



FEP Medical Policy Manual

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

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Related Policies:

2.04.115- Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies

Germline 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.

OBJECTIVE

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

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 1 or more of the following:
 - Diagnosed at age ≤ 45 years; or
 - Diagnosed 46 to 50 years with:
 - An additional breast cancer primary at any age; or
 - ≥ 1 close relative (see Policy Guidelines) with breast, ovarian, pancreatic, or prostate cancer at any age; or
 - An unknown or limited family history
 - Diagnosed ≤ 60 years with:
 - Triple-negative breast cancer
 - Diagnosed at any age with:
 - ≥ 1 close blood relative with:
 - Breast cancer diagnosed ≤ 50 years; or
 - Ovarian carcinoma; or
 - Metastatic or intraductal/ciriform prostate cancer, or high-risk group or very-high-risk group (see Policy Guidelines) prostate cancer; or
 - Pancreatic cancer; or
 - ≥ 3 total diagnoses of breast cancer in patient and/or close blood relative; or
 - Ashkenazi Jewish ancestry
 - Diagnosed at any age with male breast cancer
- Personal history of epithelial ovarian carcinoma (including fallopian tube cancer or peritoneal cancer) at any age
- Personal history of exocrine pancreatic cancer at any age
- Personal history of metastatic or intraductal/ciriform histology prostate cancer at any age; or high-risk group or very-high-risk group prostate cancer at any age
- Personal history of prostate cancer at any age with:
 - ≥ 1 close blood relative with ovarian carcinoma, pancreatic cancer, or metastatic or intraductal/ciriform prostate cancer at any age, or breast cancer ≤ 50 years; or
 - ≥ 2 close blood relatives with breast or prostate cancer (any grade) at any age; or

- o Ashkenazi Jewish ancestry
- Personal history of cancer and a mutation identified on tumor genomic testing that has clinical implications if also identified in the germline
- Personal history of cancer and to aid in systemic therapy decision-making for PARP-inhibitors for human epidermal receptor 2 (HER2)-negative metastatic and HER2-negative early stage, high-risk breast cancer (see Policy Guidelines).
- Personal history of cancer and to aid in systemic therapy decision-making for PARP-inhibitors for ovarian cancer, prostate cancer, and pancreatic cancer and platinum therapy for prostate cancer and pancreatic cancer.

Patients Without Cancer or Other Personal History of Cancer

(See Policy Guidelines section: Testing Unaffected Individuals.)

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 *BRCA1/2* pathogenic variant based on prior probability models (eg, Tyrer-Cuzick, 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 *BRCA1* or *BRCA2* are:

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

Close Relatives

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

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

Breast Cancer Risk Groups

In the OlympiA trial, patients with HER2-negative early-stage breast cancer (Clinical Stage I-III) and germline *BRCA1/2* mutations treated with (neo)adjuvant chemotherapy were considered at high risk of recurrent disease when the following eligibility criteria were met for treatment with olaparib:¹

- Patients with triple-negative breast cancer who were treated with adjuvant chemotherapy were required to have axillary node-positive disease or an invasive primary tumor measuring at least 2 cm on pathological analysis. Patients treated with neoadjuvant chemotherapy were required to have not achieved pathological complete response.
- Patients treated with adjuvant chemotherapy for hormone receptor (HR)-positive, HER2-negative breast cancer were required to have at least 4 pathologically confirmed positive lymph nodes. Those treated with neoadjuvant chemotherapy were required to have not achieved a pathological complete response with a clinical stage, pathologic stage, estrogen receptor status, and tumor grade (CPS+EG) score of 3 or higher (Table PG1). This scoring system estimates relapse probability on the basis of clinical and pathological stage (CPS) and estrogen-receptor status and histologic grade (EG). Scores range from 0 to 6, with higher scores reflecting a worse prognosis.

Table PG1. CPS+EG Score^{a,b}

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

AJCC: American Joint Committee on Cancer; CPS+EG: clinical stage, pathologic stage, ER status, and tumor grade; ER: estrogen receptor.

^a Adapted from Tung et al (2021).²

^b Add points for clinical stage, pathologic stage, ER status, and nuclear grade to yield a sum between 0 and 6.

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

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

- In patients with a known familial *BRCA* variant, targeted testing for the specific variant is recommended.
- 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. Unless the affected individual is a member of an ethnic group for which particular founder pathogenic or likely pathogenic variants are known, comprehensive genetic testing (*ie*, full sequencing of the genes and detection of large gene rearrangements) should be performed
 - If no living family member with breast or ovarian cancer exists, NCCN suggests testing first- or second-degree family members affected with cancer thought to be related to deleterious *BRCA1* or *BRCA2* variants (eg, prostate cancer, pancreatic cancer, melanoma).
 - If no familial variant can be identified, 2 possible testing strategies are:
- Full sequencing followed by testing for large genomic rearrangements (deletions, duplications) only if sequencing detects no variant (negative result).
 - More than 90% of *BRCA* variants will be detected by full sequencing.
- Alternatively, simultaneous full sequencing and testing for large genomic rearrangements (also known as comprehensive *BRCA* testing; see Comprehensive Variant Analysis below) may be performed as is recommended by NCCN
 - Comprehensive testing can detect 92.5% of *BRCA1* or *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 *BRCA1*; 6174delT in *BRCA2*) first; if testing is negative for founder mutations and if the individual's ancestry also included non-Ashkenazi ethnicity (of if other *BRCA1/2* testing criteria are met), comprehensive genetic testing should be considered.

Comprehensive Variant Analysis

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

High-Risk Ethnic Groups

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

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.

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 PG2). 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 PG3 shows the recommended standard terminology- "pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"- to describe variants identified that cause Mendelian disorders.

Table PG2. 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 PG3. 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.

BENEFIT APPLICATION

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

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

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

FDA REGULATORY STATUS

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

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 <i>BRCA</i> -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 <i>BRCA</i> -mutated (<i>gBRCAm</i>) 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 <i>gBRCAm</i> , 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 <i>gBRCAm</i> 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 <i>BRCA</i> mutation, and/or genomic instability. Select patients for therapy based on an FDA-approved companion diagnostic
	2020	Treatment of adult patients with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC) who have progressed following prior treatment with enzalutamide or abiraterone
Niraparib	2017	For the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy
	2019	Treatment of adult patients with advanced ovarian, fallopian tube, or primary peritoneal cancer who have been treated with 3 or more prior chemotherapy regimens and whose cancer is associated with homologous recombination deficiency positive status defined by either a deleterious or suspected deleterious <i>BRCA</i> 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 <i>BRCA</i> 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 <i>BRCA</i> mutation (germline and/or somatic)-associated metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor-directed therapy and a taxane based chemotherapy ^a

Talazoparib	2018	Treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm) HER2-negative locally advanced or metastatic breast cancer. Select patients for therapy based on an FDA-approved companion diagnostic
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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: BRCA1/2 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

Summary of Evidence

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

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

For individuals with HBOC Syndrome or other high-risk cancers considering systemic therapy options who receive genetic testing for a *BRCA1* or *BRCA2* variant, the evidence includes several randomized controlled trials (RCT) and single-arm trials. Relevant outcomes are OS, disease-specific survival, test validity, and quality of life. The numerous placebo-controlled RCTs of Poly Adenosine Diphosphate-Ribose Polymerase (PARP) inhibitor drugs have consistently demonstrated that, in individuals with HER2-negative metastatic breast cancer, other advanced breast cancer, or ovarian cancer and a germline *BRCA* variant, treatment with PARP inhibitor drugs significantly improve progression-free survival time. In individuals with a *BRCA1/2* mutation and high-risk, early-stage breast cancer, treatment with olaparib resulted in a 9% improvement in 3-year invasive disease-free survival. In individuals with *BRCA*-mutated metastatic castration-resistant prostate cancer, a single-arm clinical trial of rucaparib demonstrated a benefit on a surrogate outcome of objective response rate and evaluation of its effects on progression-free survival is pending completion of the ongoing randomized, standard care-controlled confirmatory TRITON3 trial (NCT02975934). Rates of overall Grade 3 or 4 adverse events ranged from 25.5% to 63.2% across PARP inhibitor drugs. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

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

National Comprehensive Cancer Network

Breast Cancer and Ovarian Cancer

Current NCCN (v.1.2022) guidelines on the genetic and familial high-risk assessment of breast and ovarian cancers include criteria for identifying individuals who should be referred for further risk assessment and separate criteria for genetic testing.⁷³ Patients who satisfy any of the testing criteria listed in CRIT-1 through CRIT-4 should undergo "further personalized risk assessment, genetic counseling, and often genetic testing and management." For these criteria, both invasive and in situ breast cancers were included. Maternal and paternal sides of the family should be considered independently for familial patterns of cancer. Testing of unaffected individuals should be considered "only when an appropriate affected family member is unavailable for testing."

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

Additionally, the NCCN Ovarian Cancer guidelines (v.3.2021) recommend tumor molecular testing prior to initiation of therapy for persistent/recurrent disease (OV-6) and describe in multiple algorithms that testing should include at least *BRCA1/2* and microsatellite instability or DNA mismatch repair, and evaluation of homologous recombination deficiency can be considered (OV-6, OV-7, OV-B Principles of Pathology, OV-C Principles of Systemic Therapy).⁷⁴

Pancreatic Adenocarcinoma

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

Prostate Cancer

The current NCCN guidelines for prostate cancer are version 1.2022.⁷⁶ The Principles of Genetics section (PROS-B) provides appropriate scenarios for germline genetic testing in individuals with a personal history of prostate cancer.

American Society of Clinical Oncology et al

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

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

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

In June 2021, the ASCO released a rapid recommendation guideline update amending the prior recommendation against PARP inhibitor use in the early disease setting on the basis of published data from the OlympiA phase 3 RCT.² The updated recommendation stated that "for patients with early-stage, HER2-negative breast cancer with high risk of recurrence and germline *BRCA1* or *BRCA2* pathogenic or likely pathogenic variants, one year of adjuvant olaparib should be offered after completion of (neo)adjuvant chemotherapy and local treatment, including radiation. For those who had surgery first, 1 year of adjuvant olaparib should be offered for patients with triple-negative breast cancer and tumor size >2 cm or any involved axillary nodes. For those with HR-positive disease, 1 year of adjuvant olaparib should be offered to those with at least four involved axillary lymph nodes. For patients who had neoadjuvant chemotherapy, 1 year of adjuvant olaparib should be offered to patients with triple-negative breast cancer and any residual cancer; for patients with HR-positive disease, 1 year of adjuvant olaparib should be offered to patients with residual disease and a clinical stage, pathologic stage, estrogen receptor, and tumor grade score (CPS+EG) ≥ 3 ."

Society of Gynecologic Oncology

In 2015, the Society of Gynecologic Oncology (SGO) published an evidence-based consensus statement on risk assessment for inherited gynecologic cancer.⁸¹ The statement included criteria for recommending genetic assessment (counseling with or without testing) to patients who may be genetically predisposed to breast or ovarian cancer. Overall, the SGO and the NCCN recommendations are very similar; the main differences are the exclusion of women with breast cancer onset at age 50 years or younger who have 1 or more first-, second-, or third-degree relatives with breast cancer at any age; women with breast cancer or history of breast cancer who have a first-, second-, or third-degree male relative with breast cancer; and men with a personal history of breast cancer. Additionally, SGO recommended genetic assessment for unaffected women who have a male relative with breast cancer. Moreover, SGO indicated that some patients who do not satisfy criteria may still benefit from genetic assessment (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.⁸² The following recommendation was based primarily on consensus and expert opinion (level C): "Genetic testing is recommended when the results of a detailed risk assessment that is performed as part of genetic counseling suggest the presence of an inherited cancer syndrome for which specific genes have been identified and when the results of testing are likely to influence medical management."

National Institute for Health and Care Excellence

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

U.S. Preventive Services Task Force

Current USPSTF recommendations (2019)⁸⁴ for genetic testing of *BRCA1* and *BRCA2* variants in women state:

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

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

Medicare National Coverage

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

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

Date	Action	Description
December 2020	New Policy	Genetic testing for a BRCA1 or BRCA2 variant is medically necessary for individuals who meet policy criteria: (1) cancer or a personal or family cancer history suggesting a risk of hereditary breast and ovarian cancer (HBOC) syndrome; (2) have other high-risk cancers (eg, cancers of the fallopian tube, pancreas, prostate); (3) HBOC Syndrome or other high-risk cancers considering systemic therapy options.
March 2021	Replace policy	Policy updated with editing/formatting changes; NCCN guideline for Prostate Cancer added to references. No change to policy statements.
March 2022	Replace policy	Policy updated with literature review through October 1, 2021; references added. Policy statement regarding genetic testing for systemic therapy options updated to include individuals with high-risk, early stage breast cancer. Other minor edits made to policy statements and policy guidelines to reflect current NCCN guidelines.

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