≥ 2 close blood relatives with breast cancer (at least one with breast cancer ≤50 years) and / or ovarian cancer.<br>II. Testing for genomic rearrangements of the *BRCA1* and *BRCA2* genes (BART—BRAC Analysis Rearrangement Test) may be considered medically necessary in patients who meet criteria for *BRCA* testing, whose testing for point mutations is negative.<br>III. Genetic testing when policy requirements are not met is experimental / investigational.<br><u>Policy Guidelines</u><br>1. Close family member is defined as a first, second, or third degree relative, which includes: Parent, Full Sibling, Half Sibling, Child, Grandparent, Great-Grandparent, Grandchild, Aunt, Great Aunt, Uncle, Great Uncle, Nephew, Niece, and First Cousin.<br>2. For purposes of this policy, breast cancer includes both invasive and ductal carcinoma in situ (DCIS).<br>3. For individuals with family history only, an affected family member should be tested first whenever possible to identify specific site mutations.<br>4. The maternal and paternal sides should be considered independently.<br>5. Other malignancies reported in some HBOC families include prostate and melanoma.<br>6. Individuals with limited family history, such as fewer than 2 first- or second-degree female relatives surviving beyond 45 years in either lineage, may have an underestimated probability of a familial mutation.<br>7. Comprehensive mutation analysis currently includes sequencing the coding regions and intron/exon splice sites, as well as tests to detect common large deletions and rearrangements (BART—BRAC Analysis Rearrangement Test) that can be missed with sequence analysis alone. However, current routine laboratory testing for genomic rearrangement is more limited than the criteria noted in the policy statement; automatic testing is specified for those with a risk of *BRCA* mutation of at least 30%. In addition, prior to August 2006, testing for large deletions and rearrangements was not performed, thus some patients with familial breast cancer who had negative *BRCA* testing prior to this time may consider repeat testing for the rearrangements (see Policy statement for criteria). These rates are calculated using the Myriad II risk model (Available online at: www.myriadpro.com/brca-risk-calculator ).<br>Testing eligible individuals who belong to ethnic populations in which there are well characterized founder mutations should begin with tests specifically for these mutations (multisite testing)." |
| | Rationale section updated |
| | In Coding section:<br>▪ Updated nomenclature for CPT code: 81215<br>▪ Updated nomenclature for ICD-9 codes: 174.8, 174.9, 175.9, 183.0, 198.6, 198.81, 233.0, V10.43, V16.41, V16.8<br>▪ Added ICD-9 codes: 233.30, 233.39<br>▪ Removed ICD-9 code: 233.3<br>▪ Removed ICD-10 codes: C50.129, C50.229, C50.529, C50.819 |
| | Removed Revision dates: 08-29-2006 effective 11-01-2-06, 10-31-2006 effective 01-01-2007, 11-23-2009, 10-08-2010, 09-02-2011. |

| **REVISIONS** | |
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| | References updated |
| 04-02-2015 | Updated Description section |
| | In Policy section:<br>▪ In Item A, added "or With History of Cancer," to read, "Patients with Cancer or With History of Cancer"<br>▪ In Item B, added "or Without History of Cancer," to read, "Patients Without Cancer or Without History of Cancer"<br>▪ In Item B, added "[d]For example, fewer than 2 1st- or 2nd-degree female relatives having lived beyond age 45 in either lineage. In families with a large number of unaffected female relates, the likelihood of mutation detection may be very low.", and removed, "Unknown or limited family history / structure is defined as fewer than 2 first- or second degree female relatives having lived beyond age 45 in either lineage"<br>▪ Removed Item C, "Testing for genomic rearrangements of the *BRCA1* and *BRCA2* genes may be considered medically necessary in patients who meet criteria for *BRCA* testing, whose testing for point mutations is negative."<br>▪ Removed Item E, "Testing for *CHEK2* abnormality (mutations, deletions, etc.) is considered experimental / investigational in affected and unaffected patients with breast cancer, irrespective of family history."<br>▪ Added Item D, "Genetic testing in minors for *BRCA1* and *BRCA2* mutations is considered experimental / investigational."<br>▪ Removed "NOTE: Clinical judgment should be used to determine if the patient has reasonable likelihood of a mutation, considering the unaffected patient's current age and the age of female unaffected relatives who link the patient with the affected relatives.", and "NOTE: Testing of unaffected individuals should only be considered when an appropriate affected family member is unavailable for testing."<br>▪ In Policy Guidelines, removed, "4. Comprehensive Mutation Analysis. Comprehensive BRCA mutation analysis should be performed in patients with breast cancer, ovarian cancer, cancer of the fallopian tube, or primary peritoneal cancer who are: ● Eligible for testing, and ● From families without a known deleterious BRCA1 or BRCA2 mutation, and ● Not from ethnic groups with known founder mutations."<br>▪ In Policy Guidelines, added "9. A Recommended Testing Strategy. Patients who meet criteria for genetic testing as outlined in the Policy Statements above should be tested for mutations in BRCA1 and BRCA2.<br>A. In patients with a known familial BRCA mutation, targeted testing for the specific mutation is recommended.<br>B. In patients with unknown familial BRCA mutation:<br>1) Non-Ashkenazi Jewish descent<br>a) To identify clinically significant mutations, NCCN advises testing a relative who has breast or ovarian cancer, especially with early-onset disease, bilateral disease, multiple primaries, or ovarian cancer, because that individual has the highest likelihood for a positive test result.<br>b) 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*/*BRCA2* mutations (e.g., prostate cancer, pancreatic cancer, melanoma).<br>c) If no familial mutation can be identified, two possible testing strategies are:<br>i. Full sequencing followed by testing for common large genomic rearrangements (deletions/duplications) only if sequencing detects no mutation (negative result).<br>i. More than 90% of BRCA mutations will be detected by full sequencing.(4)<br>ii. Alternatively, simultaneous full sequencing and testing for common large genomic rearrangements (also known as comprehensive BRCA testing; see |

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| | Comprehensive Mutation Analysis, below) may be performed as is recommended by NCCN.<br>i. Comprehensive testing can detect 92.5% of *BRCA1*/*BRCA2* mutations.(4)<br>d) If comprehensive BRCA testing is negative, testing for uncommon large genomic rearrangements (e.g., BART™) may be done.<br>i. Testing for uncommon large rearrangements should not be done unless both sequencing and testing for common large rearrangements have been performed and are negative.<br>○ Among patients with negative comprehensive testing, BART™ identified a deleterious mutation (positive result) in less than 1%.(4)<br>C. Ashkenazi Jewish descent<br>○ In patients of known Ashkenazi Jewish descent, NCCN recommends testing for the 3 known founder mutations (185delAG and 5182insC in *BRCA1*; 6174delT in *BRCA2*) first.<br>○ If testing is negative for founder mutations, comprehensive genetic testing may be considered (see Comprehensive Mutation Analysis, above)." |
| | In Coding section:<br>▪ Removed CPT code 81406. |
| | Updated Rationale section. |
| | In Coding section:<br>▪ Removed CPT code 81406. |
| | Updated References section. |
| 01-01-2016 | Updated Description section. |
| | In Policy section:<br>▪ In Policy Guidelines, added paragraph on Genetic Counseling. |
| | Updated Rationale section. |
| | In Coding section:<br>▪ Added CPT code: 81162 |
| | Updated References Section. |
| | Added Appendix section. |
| 01-04-2017 | Updated Description section. |
| | Updated Rationale section. |
| | Updated References section. |
| 03-17-2018 | Updated Description section. |
| | In Policy section:<br>▪ Changed "mutation" to "variant" throughout policy language.<br>▪ In Item A, added "Personal" to read, "Patients With Cancer or With Personal History of Cancer."<br>▪ In Item A 2 c, added "pancreatic cancer or prostate cancer" to read, "One or more 1st-, 2nd, or 3rd-degree relative[a] with breast cancer (at any age), pancreatic cancer or prostate cancer[b], or".<br>▪ In Item A 6, added "Personal history of" and "at any age AND ≥2 or more 1st-, 2nd-, or 3rd-degree relatives[a] with breast, pancreatic, or prostate cancer[b] at any age" to read, "Personal history of pancreatic or prostate cancer[b] at any age AND ≥2 or more 1st-, 2nd-, or 3rd-degree relatives[a] with breast, pancreatic, or prostate cancer[b] at any age."<br>▪ Removed previous Item C, "Unless the criteria above are met, genetic testing either for those affected by breast, ovarian, fallopian tube, or primary peritoneal cancer or for unaffected individuals, including those with a family history of pancreatic cancer, is considered experimental / investigational." |

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| | ▪ Added new Item C, "Genetic testing for *BRCA1* and *BRCA2* variants when criteria above are not met is considered experimental / investigational."<br>▪ Updated Policy Guidelines. |
| | Updated Rationale section. |
| | In Coding section:<br>▪ Removed ICD-9 codes. |
| | Updated Revisions section. |
| 01-01-2019 | In Coding section:<br>▪ Added CPT codes: 81163, 81164, 81165, 81166, 81167.<br>▪ Deleted CPT codes: 81211, 81213, 81214.<br>▪ Revised nomenclature to CPT codes: 81162, 81212, 81215, 81216, 81217.<br>▪ Added ICD-10 code: Z80.41. |
| 04-12-2019 | Policy posted to the bcbsks.com website on 03-13-2019; effective 04-12-2019. |
| | Updated Description section. |
| | In Policy section:<br>▪ Removed previous policy language: "A. Patients With Cancer or With Personal History of Cancer<br>Genetic testing for *BRCA1* and *BRCA2* variants in cancer-affected individuals may be considered medically necessary under any of the following circumstances:<br>1. Individual from a family with a known *BRCA1/BRCA2* mutation<br>2. Personal history of breast cancer and ≥1 of the following:<br>a. Diagnosed at age ≤45 years<br>b. Two primary breast cancers when 1st breast cancer diagnosis occurred at age ≤50 years<br>c. Diagnosed at age ≤50 years AND:<br>i. One or more 1st-, 2nd-, or 3rd-degree relative[a] with breast cancer (at any age), pancreatic cancer or prostate cancer[b], or<br>ii. Unknown or limited family history[c]<br>d. Diagnosed at age ≤60 years with a triple negative (estrogen receptor–negative, progesterone receptor–negative, human epidermal growth factor receptor 2–negative) breast cancer<br>e. Diagnosed at any age AND ≥1 1st-, 2nd-, or 3rd-degree relative[a] with breast cancer diagnosed at ≤50 years<br>f. Diagnosed at any age AND ≥2 1st-, 2nd-, or 3rd-degree relative[a] with breast cancer at any age<br>g. Diagnosed at any age AND ≥1 1st-, 2nd-, or 3rd-degree relative[a] with epithelial ovarian, fallopian tube, or primary peritoneal cancer<br>h. Diagnosed at any age AND ≥2 1st-, 2nd-, or 3rd-degree relative[a] with pancreatic cancer or prostate cancer[b] at any age<br>i. 1st-, 2nd-, or 3rd-degree male relative with breast cancer<br>j. Ethnicity associated with deleterious founder mutations, e.g., Ashkenazi Jewish descent[d]<br>3. Personal history of epithelial ovarian, fallopian tube, or primary peritoneal cancer<br>4. Personal history of male breast cancer<br>5. Personal history of pancreatic cancer or prostate cancer[c] at any age AND ≥1 1st-, 2nd-, or 3rd-degree relative[a] with any of the following:<br>a. Breast cancer ≤50<br>b. Ovarian, fallopian tube, or primary peritoneal cancer at any age<br>6. Personal history of pancreatic or prostate cancer[b] at any age AND ≥2 or more 1st-, 2nd-, or 3rd-degree relatives[a] with breast, pancreatic, or prostate cancer[b] at any age |

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| | 7. For pancreatic cancer, if Ashkenazi Jewish ancestry, only 1 additional affected relative is needed.<br>B. Patients Without Cancer or Without History of Cancer (see Policy Guidelines: Testing Unaffected Individuals)<br>Genetic testing for *BRCA1* and *BRCA2* variants of cancer-unaffected individuals may be considered medically necessary under any of the following circumstances:<br>1. Individual from a family with a known *BRCA1* or *BRCA2* variant<br>2. 1st- or 2nd-degree blood relative meeting any criterion listed above for Patients with Cancer<br>3. 3rd-degree blood relative with breast cancer and/or ovarian, fallopian tube, or primary peritoneal cancer AND ≥2 1st-, 2nd-, or 3rd-degree relatives[a] with breast cancer (≥1 at age ≤50 years) and/or ovarian, fallopian tube, or primary peritoneal cancer<br>[a] For familial assessment, 1st-, 2nd-, and 3rd-degree relatives are blood relatives on the same side of the family (maternal or paternal).<br>• 1st-degree relatives are parents, siblings, and children<br>• 2nd-degree relatives are grandparents, aunts, uncles, nieces, nephews, grandchildren, and half-siblings<br>• 3rd-degree relatives are great-grandparents, great-aunts, great-uncles, great-grandchildren, and first cousins.<br>[b] For familial assessment, prostate cancer is defined as Gleason score ≥7.<br>[c] For example, fewer than 2 1st- or 2nd-degree female relatives having lived beyond age 45 in either lineage. In families with a large number of unaffected female relatives, the likelihood of variant detection may be very low.<br>[d] Testing for Ashkenazi Jewish or other founder mutation(s) should be performed first (see Policy Guidelines: High-Risk Ethnic Groups).<br>C. Genetic testing for *BRCA1* and *BRCA2* variants when criteria above are not met is considered experimental / investigational.<br>D. Genetic testing in minors for *BRCA1* and *BRCA2* variants is considered experimental / investigational."<br>▪ Added new policy language: "A. Patients With Cancer or With a Personal History of Cancer<br>Genetic testing for *BRCA1* and *BRCA2* variants in cancer-affected individuals may be considered medically necessary under any of the following circumstances:<br>1. Individual from a family with a known *BRCA1* or *BRCA2* variant<br>2. Personal history of breast cancer and one or more of the following:<br>a. Diagnosed at age ≤45 years<br>b. Diagnosed 46 to 50 years with:<br>i. One or more 1st-, 2nd-, or 3rd-degree blood relative with breast cancer at any age<br>ii. An unknown or limited family history[c]<br>iii. An additional breast cancer primary at any age<br>iv. One or more 1st-, 2nd-, or 3rd-degree blood relative with high grade (Gleason score ≥7) prostate cancer<br>c. Diagnosed ≤60 years with:<br>i. Triple negative breast cancer<br>d. Diagnosed at any age with:<br>i. One or more 1st-, 2nd-, or 3rd-degree blood relative with<br>v. Breast cancer diagnosed at ≤50 years; or<br>vi. Ovarian, fallopian tube, or primary peritoneal cancer; or<br>vii. Male breast cancer; or<br>viii. Metastatic prostate cancer; or |

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| | ix. Pancreatic cancer<br>ii. ≥2 additional diagnoses of breast cancer at any age in patient and/or 1st-, 2nd-, or 3rd-degree blood relative<br>e. Ashkenazi Jewish ancestry<br>3. Personal history of ovarian, fallopian tube, or primary peritoneal cancer<br>4. Personal history of male breast cancer<br>5. Personal history of pancreatic cancer<br>6. Personal history of metastatic prostate cancer<br>7. Personal history of high-grade prostate cancer (Gleason score ≥7) at any age with:<br>a. One or more 1st-, 2nd-, or 3rd-degree blood relative with ovarian, fallopian tube, or primary peritoneal cancer, pancreatic cancer, or metastatic prostate cancer at any age or breast cancer ≤50 years; or<br>i. Two or more 1st-, 2nd-, or 3rd-degree blood relatives with breast or prostate cancer (any grade) at any age; or<br>b. Ashkenazi Jewish ancestry<br>8. BRCA1 or BRCA2 pathogenic or likely pathogenic variant detected by tumor profiling on any tumor type in the absence of germline pathogenic or likely pathogenic variant analysis<br>9. Regardless of family history, some individuals with an BRCA-related cancer may benefit from genetic testing to determine eligibility for targeted treatment<br>10. An individual who does not meet the other criteria but with one or more 1st- or 2nd-degree blood relatives meeting any of the above criteria.<br>B. Patients Without Cancer or Without History of Cancer (see Policy Guidelines: Testing Unaffected Individuals)<br>1. Genetic testing for *BRCA1* and *BRCA2* variants of cancer-unaffected individuals may be considered medically necessary under any of the following circumstances:<br>i. Individual from a family with a known *BRCA1* or *BRCA2* variant<br>ii. 1st- or 2nd-degree blood relative meeting any criterion listed above for Patients With Cancer<br>iii. 3rd-degree blood relative with breast cancer and/or ovarian, fallopian tube, or primary peritoneal cancer AND two or more 1st-, 2nd-, or 3rd-degree relatives[a] with breast cancer (≥1 at age ≤50 years) and/or ovarian, fallopian tube, or primary peritoneal cancer<br>[a] For familial assessment, 1st-, 2nd-, and 3rd-degree relatives are blood relatives on the same side of the family (maternal or paternal).<br>• 1st-degree relatives are parents, siblings, and children<br>• 2nd-degree relatives are grandparents, aunts, uncles, nieces, nephews, grandchildren, and half-siblings<br>• 3rd-degree relatives are great-grandparents, great-aunts, great-uncles, great-grandchildren, and first cousins.<br>2. Genetic testing for *BRCA1* and *BRCA2* variants in cancer-affected individuals or of cancer-unaffected individuals with a family history of cancer when criteria above are not met is considered experimental / investigational.<br>3. Genetic testing in minors for *BRCA1* and *BRCA2* variants is considered experimental / investigational. |
| | Updated Rationale section. |
| | Updated References section. |
| | Removed Appendix section. |
| 04-16-2021 | Updated Description section |
| | In Policy section: |

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| | ITEM A<br>• Added underlined section to and removed the strikethrough text from Item A.2.b.:<br>b. Diagnosed 46 to 50 years with:<br>I. One or more 1st-, 2nd-, or 3rd-degree blood relative with breast cancer, ovarian, pancreatic, or prostate cancer at any age; or<br>II. An unknown or limited family history; or<br>III. An additional breast cancer primary at any age<br>~~IV. One or more 1st-, 2nd-, or 3rd-degree blood relative with high grade (Gleason score ≥7) prostate cancer~~<br>• Added underlined text to Item A.2.d.i:<br>x. Metastatic or intraductal/cribriform prostate cancer, or high-risk group or very-high-risk group (see Policy Guidelines) prostate cancer; or<br>• Added "at any age" to Item A.3. and A.5.<br>• Added underlined text to and removed the strikethrough text from Item A.6 and A.7:<br>6. 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<br>7. Personal history of ~~high-grade~~ prostate cancer ~~(Gleason score ≥7)~~ at any age with:<br>a. One or more 1st-, 2nd-, or 3rd-degree blood relative with ovarian, fallopian tube, or primary peritoneal cancer, pancreatic cancer, or metastatic or intraductal/cribriform prostate cancer at any age or breast cancer ≤50 years; or<br>b. Two or more 1st-, 2nd-, or 3rd-degree blood relatives with breast or prostate cancer (any grade) at any age; or<br>c. Ashkenazi Jewish ancestry<br>• Added Item A.8. and Item A.9.<br>ITEM B<br>• Added underlined section to and removed the strikethrough text from Item B.1.b, c, & d:<br>b. An unaffected individual with 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.<br>c. An unaffected individual who otherwise does not meet the criteria above but has a probability >5% of a *BRCA1/2* pathogenic variant based on prior probability models (*e.g.*, Tyrer-Cuzick, BRCAPro, Pennll)<br>d. ~~3rd-degree blood relative with breast cancer and/or ovarian, fallopian tube, or primary peritoneal cancer AND two or more 1st-, 2nd-, or 3rd-degree relatives[a] with breast cancer (≥1 at age ≤50 years) and/or ovarian, fallopian tube, or primary peritoneal cancer~~<br>POLICY GUIDELINES<br>• Added underlined section to and removed the strikethrough text from policy guidelines 1, 2, and 3:<br>N. Current U.S. Preventive Services Task Force (USPSTF) guidelines recommend screening women with a personal or ~~any~~ family history of breast, ovarian, tubal, or peritoneal cancer or who have an ancestry associated with *BRCA1/2* gene mutation. Women with positive screening result on the risk assessment tool should receive genetic counseling and, if indicated after counseling, ~~*BRCA* testing (grade~~ genetic testing (B Recommendation). |

| **REVISIONS** | |
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| | O. Recommended screening tools designed to identify a family history that may be associated with an increased risk for potentially harmful variants ~~mutations~~ in *BRCA1* or *BRCA2* are:<br>o Ontario Family History Assessment Tool (FHAT)<br>o Manchester Scoring System<br>o Referral Screening Tool (RST)<br>o Pedigree Assessment Tool (PAT)<br>o Family History Screen (FHS-7)<br>o International Breast Cancer Intervention Study instrument (Tyrer-Cuziak)<br>o Brief versions of the BRCAPRO<br>P. Prostate Cancer Risk Groups: Risk groups for prostate cancer in this policy include high-risk groups and very-high-risk groups.<br>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<br>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<br>• Added underlined section to and removed the strikethrough text from policy guidelines 4:<br>In patients with unknown familial *BRCA* variant:<br>1) Non-Ashkenazi Jewish descent<br>a) To identify clinically significant variants, National Comprehensive Cancer Network (NCCN) advises testing a relative who has ~~breast or ovarian cancer, especially with~~ early-onset disease, bilateral disease, multiple primaries, ~~or ovarian cancer~~, because that individual has the highest likelihood of obtaining a positive test result. Unless the affected individual is a member of an ethnic group for which particular founder pathogenic or likely pathogenic variants are known, comprehensive genetic testing (*i.e.,* full sequencing of the genes and detection of large gene rearrangements) should be performed<br>b) If no living family member with breast or ovarian cancer exists, NCCN suggests testing first- or second-degree family members affected with cancer thought to be related to deleterious *BRCA1* or *BRCA2* variants (e.g., prostate cancer, pancreatic cancer, melanoma).<br>c) If no familial variant can be identified, two possible testing strategies are:<br>i. Full sequencing followed by testing for ~~*common*~~ large genomic rearrangements (deletions/duplications) only if sequencing detects no variant (negative result).<br>ii. More than 90% of *BRCA* variants will be detected by full sequencing.<br>ii. Alternatively, simultaneous full sequencing and testing for ~~*common*~~ large genomic rearrangements (also known as comprehensive *BRCA* testing; see Comprehensive Variant Analysis, below) may be performed as is recommended by NCCN.<br>ii. Comprehensive testing can detect 92.5% of *BRCA1* or *BRCA2* variants.<br>d) If comprehensive *BRCA* testing is negative, testing for *uncommon* large genomic rearrangements (e.g., BART) may be done. |

| **REVISIONS** | |
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| | i. Testing for *uncommon* large rearrangements should not be done unless both sequencing and testing for *common* large rearrangements have been performed and are negative.<br>o Among patients with negative comprehensive testing, BART identified a deleterious variant (positive result) in less than 1%.<br>2) Ashkenazi Jewish descent<br>a) In patients of known Ashkenazi Jewish descent, ~~NCCN recommends~~ 1 approach is to test for the 3 known founder mutations (185delAG and 5182insC in *BRCA1*; 6174delT in *BRCA2*) first.<br>b) If testing is negative for founder mutations, comprehensive genetic testing may be considered (see Comprehensive Mutation Analysis).<br>c) However, NCCN version 1.2021 states "However, with new panels available, many clinicians are moving away from this stepped approach and are increasingly using comprehensive testing" |
| | Updated Rationale section |
| | In Coding section:<br>Added CPT codes 81432, 81433, 0102U, 0103U, 0129U, 0131U, 0132U, 0134U. 0138U, and 0172U<br>Added ICD-10 diagnosis codes C25.0, C25.1, C25.2, C25.3, C25.4, C25.7, C25.8,C57.00, C57.01, C57.02, C61, and Z13.71<br>Deleted ICD-10 diagnosis code Z80.8 |
| | Updated References section |
| 07-28-2021 | In Policy section:<br>▪ Item B.2 and B.3 were reformatted to become Item C and Item D. |
| 02-14-2022 | Updated Title<br>▪ Added Germline to title |
| | Updated Description Section |
| | Updated Policy Section<br>▪ Added Section A.2: Individuals meeting the criteria below but with previous limited testing (e.g., single gene and/or absent deletion duplication analysis)<br>▪ Removed Section A.3.d.i."male breast cancer"<br>▪ Section A.3.d.ii changed "≥ 2 additional" to "≥3 total"<br>▪ Added Section A.3.e"Diagnosed at any age with male breast cancer"<br>▪ Removed A.5 "Personal history of male breast cancer"<br>▪ Section A.6 added word "exocrine"<br>▪ Section A.10 Changed to read "Personal history of cancer and to aid in systemic therapy decision-making, for PARP-inhibitors for human epidermal receptor 2 (HER2)-negative metastatic and HER2-negative early stage, high-risk breast cancer (see Policy Guidelines)."<br>▪ Removed footnote [a] |
| | Updated Policy Guideline Section<br>▪ Added Section 3 (C) and 4 (D),<br>▪ Section 6B Removed B.1-title "Non-Ashkenazi Jewish descent" and B.1.IV.c<br>▪ Reformatted section to following A.1.a.I.i format |
| | Updated Rationale Section |
| | Updated References Section |

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