2.04.02	Genetic Testing for BRCA1 or BRCA2 for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers		
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Section:	2.0 Medicine	**Page:**	Page 1 of 37

Policy Statement

Genetic testing should be performed in a setting that has suitably trained health care providers who can give appropriate pre- and posttest counseling and that has access to a Clinical Laboratory Improvement Amendments-licensed laboratory that offers comprehensive variant analysis (see Policy Guidelines section: Comprehensive Variant Analysis). As other genes have become associated with hereditary breast and ovarian cancer, small panels (using CPT code 81432) are now the preferred tests (rather than just testing for BRCA1 and BRCA2, such as 81162).

Patients With Cancer or With a Personal History of Cancer

Full sequence and duplication/deletion analysis genetic testing for *BRCA1* and *BRCA2* gene variants (including when part of an approved small panel such as 81432) in cancer-affected individuals age 18 or over may be considered **medically necessary** under **any** of the following circumstances:

I. Individuals meeting criteria for medically necessary testing below but with previous limited testing (*e.g.*, single gene and/or absent deletion duplication analysis)

II. Individuals (with or without a history of cancer) with any close blood relative with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene (included in the small panel)

III. Personal history of breast cancer (including invasive and ductal carcinoma in situ) and **one or more** of the following:
   - A. Diagnosed at age 45 or younger
   - B. Diagnosed 46 to 50 years of age and **one or more** of the following:
     1. An additional breast cancer primary at any age
     2. One or more close relative (see Policy Guidelines) with breast, ovarian, pancreatic, or prostate cancer at any age
     3. An unknown or limited family history
   - C. Diagnosed on or before 60 years of age with
     1. Triple-negative breast cancer (estrogen receptor–negative, progesterone receptor–negative, human epidermal growth factor receptor 2–negative)
   - D. Diagnosed at any age with **one or more** of the following:
     1. One or more close blood relative with **one or more** of the following:
        a. Breast cancer diagnosed on or before 50 years of age
        b. Ovarian carcinoma
        c. Metastatic or intraductal/cribriform prostate cancer, or high-risk group or very-high-risk group (see Policy Guidelines) prostate cancer
        d. Pancreatic cancer
     2. Three or more total diagnoses of breast cancer in patient and/or close blood relative
     3. Ashkenazi Jewish ancestry

IV. Personal history of **one or more** of the following at any age:
   - A. Male breast cancer
   - B. Epithelial ovarian carcinoma (including fallopian tube cancer or peritoneal cancer)
   - C. Exocrine pancreatic cancer
   - D. Metastatic, intraductal/cribiform histology prostate cancer or high-risk group or very-high-risk group prostate cancer
   - E. Prostate cancer with **one or more** of the following:
     1. One or more close blood relative with ovarian carcinoma, pancreatic cancer, or metastatic or intraductal/cribiform prostate cancer at any age, or breast cancer at age 50 or younger

2. Two or more close blood relatives with breast or prostate cancer (any grade) at any age
3. Ashkenazi Jewish ancestry

F. Any cancer and a mutation identified on somatic tumor genomic testing that has clinical implications if also identified in the germline
G. Any cancer and to aid in systemic therapy decision-making, such as for PARP-inhibitors for human epidermal receptor 2 (HER2)-negative metastatic breast cancer, ovarian cancer, prostate cancer, pancreatic cancer; platinum therapy for prostate cancer and pancreatic cancer

V. An affected or unaffected individual with a first or second degree blood relative meeting any of the criteria above as documented by the requesting provider.

Patients Without Cancer or With any Other Personal History of Cancer (not noted above)
(See Policy Guidelines section: Testing Unaffected Individuals)

Genetic testing for *BRCA1* and *BRCA2* (including deletions and duplications) variants of individuals without cancer or any other type of cancer (not noted above) may be considered **medically necessary** under the following circumstance:

I. Has a probability of greater than 5% of a BRCA 1/2 pathogenic variant based on prior probability models (e.g. Tyrer-Cuzick, BRCAPro, Pennll) as documented by the requesting provider.
II. Individuals (with or without a history of cancer) with any close blood relative with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene (included in the small panel).
III. An affected or unaffected individual with a first or second degree blood relative meeting any of the criteria in the "Patients with cancer.." section above and as documented by the requesting provider.

Genetic testing for *BRCA*1 and *BRCA2* variants in cancer-affected individuals or of cancer-unaffected individuals with or without a family history of cancer when criteria above are not met (including genetic screening in the general population) is considered **investigational**.

Genetic testing in minors (younger than age 18) for *BRCA1* and *BRCA2* variants is considered **investigational**.

Confirmatory BRCA Testing
Confirmatory BRCA testing may be considered **medically necessary** for patients who underwent over-the-counter (OTC) U.S. Food and Drug Administration (FDA) approved genetic screening and were found to have a pathogenic *BRCA1* or *BRCA2* mutation (including one of the three Ashkenazi founder mutations).

Large multi-gene panels including multiple genes that are not highly associated with hereditary breast and ovarian cancer (see Policy Guidelines) are considered **investigational**.

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

When criteria are met, small panel testing using CPT code 81432 is the preferred testing for breast and ovarian cancer risk. As an alternative, 81162 is allowed for BRCA 1 and 2 testing. If BRCA testing in 81162 is negative, PALB2 (81406 molecular pathology procedure level 7) testing can also be allowed (see 2.04.126 Gene Variants Associated with Breast Cancer in Individuals at High Breast Cancer Risk). After 81162 is performed, the remaining genes in the 81432 or similar panels (with the exception of PALB2) are considered investigational and are not covered if requested at a later time.

Testing related to hereditary colorectal cancer, see Blue Shield of California Medical Policy: Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes.
Panel testing related to non-small-cell lung cancer, see Blue Shield of California Medical Policy: Circulating Tumor DNA for Management of Non-Small-Cell Lung Cancer (Liquid Biopsy).

Panel testing related to cancers other than breast, ovarian, colorectal, and non-small-cell lung cancer, see Blue Shield of California Medical Policy: Genetic Cancer Susceptibility Panels Using Next-Generation Sequencing.

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

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

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

Note: For payment authorization, this testing will be limited to single-site analysis of the mutation identified and will be performed at contracted laboratories.

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

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

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

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

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

Recommended Testing Strategies
As other genes have become associated with hereditary breast and ovarian cancer and as ethnicity becomes more mixed, small panels (using CPT code 81432) are now the preferred tests (rather than just testing for BRCA1 and BRCA2,(such as 81162), or testing for founder mutations in those of Ashkenazi descent). Complete testing includes at a minimum: Full sequence and duplication/deletion analysis of *BRCA1*and *BRCA2.* PALB2 is indicated if initial testing is negative (or preferably to be included in an initial limited panel).

Patients who meet criteria for genetic testing as outlined in the policy statements above should have complete testing. Additional testing does not need to continue once a known harmful (pathogenic) variant is found:

- In patients with a known familial *BRCA* variant, targeted testing for the specific variant is recommended as the first step.
- In patients with unknown familial *BRCA* variant:
  - To identify clinically significant variants, National Comprehensive Cancer Network (NCCN) advises testing a relative who has early-onset disease, bilateral disease, or multiple primaries, because that individual has the highest likelihood of obtaining a positive test result.

Comprehensive Variant Analysis
Standard comprehensive variant analysis (e.g. 81162) 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).

- More than 90% of BRCA variants will be detected by full sequencing alone
- Adding common deletions and duplications will detect another 2.5%
- Adding uncommon large deletions and duplications (e.g., previously known as BART or BRCA Analysis Rearrangement Test) detects less than 1% more
- Standard comprehensive testing will detect 93.5% of BRCA related variants

High-Risk Ethnic Groups
Testing of eligible individuals who belong to ethnic populations in which there are well-characterized founder mutations can 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. However, as ethnicities become more mixed and harder to identify, standard small panel testing is preferred.

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.

Note: 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

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.

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.

Panel Testing
Limited genetic panels (such as CPT code 81432, including but not limited to: ***BRCA1***, ***BRCA2***, ***CDH1***, ***MLH1***, ***MSH2***, ***MSH6***, ***PALB2***, ***STK11***, ***PTEN***, and ***TP53***), when they include both full sequence and deletion/duplication analysis, may be considered **medically necessary** as an alternative to serial testing of individual genes when criteria are met for genetic testing of hereditary breast and ovarian cancer.

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

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

Table PG1. Nomenclature to Report on Variants Found in DNA

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

Table PG2. 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.

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.

Coding

The following CPT codes may be used for genetic testing for BRCA1 and BRCA2 variants:

- **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)
  Note: This code includes both 81163 and 81164 (and previously 81211 and 81213).
- **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:** BRCA1 (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:** Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); genomic sequence analysis panel, must include sequencing of at least 10 genes, always including BRCA1, BRCA2, CDH1, MLH1, MSH2, MSH6, PALB2, PTEN, STK11, and TP53
- **81433:** Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); duplication/deletion analysis panel, must include analyses for BRCA1, BRCA2, MLH1, MSH2, and STK11

Effective July 1, 2020, The following test is not used for hereditary BRCA testing and this policy does not apply to it. It represents the myChoice test by Myriad. It is done as a companion test (related to drug use) on tumor tissue (not blood) to see if there is a mutation present that would make the tumor susceptible to either Zejula (ovarian cancer) or Lynparza (prostate cancer). Since somatic (tumor) mutations can occur independent of inherited (germline) genetics, it is indicated even if prior BRCA hereditary testing is negative, and to confirm the presence of the mutation in the tumor when germline testing was positive:

- **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

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.

Related Policies

- Gene Variants Associated with Breast Cancer in Individuals at High Breast Cancer Risk
- Genetic Cancer Susceptibility Panels Using Next-Generation Sequencing

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. 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.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

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. F1CDx is FDA approved to assess *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 homologous recombination deficiency based on genomic loss of heterozygosity (LOH) and *BRCA* mutant status. Also, FoundationOne Liquid CDx is FDA approved for detection of *BRCA1* and *BRCA2* alterations in individuals with prostate cancer considering treatment with rucaparib. However, further discussion of these multigene panel tests are outside of the scope of this review, but can be found in policies 2.04.115 and 2.04.141.

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*-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 FDA-approved companion diagnostic
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
	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]

PARP Inhibitor	Year Approved	Indication
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

Rationale

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. For this evidence review, BCBSA refers collectively to both as *hereditary breast and/or ovarian cancer*.

Germline variants in the *BRCA1* and *BRCA2* genes are responsible for the cancer susceptibility in most HBOC families, especially if ovarian cancer or male breast cancer are features. However, in site-specific cancer, BRCA variants are responsible only for a proportion of affected families. *BRCA* gene variants are inherited in an autosomal dominant fashion through maternal or paternal lineage. It is possible to test for abnormalities in *BRCA1* and *BRCA2* genes to identify the specific variant in cancer cases and to identify family members at increased cancer risk. Family members without existing cancer who are found to have *BRCA* variants can consider preventive interventions for reducing risk and mortality.

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.[1] 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).[1,2,3,4] In cancer-prone families, the mean age of breast cancer diagnosis among women carrying *BRCA1* or *BRCA2* variants is in the 40s.[5] 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.[2] 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.[6] 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.[7,8,9]

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.[4,] Several other studies have documented the significant influence of family history.[6,7,8,9,10,]

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.[11,] 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.[12,]*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.[13,] 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*).[14,]

Literature Review

This review was informed by a Blue Cross Blue Shield Association Technology Evaluation Center (TEC) Assessment (1997).[15,]

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.

Intervention

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.

Comparator
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.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires a review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

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).

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=0.034).[16] 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.[17] 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.[18] 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.[19] 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*.[7,10,20,21] 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).[21] 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.[22] 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.[23] 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%.[24] 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*.[17] Table 2 lists the results from several additional studies measuring the presence of *BRCA* variants among patients with ovarian cancer.[25,26,27,28,29] One study noted that variant prevalence was higher for women in their 40s (24%) and for women with serous ovarian cancer (18%).[25] 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.[25]

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

Study	Population	N	*BRCA* Variant, n (%)	
			BRCA1	*BRCA2*
Harter et al (2017)[29.]	Patients with invasive ovarian cancer across 20 medical centers	523	81 (15.5)	29 (5.5)
Kurian et al (2017)[26.]	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)[27.]	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)[28.]	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)[25.]	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.[30.] 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.[31.] 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.[32.] Table 3 lists the results from several studies measuring the presence of *BRCA* variants among patients with pancreatic adenocarcinoma.[33,34,35,36,37,38.] 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)[38.,a]	Patients with pancreatic adenocarcinoma from a prospective pancreatic cancer registry	3030	18 (0.6)	59 (1.9)
Yurgelun et al (2018)[37.]	Patients with pancreatic adenocarcinoma from 3 medical centers	289	3 (1.0)	4 (1.4)
Shindoet al (2017)[36.]	Patients with pancreatic adenocarcinoma from 1 medical center	854	3 (0.3)	12 (1.4)
Holter et al (2015)[35.]	Patients with pancreatic adenocarcinoma from a large academic health care complex	306	3 (1.0)	11 (3.6)
Ferrone et al (2009)[34.]	Jewish patients with pancreatic adenocarcinoma from 1 hospital	145	2 (1.3)	6 (4.1)

Study	Population	N	*BRCA* Variant, n (%)
Couch et al (2007)[33]	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.[39,40,41]

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

Study	Population	N	*BRCA* Variant, n (%)	
			BRCA1	*BRCA2*
Abida et al (2017)[41]	Patients with prostate cancer from 1 clinical practice	221	2 (1)	20 (9)
Pritchard et al (2016)[40]	Patients with metastatic prostate cancer from 7 case series across multiple centers	692	6 (0.9)	37 (5.3)
Edwards et al (2003)[39]	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 re-arrangements (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*.[42] 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%.[43] 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.[44]

Knowledge of variant status in individuals at potentially increased risk of a *BRCA* variant may impact health care decisions to reduce risk.[45,46,47,48,49,50,51] 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%.[46] Prophylactic oophorectomy significantly reduces the risk of ovarian cancer by 80% or more[49,50,52] and reduces the risk of breast cancer by approximately 50%.[50] In women who have already had breast cancer, prophylactic oophorectomy reduces the risk of cancer relapse.[36] Prophylactic oophorectomy or salpingo-oophorectomy in women with *BRCA1* or *BRCA2* reduced the risk of all-cause mortality by 60% to 77%.[52,53] 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.[54]

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.[55,56,57] Studies have indicated that the results of genotyping significantly influenced treatment choices.[47,58,51]

In a systematic review for the USPSTF, Nelson et al (2019) assessed the efficacy of risk-reducing surgery in *BRCA*-positive women.[44] 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.[59] 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.

Intervention

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

Comparator

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).

Technically Reliable

Assessment of technical reliability focuses on specific tests and operators and requires a review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

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.

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.

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.

Clinical Utility
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
OlympiAD is a phase 3 RCT in which patients with human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer and a germline *BRCA* variant were randomized to olaparib (n=205) or standard therapy (n=97).[60] *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).[61] 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).[62]

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).[63] 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).[64] 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%).

Niraparib

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).[65] 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).[63] 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

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).[66] 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).[67] 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%).

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).[68] 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

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).[69] *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 *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.

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 a meaningful 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 *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 a meaningful improvement in the net health outcome.

Supplemental Information

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.

In response to requests from Blue Cross Blue Shield Association, input was received for 3 physician specialty societies (5 reviewers) and 3 academic medical centers (5 reviewers) 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

National Comprehensive Cancer Network

Breast Cancer and Ovarian Cancer

Current NCCN (v.1.2021) 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.[70,] Patients who satisfy any of the testing criteria listed in Table 5 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.

Table 5. *BRCA1* and *BRCA2* Testing Criteria for Hereditary Breast and Ovarian Cancer Syndrome

Recommendations
Testing is clinically indicated in the following scenarios: 1. Individuals with any blood relative with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene. 2. Individuals meeting the criteria below but with previous limited testing (e.g., single gene and/or absent deletion duplication analysis) interested in pursuing multi-gene testing. 3. Personal history of cancer o Breast Cancer with at least 1 of the following: a. Diagnosed age ≤45 years b. Diagnosed age ≤ 46 to 50 years AND: ▪ Unknown or limited family history; or ▪ A second breast cancer diagnosed at any age; or ▪ ≥1 close blood relative with breast, ovarian, pancreatic or prostate cancer at any age c. Diagnosed age ≤60 years with a triple-negative (ER-, PR-, HER2-) breast cancer

Recommendations

- d. Diagnosed any age AND:
  - Ashkenazi Jewish Ancestry; or
  - ≥1 close blood relative with breast cancer at age ≤50 y or ovarian, pancreatic, or metastatic or intraductal/cribriform prostate cancer at any age or high-risk group or very-high-risk group prostate cancer at any age; or
  - ≥ 3 total diagnoses of breast cancer in patient and/or close blood relatives
- e. Diagnosed any age with male breast cancer.

- Personal history of epithelial ovarian cancer (including fallopian tube cancer or peritoneal cancer) at any age
- Exocrine pancreatic cancer at any age
- Metastatic or intraductal/cribriform prostate cancer at any age; or high-risk or very-high-risk prostate cancer
- Prostate cancer at any age with:
  - a. Ashkenazi Jewish ancestry; or
  - b. ≥1 close relative with breast cancer at age ≤50 y or ovarian, pancreatic, or metastatic or intraductal/cribriform prostate cancer at any age; or
  - c. ≥2 close relatives with breast or prostate cancer (any grade) at any age.
- A mutation identified on tumor genomic testing that has clinical implications if also identified in the germline
- To aid in systemic therapy decision-making, such as for HER2-negative metastatic breast cancer (*e.g.*, PARP inhibitors for ovarian cancer, prostate cancer, pancreatic cancer, and metastatic HER2-negative breast cancer; platinum therapy for prostate cancer and pancreatic cancer)

4. Family history of cancer
   - An affected or unaffected individual with a first- or second-degree blood relative meeting any of the criteria listed above (except individuals who meet criteria only for systemic therapy decision-making) (this may be extended to an affected third-degree relative if related through 2 male relatives [e.g., paternal grandfather's mother or sister]). Note: if the individual with cancer has pancreatic cancer or prostate cancer (metastatic or intraductal/cribriform or high-risk group or very-high-risk group) then only first-degree relatives should be offered testing unless there are other family history indications for testing.
   - An affected or unaffected individual who 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).

Testing may be considered in the following scenarios (with appropriate pre-test education and access to post-test management):

1. Bilateral breast cancer, first diagnosed between the ages of 50 and 65 y.
2. An unaffected Ashkenazi Jewish individual (Testing for 3 founder mutations of BRCA ½ may be offered to Jewish ancestry, irrespective of cancer history in the family, as part of longitudinal studies)
3. An affected or unaffected individual who otherwise does not meet any of the above criteria but with a 2.5%-5% probability of *BRCA1/2* pathogenic variant based on prior probability models (e.g., Tyrer-Cuzick, BRCAPro, Pennll)

There is a low probability (<2.5%) that testing will have findings of documented clinical utility in the following scenarios:

1. Women diagnosed with breast cancer at age >65 y, with no close relative with breast, ovarian, pancreatic, or prostate cancer.
2. Men diagnosed with localized prostate cancer with Gleason Score <7 and no close relative with breast, ovarian, pancreatic, or prostate cancer.

ER: estrogen receptor; *HER2*: human epidermal growth factor receptor 2; PR: progesterone receptor.

Additionally, the NCCN Ovarian Cancer guidelines (v1.2020) 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).[70,]

Pancreatic Adenocarcinoma
Current NCCN guidelines for pancreatic adenocarcinoma (v.1.2020) 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."[71,]

Prostate Cancer
The current NCCN guidelines for prostate cancer are version 1.2020.[71,] The Principles of Genetics section (PROS-B) includes the following statements regarding Germline Testing:

- Germline genetic testing is recommended for patients with prostate cancer and a family history of high-risk germline mutations (e.g., *BRCA1/2,* Lynch mutation)
- "Family history for known germline variants and genetic testing for germline variants should include *MLH1, MSH2, MSH6, and PMS2* (for Lynch Syndrome) and homologous recombination genes *BRCA1, BRCA2, ATM, PALB2, and CHEK2.* Consider cancer predisposition NGS panel testing, which includes *BRCA1, BRCA2, ATM, CHEK2, PALB2, MLH1, MSH2, MSH6, and PMS2."*

The Principles of Genetics section (PROS-B) includes the following statements regarding Somatic Tumor Testing:

- "Recommend evaluating tumor for alterations in homologous recombination DNA repair such as: BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51D, CHEK2 and CDK12, in patients with metastatic prostate cancer. This testing can be considered in men with regional prostate cancer."
- "At present, this information may be used for genetic counseling, early use of platinum chemotherapy, olaparib, and/or eligibility for clinical trials (e.g., PARP inhibitors)."
- "If mutations in BRCA2, BRCA1, ATM, CHEK2, or PALB2 are found and/or there is a strong family history of cancer, refer to genetic counseling for confirmatory germline testing."

American Society of Clinical Oncology
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.[72,] 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."[73,] 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."[74,]

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.[75,] 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.[76.] 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).[77.] 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)[78.] 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 who's personal or family history or ancestry is not associated with potentially harmful *BRCA1/2* gene mutations. (D recommendation)"

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

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

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 6.

Table 6. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date (status if beyond Completion Date)
Ongoing			
NCT02154672	Prostate Cancer Screening in Men With Germline BRCA2 Mutations	100	May 2018 (unknown)
NCT02225015	Cancer Prevention in Women With a BRCA Mutation	300	Jun 2019 (unknown)
NCT02975934	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

NCT No.	Trial Name	Planned Enrollment	Completion Date (status if beyond Completion Date)
NCT03246841	Investigation of Tumour Spectrum, Penetrance and Clinical Utility of Germline Mutations in New Breast and Ovarian Cancer Susceptibility Genes	500	Dec 2023
NCT02855944	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
NCT04090567	Overcoming PARP Inhibitor Resistance in BRCA Germline Mutation Positive Advanced Breast Cancer	60	June 2021
NCT03740165	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)	1086	August 2025
NCT02032823	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	1836	Nov 2028

NCT: national clinical trial.

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Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or consultation notes including:
  - Ethnicity/Ancestry
  - Personal and/or family history of cancer (if applicable) including:
    - Family relationship(s): (maternal or paternal), (family member [e.g., sibling, aunt, grandparent]), (living or deceased) ((if applicable)
    - Site(s) of cancer
    - Age at diagnosis (including family members)
    - If breast cancer, indicate if bilateral, premenopausal, or triple negative cancer
  - BRCA1/BRCA2 mutation history (if applicable)
- Genetic counseling/professional results (if applicable)
- Laboratory or Pathology reports

Post Service (in addition to the above, please include the following):

- Procedure report(s)

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

Type	Code	Description
CPT®	0102U	Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA, and array CGH, with mRNA analytics to resolve variants of unknown significance when indicated (17 genes [sequencing and deletion/duplication])
	0103U	Hereditary ovarian cancer (e.g., hereditary ovarian cancer, hereditary endometrial cancer), genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA, and array CGH, with mRNA analytics to resolve variants of unknown significance when indicated (24 genes [sequencing and deletion/duplication], EPCAM [deletion/duplication only])
	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)
	0131U	Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), targeted mRNA sequence analysis panel (13 genes) (List separately in addition to code for primary procedure)
	0132U	Hereditary ovarian cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), targeted mRNA sequence analysis panel (17 genes) (List separately in addition to code for primary procedure)
	0135U	Hereditary gynecological cancer (e.g., hereditary breast and ovarian cancer, hereditary endometrial cancer, hereditary colorectal cancer), targeted mRNA sequence analysis panel (12 genes) (List separately in addition to code for primary procedure)
	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 ***(Code effective 7/1/2020)***
	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)

Type	Code	Description
	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	BRCA1 (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
	81307	PALB2 (partner and localizer of BRCA2) (e.g., breast and pancreatic cancer) gene analysis; full gene sequence
	81308	PALB2 (partner and localizer of BRCA2) (e.g., breast and pancreatic cancer) gene analysis; known familial variant
	81432	Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); genomic sequence analysis panel, must include sequencing of at least 10 genes, always including BRCA1, BRCA2, CDH1, MLH1, MSH2, MSH6, PALB2, PTEN, STK11, and TP53
	81433	Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); duplication/deletion analysis panel, must include analyses for BRCA1, BRCA2, MLH1, MSH2, and STK11
	81479	Unlisted molecular pathology procedure
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
10/15/1997	New Policy Adoption
06/01/1999	BCBSA Medical Policy adoption
05/01/2001	Administrative Review
08/01/2005	BCBSA Medical Policy adoption
10/01/2005	Administrative Review
01/11/2008	Policy Revision
12/05/2008	Policy Revision

Effective Date	Action
05/06/2009	Coding Update
07/28/2009	Criteria Revised
11/04/2009	Coding update
04/02/2010	Policy revision with position change to clarify BART testing
07/15/2010	Policy Revision with position change adopting 2010 NCCN guidelines
09/13/2010	Coding Update
03/30/2012	Title change from BRCA1 and BRCA2 Genetic Testing with position change
06/13/2012	Coding Update
08/21/2012	Administrative Update (Clarification of Policy Guideline)
02/22/2013	Coding Update
03/29/2013	Policy revision with position change
10/9/2013	Administrative Update (Clarification of BART testing policy statement)
12/19/2013	Policy revision with position change
03/30/2015	Administrative Update (Revision and clarification of the Documentation Required section)
08/31/2015	Policy title change from Genetic Testing for Hereditary Breast and/or Ovarian Cancer Administrative Update (Formatting changes only)
02/01/2016	Coding update
01/01/2017	Policy title change from Genetic Testing for Hereditary Breast and/or Ovarian Cancer Syndrome (BRCA1/BRCA2). Policy revision without position change.
09/01/2017	Policy revision without position change
01/01/2018	Policy revision without position change
04/01/2018	Policy revision without position change
07/01/2018	Policy revision without position change
01/01/2019	Policy title change from Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome (BRCA1 or BRCA2). Policy statement clarification. Coding update.
05/01/2019	Policy revision without position change. Coding update.
08/01/2019	Administrative Update
11/01/2019	Administrative Update
04/01/2020	Annual review. No change to policy statement. Literature review updated.
06/01/2020	Administrative update. Policy statement and guidelines updated. Coding Update.
07/01/2020	Administrative update. Policy statement and guidelines updated.
08/01/2020	Coding Update
01/01/2021	Annual review. Policy statement, guidelines and literature updated.
02/01/2021	Administrative update.
04/01/2021	Annual review. Policy statement and guidelines updated.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT	
BEFORE	**AFTER** **Blue font: Verbiage Changes/Additions**
Genetic Testing for BRCA1 or BRCA2 for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers 2.04.02 **Policy Statement:** Genetic testing should be performed in a setting that has suitably trained health care providers who can give appropriate pre- and posttest counseling and that has access to a Clinical Laboratory Improvement Amendments-licensed laboratory that offers comprehensive variant analysis (see Policy Guidelines section: Comprehensive Variant Analysis). As other genes have become associated with hereditary breast and ovarian cancer, small panels (using CPT code 81432) are now the preferred tests (rather than just testing for BRCA1 and BRCA2, such as 81162). **Patients With Cancer or With a Personal History of Cancer** Full sequence and duplication/deletion analysis genetic testing for *BRCA1* and *BRCA2* gene variants (including when part of an approved small panel such as 81432) in cancer-affected individuals may be considered **medically necessary** under **any** of the following circumstances: I. Individuals meeting criteria for medically necessary testing below but with previous limited testing (*e.g.*, single gene and/or absent deletion duplication analysis) II. Individuals with any close blood relative with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene (included in the small panel) III. Personal history of breast cancer (including invasive and ductal carcinoma in situ) and **one or more** of the following: A. Diagnosed at age 45 or younger B. Diagnosed 46 to 50 years of age and **one or more** of the following: 1. An additional breast cancer primary at any age	**Genetic Testing for BRCA1 or BRCA2 for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers 2.04.02** **Policy Statement:** Genetic testing should be performed in a setting that has suitably trained health care providers who can give appropriate pre- and posttest counseling and that has access to a Clinical Laboratory Improvement Amendments-licensed laboratory that offers comprehensive variant analysis (see Policy Guidelines section: Comprehensive Variant Analysis). As other genes have become associated with hereditary breast and ovarian cancer, small panels (using CPT code 81432) are now the preferred tests (rather than just testing for BRCA1 and BRCA2, such as 81162). **Patients With Cancer or With a Personal History of Cancer** Full sequence and duplication/deletion analysis genetic testing for *BRCA1* and *BRCA2* gene variants (including when part of an approved small panel such as 81432) in cancer-affected individuals age 18 or over may be considered **medically necessary** under **any** of the following circumstances: I. Individuals meeting criteria for medically necessary testing below but with previous limited testing (*e.g.*, single gene and/or absent deletion duplication analysis) II. Individuals (with or without a history of cancer) with any close blood relative with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene (included in the small panel) III. Personal history of breast cancer (including invasive and ductal carcinoma in situ) and **one or more** of the following: A. Diagnosed at age 45 or younger B. Diagnosed 46 to 50 years of age and **one or more** of the following: 1. An additional breast cancer primary at any age

POLICY STATEMENT	
BEFORE	**AFTER** **Blue font: Verbiage Changes/Additions**
2. One or more close relative (see Policy Guidelines) with breast, ovarian, pancreatic, or prostate cancer at any age 3. An unknown or limited family history C. Diagnosed on or before 60 years of age with 1. Triple-negative breast cancer (estrogen receptor–negative, progesterone receptor–negative, human epidermal growth factor receptor 2–negative) D. Diagnosed at any age with **one or more** of the following: 1. One or more close blood relative with **one or more** of the following: a. Breast cancer diagnosed on or before 50 years of age b. Ovarian carcinoma c. Metastatic or intraductal/cribriform prostate cancer, or high-risk group or very-high-risk group (see Policy Guidelines) prostate cancer d. Pancreatic cancer 2. Three or more total diagnoses of breast cancer in patient and/or close blood relative 3. Ashkenazi Jewish ancestry IV. Personal history of **one or more** of the following at any age: A. Male breast cancer B. Epithelial ovarian carcinoma (including fallopian tube cancer or peritoneal cancer) C. Exocrine pancreatic cancer D. Metastatic, intraductal/cribiform histology prostate cancer or high-risk group or very-high-risk group prostate cancer E. Prostate cancer with **one or more** of the following: 1. One or more close blood relative with ovarian carcinoma, pancreatic cancer, or metastatic or intraductal/cribiform prostate cancer at any age, or breast cancer at age 50 or younger 2. Two or more close blood relatives with breast or prostate cancer (any grade) at any age 3. Ashkenazi Jewish ancestry	2. One or more close relative (see Policy Guidelines) with breast, ovarian, pancreatic, or prostate cancer at any age 3. An unknown or limited family history C. Diagnosed on or before 60 years of age with 1. Triple-negative breast cancer (estrogen receptor–negative, progesterone receptor–negative, human epidermal growth factor receptor 2–negative) D. Diagnosed at any age with **one or more** of the following: 1. One or more close blood relative with **one or more** of the following: a. Breast cancer diagnosed on or before 50 years of age b. Ovarian carcinoma c. Metastatic or intraductal/cribriform prostate cancer, or high-risk group or very-high-risk group (see Policy Guidelines) prostate cancer d. Pancreatic cancer 2. Three or more total diagnoses of breast cancer in patient and/or close blood relative 3. Ashkenazi Jewish ancestry IV. Personal history of **one or more** of the following at any age: A. Male breast cancer B. Epithelial ovarian carcinoma (including fallopian tube cancer or peritoneal cancer) C. Exocrine pancreatic cancer D. Metastatic, intraductal/cribiform histology prostate cancer or high-risk group or very-high-risk group prostate cancer E. Prostate cancer with **one or more** of the following: 1. One or more close blood relative with ovarian carcinoma, pancreatic cancer, or metastatic or intraductal/cribiform prostate cancer at any age, or breast cancer at age 50 or younger 2. Two or more close blood relatives with breast or prostate cancer (any grade) at any age 3. Ashkenazi Jewish ancestry

POLICY STATEMENT	
BEFORE	**AFTER** **Blue font: Verbiage Changes/Additions**
F. Any cancer and a mutation identified on tumor genomic testing that has clinical implications if also identified in the germline G. Any cancer and to aid in systemic therapy decision-making, such as for PARP-inhibitors for human epidermal receptor 2 (HER2)-negative metastatic breast cancer, ovarian cancer, prostate cancer, pancreatic cancer; platinum therapy for prostate cancer and pancreatic cancer	F. Any cancer and a mutation identified on somatic tumor genomic testing that has clinical implications if also identified in the germline G. Any cancer and to aid in systemic therapy decision-making, such as for PARP-inhibitors for human epidermal receptor 2 (HER2)-negative metastatic breast cancer, ovarian cancer, prostate cancer, pancreatic cancer; platinum therapy for prostate cancer and pancreatic cancer V. An affected or unaffected individual with a first or second degree blood relative meeting any of the criteria above as documented by the requesting provider.
Patients Without Cancer or With any Other Personal History of Cancer (not noted above) (See Policy Guidelines section: Testing Unaffected Individuals)	**Patients Without Cancer or With any Other Personal History of Cancer (not noted above)** (See Policy Guidelines section: Testing Unaffected Individuals)
Genetic testing for *BRCA1* and *BRCA2* (including deletions and duplications) variants of individuals without cancer or any other type of cancer (not noted above) may be considered **medically necessary** under the following circumstance: I. Has a probability of greater than 5% of a BRCA 1/2 pathogenic variant based on prior probability models (e.g. Tyrer-Cuzick, BRCAPro, PennII)	Genetic testing for *BRCA1* and *BRCA2* (including deletions and duplications) variants of individuals without cancer or any other type of cancer (not noted above) may be considered **medically necessary** under the following circumstance: I. Has a probability of greater than 5% of a BRCA 1/2 pathogenic variant based on prior probability models (e.g. Tyrer-Cuzick, BRCAPro, PennII) as documented by the requesting provider. II. Individuals (with or without a history of cancer) with any close blood relative with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene (included in the small panel). III. An affected or unaffected individual with a first or second degree blood relative meeting any of the criteria in the "Patients with cancer.." section above and as documented by the requesting provider.
Genetic testing for *BRCA*1 and *BRCA2* variants in cancer-affected individuals or of cancer-unaffected individuals with or without a family history of cancer when criteria above are not met (including genetic screening in the general population) is considered **investigational**.	Genetic testing for *BRCA*1 and *BRCA2* variants in cancer-affected individuals or of cancer-unaffected individuals with or without a family history of cancer when criteria above are not met (including genetic screening in the general population) is considered **investigational**.

POLICY STATEMENT	
BEFORE	**AFTER** **Blue font: Verbiage Changes/Additions**
Genetic testing in minors (younger than age 18) for *BRCA1* and *BRCA2* variants is considered **investigational**. **Confirmatory BRCA Testing** Confirmatory BRCA testing may be considered **medically necessary** for patients who underwent over-the-counter (OTC) U.S. Food and Drug Administration (FDA) approved genetic screening and were found to have a pathogenic *BRCA1* or *BRCA2* mutation (including one of the three Ashkenazi founder mutations). Large multi-gene panels including multiple genes that are not highly associated with hereditary breast and ovarian cancer (see Policy Guidelines) are considered **investigational**.	Genetic testing in minors (younger than age 18) for *BRCA1* and *BRCA2* variants is considered **investigational**. **Confirmatory BRCA Testing** Confirmatory BRCA testing may be considered **medically necessary** for patients who underwent over-the-counter (OTC) U.S. Food and Drug Administration (FDA) approved genetic screening and were found to have a pathogenic *BRCA1* or *BRCA2* mutation (including one of the three Ashkenazi founder mutations). Large multi-gene panels including multiple genes that are not highly associated with hereditary breast and ovarian cancer (see Policy Guidelines) are considered **investigational**.