Genetic Testing for BRCA1 or BRCA2 for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers

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.

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**

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 (eg, 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.

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. 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). In cancer-prone families, the mean age of breast cancer diagnosis among women carrying **BRCA1** or **BRCA2** variants is in the 40s. In the Ashkenazi Jewish population, Frank et al (2002) reported that 13% of 248 cases with no known family history and diagnosed before 50 years of age had **BRCA** variants. In a similar study by Gershoni-Baruch et al (2000), 31% of Ashkenazi Jewish women, unselected for family history, diagnosed with breast cancer at younger than 42 years of age had **BRCA** variants. Other studies have indicated that early age of breast cancer diagnosis is a significant predictor of **BRCA** variants in the absence of family history in this population.

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

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

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**OBJECTIVE**

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

**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).

**Patients With Cancer or With a Personal History of Cancer**

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

- Individuals with any blood relative with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene
- Individuals meeting the criteria below but with previous limited testing (eg, single gene and/or absent deletion duplication analysis)
- Personal history of breast cancer and one or more of the following:
  - Diagnosed at age ≤45 years; or
  - Diagnosed 46 to 50 years with:
    - An additional breast cancer primary at any age; or
    - ≥1 close relative (see Policy Guidelines) with breast, ovarian, pancreatic, or prostate cancer at any age; or
    - An unknown or limited family history
  - Diagnosed ≤60 years with:
    - Triple-negative breast cancer
  - Diagnosed at any age with:
    - ≥1 close blood relative with:
      - Breast cancer diagnosed ≤50 years; or
      - Ovarian carcinoma; or
      - Metastatic, or intraductal/cribiform prostate cancer, or high-risk group or very high risk group (see Policy Guidelines) prostate cancer; or
      - Pancreatic cancer; or

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 Genetic testing for BRCA1 and BRCA2 variants of cancer-unaffected individuals may be considered medically necessary under any of the following circumstances:

- An individual with any type of cancer or unaffected individual with a 1st- or 2nd-degree blood relative meeting any criterion listed above for Patients With Cancer (except individuals who meet criteria only for systemic therapy decision-making). If the individual with cancer has pancreatic cancer or prostate cancer (metastatic or intraductal/cribriform or high-risk group or very-high-risk group) then only first-degree relatives should be offered testing unless there are other family history indications for testing.

- An individual with any type of cancer or unaffected individual who otherwise does not meet the criteria above but has a probability >5% of a BRCA 1/2 pathogenic variant based on prior probability models (cf, Tyrer-Cuzik, BRCAPro, PennII)

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

Genetic testing in minors for BRCA1 and BRCA2 variants is considered investigational.
POLICY GUIDELINES

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 \textit{BRCA1} or \textit{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-Cuzik)
- Brief versions of the BRCAPRO

Close relatives

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

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

Prostate Cancer Risk Groups

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

- High-risk group: no very-high-risk features and are T3a (American Joint Committee on Cancer staging T3a=tumor has extended outside of the prostate but has not spread to the seminal vesicles); OR Grade Group 4 or 5; OR prostate specific antigen of 20 ng/ml or greater
- Very-high-risk group: T3b-T4 (tumor invades seminal vesicle(s); or tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall); OR Primary Gleason Pattern 5; OR 2 or 3 high-risk features; OR greater than 4 cores with Grade Group 4 or 5

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Recommended Testing Strategies

Patients who meet criteria for genetic testing as outlined in the policy statements above should be tested for variants in \textit{BRCA1} and \textit{BRCA2}. Recommended strategies are listed below.

- In patients with a known familial \textit{BRCA} variant, targeted testing for the specific variant is recommended.

- In patients with unknown familial \textit{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. Unless the affected individual is a member of an ethnic group for which particular founder pathogenic or likely pathogenic variants are known, comprehensive genetic testing (ie, full sequencing of the genes and detection of large gene rearrangements) should be performed.
  - If no living family member with breast or ovarian cancer exists, NCCN suggests testing first- or second-degree family members affected with cancer thought to be related to deleterious \textit{BRCA1} or \textit{BRCA2} variants (eg, prostate cancer, pancreatic cancer, melanoma).
  - If no familial variant can be identified, 2 possible testing strategies are:
    - Full sequencing followed by testing for large genomic rearrangements (deletions, duplications) only if sequencing detects no variant (negative result).
    - More than 90% of \textit{BRCA} variants will be detected by full sequencing.
    - Alternatively, simultaneous full sequencing and testing for large genomic rearrangements (also known as comprehensive \textit{BRCA} testing; see Comprehensive Variant Analysis below) may be performed as is recommended by NCCN.
    - Comprehensive testing can detect 92.5% of \textit{BRCA1} or \textit{BRCA2} variants.
  - Ashkenazi Jewish descent
    - In patients of known Ashkenazi Jewish descent, one approach is to test for the 3 known founder mutations (185delAG and 5182insC in \textit{BRCA1}; 6174delT in \textit{BRCA2}) first; if testing is negative for founder mutations and if the individual's ancestry also included non-Ashkenazi ethnicity (or if other \textit{BRCA1}/\textit{BRCA2} testing criteria are met), comprehensive genetic testing should be considered.
    - However, NCCN version 1.2021 states "However, with new panels available, many clinicians are moving away from this stepped approach and are increasingly using comprehensive testing."

Comprehensive Variant Analysis

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

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

Testing Unaffected Individuals

In unaffected family members of potential BRCA 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.

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.

Genetic 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.

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Table PG1. Nomenclature to Report on Variants Found in DNA

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated variant</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
<tr>
<td>Variant</td>
<td>Change in the DNA sequence</td>
<td></td>
</tr>
<tr>
<td>Familial variant</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
<td></td>
</tr>
</tbody>
</table>

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Likely pathogenic</td>
<td>Likely disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Variant of uncertain significance</td>
<td>Change in DNA sequence with uncertain effects on disease</td>
</tr>
<tr>
<td>Likely benign</td>
<td>Likely benign change in the DNA sequence</td>
</tr>
<tr>
<td>Benign</td>
<td>Benign change in the DNA sequence</td>
</tr>
</tbody>
</table>

Genetic Counseling

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

BENEFIT APPLICATION

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

Under the Patient Protection and Affordable Care Act, preventive services with a U.S. Preventive Services Task Force recommendation grade of A or B will be covered with no cost-sharing requirements.

Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.
Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing.

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

In addition to the various individual variant tests which are the focus of this policy, numerous other multigene panel tests exist that include BRCA1/2 among other genes. Although these multigene panel tests are outside of the scope of this review, among them, it is worth noting that FoundationOne CDx™ (F1CDx) is an FDA-approved companion diagnostic for use of Lynparza (olaparib) and Rubraca (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 (eg, BRCA mutation). Table 1 provides a list of FDA-approved PARP inhibitor drugs and their BRCA mutation-related approved indications.
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**Table 1. FDA-Approved BRCA Mutation-Related Indications for Poly (Adenosine Diphosphate–Ribose) Polymerase (PARP) Inhibitors**

<table>
<thead>
<tr>
<th>PARP Inhibitor</th>
<th>Year Approved</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olaparib</td>
<td>2018</td>
<td>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</td>
</tr>
<tr>
<td></td>
<td>2018</td>
<td>Treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic</td>
</tr>
<tr>
<td></td>
<td>2018</td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td>2018</td>
<td>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</td>
</tr>
<tr>
<td></td>
<td>2019</td>
<td>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</td>
</tr>
<tr>
<td></td>
<td>2019</td>
<td>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 BRCA mutation, and/or genomic instability. Select patients for therapy based on an FDA-approved companion diagnostic</td>
</tr>
<tr>
<td>Niraparib</td>
<td>2017</td>
<td>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</td>
</tr>
<tr>
<td></td>
<td>2019</td>
<td>Treatment of adult patients with advanced ovarian, fallopian tube, or primary peritoneal cancer who have been treated with three 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</td>
</tr>
<tr>
<td></td>
<td>2019</td>
<td>Treatment of patients with deleterious BRCA mutation-associated epithelial ovarian, fallopian tube, or primary peritoneal cancer who have been treated with two or more chemotherapies. Select patients for therapy based on an FDA-approved companion diagnostic</td>
</tr>
<tr>
<td></td>
<td>2020</td>
<td>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 chemotherapya</td>
</tr>
<tr>
<td></td>
<td>2020</td>
<td>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</td>
</tr>
<tr>
<td>Talazoparib</td>
<td>2018</td>
<td>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</td>
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<td>2018</td>
<td>Treatment of adult patients with deleterious or suspected deleterious germline or somatic BRCA-mutated advanced 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</td>
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<tr>
<td></td>
<td>2018</td>
<td>Treatment of adult patients with deleterious or suspected deleterious BRCA-mutated advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic</td>
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<td>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.</td>
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*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: Food and Drug Administration; gBRCAm: germline BRCA mutated; HER2: human epidermal growth factor receptor 2; PARP: Poly (adenosine diphosphate–ribose) polymerase*
RATIONALE

Summary of Evidence

For individuals who have cancer or a personal or family cancer history and meet criteria suggesting a risk of hereditary breast and ovarian cancer (HBOC) syndrome who receive genetic testing for a BRCA1 or BRCA2 variant, the evidence includes a TEC Assessment and studies of variant prevalence and cancer risk. The relevant outcomes are overall survival (OS), disease-specific survival, test validity, and quality of life (QOL). The accuracy of variant testing has been shown to be high. Studies of lifetime risk of cancer for carriers of a BRCA variant have shown a risk as high as 85%. Knowledge of BRCA variant status in individuals at risk of a BRCA variant may impact health care decisions to reduce risk, including intensive surveillance, chemoprevention, and/or prophylactic intervention. In individuals with BRCA1 or BRCA2 variants, prophylactic mastectomy and oophorectomy have been found to significantly increase disease-specific survival and OS. Knowledge of BRCA variant status in individuals diagnosed with breast cancer may impact treatment decisions. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have other high-risk cancers (eg, cancers of the fallopian tube, pancreas, prostate) who receive genetic testing for a BRCA1 or BRCA2 variant, the evidence includes studies of variant prevalence and cancer risk. The relevant outcomes are OS, disease-specific survival, test validity, and QOL. The accuracy of variant testing has been shown to be high. Knowledge of BRCA variant status in individuals with other high-risk cancers can inform decisions regarding genetic counseling, chemotherapy, and enrollment in clinical trials. The evidence is sufficient to determine that the technology results in 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

Practice Guidelines and Position Statements

National Comprehensive Cancer Network

Breast Cancer and Ovarian Cancer

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.

Patients who...
satisfy any of the testing criteria listed in Table 2 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 2. *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 (eg, single gene and/or absent deletion duplication analysis) interested in pursuing multi-gene testing.
3. Personal history of cancer:
   - Breast Cancer with at least one of the following
     - Diagnosed age ≤45 years
     - 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
     - Diagnosed age ≤60 years with a triple-negative (ER-, PR-, HER2-) breast cancer
     - 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 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
     - 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

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Recommendations

- Metastatic or intraductal/cribiform prostate cancer at any age; or high-risk or very-high-risk prostate cancer

- Prostate cancer at any age with:
  - Ashkenazi Jewish ancestry; or
  - ≥1 close relative with breast cancer at age ≤50 y or ovarian, pancreatic, or metastatic or intraductal/cribiform prostate cancer at any age; or
  - ≥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 (eg, 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 two male relatives [eg, paternal grandfather’s mother or sister]).

- 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 (eg, 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 three founder mutations of BRCA 1/2 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 (eg, 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).
Pancreatic Adenocarcinoma

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".70

Prostate Cancer

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 (eg, 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 has released statements on genetic and genomic testing for cancer susceptibility since 1996. The Society (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

The SGO (2015) 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 (eg, few female relatives, hysterectomy, or oophorectomy at a young age in multiple family members, or adoption in the lineage).

**American College of Obstetricians and Gynecologists**

The American College of Obstetricians and Gynecologists (2017, reaffirmed 2019) published a Practice Bulletin on hereditary breast and ovarian cancer syndrome. 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**

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 in 2019 (TA598). 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**

USPSTF recommendations (2019) for genetic testing of BRCA1 and BRCA2 variants in women state: "The USPSTF recommends that primary care clinicians assess women with a personal or family history of breast, ovarian, tubal, or peritoneal cancer or who have an ancestry associated with BRCA1/2 gene mutation with an appropriate brief familial risk assessment tool. Women with a positive result on the risk assessment tool should receive genetic counseling and, if indicated after counseling, genetic testing (B recommendation). The USPSTF recommends against routine risk assessment, genetic counseling, or genetic testing for women whose personal or family history or ancestry is not associated with potentially harmful BRCA1/2 gene mutations. (D recommendation)"

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

**Medicare National Coverage**

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

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REFERENCES

15. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). BRCA1 and BRCA2 testing to determine the risk of breast and ovarian cancer. TEC Assessments. 1997;Volume 12:Tab 4.

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42. Walsh T, Casadei S, Coats KH, et al. Spectrum of mutations in BRCA1, BRCA2, CHEK2, and TP53 in families at high risk of breast cancer. JAMA. Mar 22 2006; 295(12): 1379-88. PMID 16551709

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

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
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<tr>
<td>December 2020</td>
<td>New Policy</td>
<td>Genetic testing for a BRCA1 or BRCA2 variant is medically necessary for individuals who meet policy criteria: (1) cancer or a personal or family cancer history suggesting a risk of hereditary breast and ovarian cancer (HBOC) syndrome; (2) have other high-risk cancers (eg, cancers of the fallopian tube, pancreas, prostate); (3) HBOC Syndrome or other high-risk cancers considering systemic therapy options.</td>
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