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

Policy # 00047
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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Risk-Reducing Mastectomy is addressed separately in medical policy 00141.

Note: Genetic Cancer Susceptibility Panels Using Next Generation Sequencing is addressed separately in medical policy 00382.

Note: Gene Variants (PALB2, CHEK2 and ATM) Associated With Breast Cancer in Individuals at High Breast Cancer Risk is addressed separately in medical policy 00504.

Note: Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Breast Cancer is addressed separately in medical policy 00731.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Patients with Cancer or with a Personal History of Cancer

Based on review of available data, the Company may consider genetic testing for *BRCA1* and *BRCA2* variants in cancer-affected individuals to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for genetic testing for *BRCA1* and *BRCA2* variants in cancer-affected individuals will be considered when ANY of the following criteria are met:

- Individuals with any blood relative with a known pathogenic/likely pathogenic variant in a *BRCA1* or *BRCA2* gene; OR
- Individuals meeting the criteria below but with previous limited testing (e.g., single gene and/or absent deletion duplication analysis); OR
- Personal history of breast cancer and ONE OR MORE of the following:
    - Diagnosed at age ≤45 years;
    - Diagnosed at age 46 to 50 years with:
        - Multiple primary breast cancers (synchronous or metachronous);
        - ≥1 close relative with breast, ovarian, pancreatic, or prostate cancer at any age (see Policy Guidelines section);
        - An unknown or limited family history;
    - Diagnosed at age ≥ 51 years: ≥1 close blood relative (see Policy Guidelines section) with ANY:
        - ❖ Breast cancer diagnosed ≤50 years; OR
        - ❖ Ovarian/fallopian tube/primary peritoneal cancer; OR
        - ❖ Male breast cancer; OR
        - ❖ Metastatic or intraductal/cribriform histology prostate cancer, or high-risk group or very-high-risk group (see Policy Guidelines section) prostate cancer; OR
        - ❖ Pancreatic cancer; OR
        - ≥2 close blood relatives with either breast or prostate cancer (any grade) at any age (see Policy Guidelines section); OR
        - ≥3 total diagnoses of breast cancer in patient and/or in close blood relative (see Policy Guidelines section);
    - Diagnosed at any age with:
        - Triple-negative breast cancer
    - Ashkenazi Jewish ancestry;

OR

- Personal history of epithelial ovarian/fallopian tube/primary peritoneal cancer at any age
- Personal history of male breast cancer at any age

- Personal history of exocrine pancreatic cancer at any age
- Personal history of metastatic or intraductal/cribriform histology prostate cancer, 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/fallopian tube/primary peritoneal cancer, pancreatic cancer, or metastatic or intraductal/cribriform histology prostate cancer at any age, or breast cancer ≤50 years; OR
    - ≥2 close blood relatives with breast or prostate cancer (any grade) at any age; OR
    - Ashkenazi Jewish ancestry;

OR

- Personal history of cancer and a *BRCA1* or *BRCA2* pathogenic or likely pathogenic variant identified on tumor genomic testing that has clinical implications if also identified in the germline, variant analysis; OR
- Personal history of cancer and to aid in systemic therapy decision-making for PARP-inhibitors for advanced ovarian cancer, metastatic prostate cancer, and metastatic pancreatic cancer and platinum therapy for metastatic prostate cancer and metastatic pancreatic cancer.

Patients without Cancer or Other Personal History of Cancer (see Policy Guidelines)
Based on review of available data, the Company may consider genetic testing for BRCA1 and BRCA2 variants in cancer-unaffected individuals to be **eligible for coverage.****

Patient Selection Criteria
Coverage eligibility for genetic testing for BRCA1 and BRCA2 variants in cancer-unaffected individuals will be considered when ANY of the following criteria are met:

- 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 histology 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; OR

- 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 (e.g., PennII Risk Model) and has received comprehensive genetic counseling that included at minimum detailed kindred analysis, risk assessment for potentially harmful BRCA1/2 variants, patient education, discussion of the benefits and harms of testing, interpretation of results, and discussion of management options, when comprehensive genetic counseling resulted in a recommendation for BRCA genetic testing.

Note: 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).

When Services Are Considered Not Medically Necessary

Repeated germline BRCA 1 and 2 genetic testing is considered to be **not medically necessary****, except as noted on page 1 under Patient Selection Criteria.

Note: If BRCA testing done before August 2006 was negative, repeated testing for large deletions and rearrangements in BRCA 1 and 2 may be warranted.

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers genetic testing for *BRCA*1 and *BRCA2* variants in cancer-affected individuals or of cancer-unaffected individuals with a family history of cancer when criteria above are not met to be **investigational**.*

Based on review of available data, the Company considers genetic testing in minors for *BRCA1* and *BRCA2* variants to be **investigational.***

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

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When Services Are Not Covered

The Company does not consider *BRCA* gene testing to be eligible for coverage if testing is performed primarily for the medical management of persons **not covered**** by Blue Cross and Blue Shield of Louisiana or HMO Louisiana, Inc.

Policy Guidelines

Genetic testing for *BRCA1* and *BRCA2* variants in breast cancer-affected individuals who are considering systemic therapy is addressed separately in medical policy 00731.

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

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

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

Close Relatives

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

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

- 3rd-degree relatives are great-grandparents, great-aunts, great-uncles, great-grandchildren, and first cousins.

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

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

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

Recommended Testing Strategies
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:
    - Non-Ashkenazi Jewish descent
        - 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 *BRCA*1 or *BRCA2* variants.
- Ashkenazi Jewish descent
    - In patients of known Ashkenazi Jewish descent, 1 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 When Services May Be Eligible for Coverage section for Patient Selection 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.

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 (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.

Background/Overview

Hereditary Breast and Ovarian Cancer (HBOC) 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 medical policy, BCBSLA 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. 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*).

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

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 medical policy 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. 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.

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 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]

[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/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

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.

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

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Summary of Evidence

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

For individuals who have other high-risk cancers (eg, cancers of the fallopian tube, pancreas, prostate) who receive genetic testing for a *BRCA1* or *BRCA2* variant, the evidence includes studies of variant prevalence and cancer risk. Relevant outcomes are OS, disease-specific survival, test validity, and 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 and ovarian cancer 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 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 an improvement in the net health outcome.

Supplemental Information

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

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.

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. Patients who satisfy any of the testing criteria 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).

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."

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

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. 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
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). 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) 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.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 2.

Table 2. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date (status if beyond Completion Date)
Ongoing			
NCT02225015	Cancer Prevention in Women With a BRCA Mutation	300	Jun 2019 (unknown)
NCT04090567	Overcoming PARP Inhibitor Resistance in BRCA Germline Mutation Positive Advanced Breast Cancer	60	June 2021 (recruiting)
NCT02163694[a]	A Phase 3 Randomized, Placebo-Controlled Trial of Carboplatin and Paclitaxel With or Without the PARP Inhibitor Veliparib (ABT-888) in HER2 Negative Metastatic or Locally Advanced Unresectable BRCA-Associated Breast Cancer	500	Nov 2021

NCT02975934[a]	TRITON3: A Multicenter, Randomized, Open Label Phase 3 Study of Rucaparib Versus Physician's Choice of Therapy for Patients With Metastatic Castration Resistant Prostate Cancer Associated With Homologous Recombination Deficiency	400	Apr 2022 (recruiting)
NCT04009148	Cascade Testing in Families With Newly Diagnosed Hereditary Breast and Ovarian Cancer Syndrome	300	Mar 2023
NCT03246841	Investigation of Tumour Spectrum, Penetrance and Clinical Utility of Germline Mutations in New Breast and Ovarian Cancer Susceptibility Genes (TUMOSPEC)	500	Dec 2023
NCT02855944[a]	ARIEL4 (Assessment of Rucaparib In Ovarian CancEr TriaL): A Phase 3 Multicenter, Randomized Study of Rucaparib Versus Chemotherapy in Patients With Relapsed, BRCA Mutant, High Grade Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer	345	Jun 2024
NCT02321228	Early Salpingectomy (Tubectomy) With Delayed Oophorectomy in BRCA1/2 Gene Mutation Carriers (TUBA)	510	Jan 2035
NCT03740165[a]	A Randomized Phase 3, Double-Blind Study of Chemotherapy With or Without Pembrolizumab Followed by Maintenance With Olaparib or Placebo for the First-Line Treatment of BRCA Non-mutated Advanced Epithelial Ovarian Cancer (EOC) (KEYLYNK-001/ENGOT-ov43)	1284	May 2025
NCT02032823[a]	A Randomised, Double-blind, Parallel Group, Placebo-controlled Multi-centre Phase III Study to Assess the Efficacy and Safety of Olaparib Versus Placebo as Adjuvant Treatment in Patients With gBRCA1/2 Mutations and High Risk HER2 Negative Primary Breast Cancer Who Have Completed Definitive Local Treatment and Neoadjuvant or Adjuvant Chemotherapy (OlympiA)	1836	Nov 2028

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

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Policy History

Original Effective Date: 05/13/2003
Current Effective Date: 04/11/2022

04/25/2003	Medical Policy Committee review
05/12/2003	Managed Care Advisory Council approval
05/07/2004	Medical Director review
05/18/2004	Medical Policy Committee review. Format revision. No substance changes to policy.
06/28/2004	Managed Care Advisory Council approval
04/05/2005	Medical Director review

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

Policy # 00047
Original Effective Date: 05/13/2003
Current Effective Date: 04/11/2022

04/19/2005	Medical Policy Committee review. Investigational statements added to address: BRCA testing for unaffected individuals without family history or early age diagnosis as well as the use of BRCA testing in minors.
05/23/2005	Managed Care Advisory Council approval
06/07/2006	Medical Director review
06/21/2006	Medical Policy Committee approval. Format changes, FDA/Governmental, Rational/Source updated in response to literature review. Coverage eligibility unchanged.
05/02/2007	Medical Director review
05/23/2007	Medical Policy Committee approval
05/07/2008	Medical Director review
05/21/2008	Medical Policy Committee approval. Title changed. No change to coverage eligibility.
07/02/2009	Medical Director review
07/22/2009	Medical Policy Committee approval. No change to coverage eligibility.
07/01/2010	Medical Policy Committee approval
07/21/2010	Medical Policy Implementation Committee approval. Two statements were added to the coverage section: one to indicate testing for genomic rearrangements may be considered to be eligible with criteria and a second that testing for CHEK2 mutations is investigational. Fallopian tube cancer and primary peritoneal cancer added to the coverage statements as additional cancers to be assessed in determining family history to assess risk.
07/07/2011	Medical Policy Committee review
07/20/2011	Medical Policy Implementation Coverage eligibility unchanged.
04/12/2012	Medical Policy Committee review
04/25/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
09/06/2012	Medical Policy Committee review
09/19/2012	Medical Policy Implementation Committee approval. Replaced the Patient Selection Criteria for both Cancer-affected Individuals and Unaffected Adults with criteria from the 2012 NCCN Guidelines. Added a *Note* following the Patient Selection Criteria for clarification.
11/01/2012	Medical Policy Committee review

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

Policy # 00047
Original Effective Date: 05/13/2003
Current Effective Date: 04/11/2022

11/28/2012	Medical Policy Implementation Committee approval. Removed "and either (1) there are 3 or more family members (1 lineage) affected with breast or ovarian or fallopian tube or primary peritoneal cancer or (2) who have a risk of a BRCA mutation of at least 10%" from that last eligible for coverage statement on testing for genomic rearrangements of the BRCA1 and BRCA 2 genes.
03/04/2013	Coding updated
04/04/2013	Medical Policy Committee review
04/24/2013	Medical Policy Implementation Committee approval. Criteria revised.
06/05/2014	Medical Policy Committee review
06/18/2014	Medical Policy Implementation Committee approval. Policy coverage statement rewritten for clarity and policy was updated with current NCCN guidelines. Added a 4th criteria bullet for patients without cancer regarding BRCA testing. "Including those with a family history of pancreatic cancer" added to investigational statement.
06/04/2015	Medical Policy Committee review
06/17/2015	Medical Policy Committee approval. Title changed. No change to coverage eligibility.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
01/01/2016	Coding update
06/02/2016	Medical Policy Committee review
06/20/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
06/01/2017	Medical Policy Committee review
06/21/2017	Medical Policy Implementation Committee approval. Removed *CHEK2* statement and added reference to 00504 which addresses *CHEK2, PALB* and A*TM* testing.
06/07/2018	Medical Policy Committee review
06/20/2018	Medical Policy Implementation Committee approval. Replaced "mutation(s)" with "variant(s)" throughout the policy. Created a "When Services Are Eligible for Coverage" section for the first coverage statement, since it stands alone with no criteria. Changed the last three criteria bullets in the "Patients with Cancer" section to as follows:

- Personal history of pancreatic cancer or prostate cancer[c] at any age AND ≥1 1st-, 2nd-, or 3rd-degree relatives[a] with either of the following.
  - Breast cancer ≤50; or
  - Ovarian/fallopian tube/primary peritoneal cancer at any age.
- Personal history of pancreatic cancer or prostate cancer[b] at any age AND ≥2 1st-, 2nd-, or 3rd-degree relatives[a] with breast, pancreatic or prostate cancer[b] at any age.
- For pancreatic cancer, if Ashkenazi Jewish ancestry no additional affected relative is needed.

Added footnotes (a-d) to the end of the "When Services May Be Eligible for Coverage" section.

01/10/2019 Medical Policy Committee review

01/23/2019 Medical Policy Implementation Committee approval. Changed title from "Genetic Testing for Hereditary Breast and/or Ovarian Cancer" to "Genetic Testing for BRCA1 or BRCA2 for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers". Removed the "When Services Are Eligible for Coverage" section. Coverage section with criteria on Patients with Cancer revised. Added a *Note* after the coverage criteria for Patients without Cancer. After the coverage criteria, replaced the explanation of familial assessment of 1st, 2nd, and 3rd degree relatives with verbiage defining close relatives from NCCN Guidelines. Added a Not Medically Necessary section. Changed investigational statement for when criteria are not met.

03/07/2019 Medical Policy Committee review

03/20/2019 Medical Policy Implementation Committee approval. Changed "ovarian carcinoma" to "ovarian/fallopian tube/primary peritoneal cancer" throughout the coverage section to be consistent with the NCCN guidelines Genetic/Familial High-Risk Assessment: Breast and Ovarian Version 3.2019 that footnotes, "Ovarian carcinoma includes fallopian tube and primary peritoneal cancers."

06/17/2019 Coding update

09/09/2019 Coding update

03/05/2020 Medical Policy Committee review

03/11/2020 Medical Policy Implementation Committee approval. The definition of two breast cancer primaries was added as a footnote [a] from NCCN Guidelines for genetic

	testing for *BRCA1* and *BRCA2* variants in cancer-affected individuals for two criteria bullets. Removed the last criterion from genetic testing for BRCA1 and BRCA2 variants in unaffected individuals and replaced it with information from the U.S. Preventative Services Task Force regarding individuals with a family history of breast, ovarian, tubal, or peritoneal cancer or an ancestry associated with BRCA 1/ 2 gene mutations. Four familial risk assessment tools tables added at the end of the When Services May Be Eligible for Coverage section.
04/02/2020	Medical Policy Committee review
04/08/2020	Medical Policy Implementation Committee approval. Replaced 3rd criteria bullet for Patients without Cancer with information regarding individuals with a family history. Added tables for the Ontario Family History Assessment Tool, the Manchester Scoring System, the Referral Screening Tool, and the Pedigree Assessment Tool to the end of the eligible for coverage section.
06/09/2020	Coding update
08/17/2020	Coding update
03/04/2021	Medical Policy Committee review
03/10/2021	Medical Policy Implementation Committee approval. Revised coverage section and Policy Guidelines.
09/30/2021	Coding update
03/03/2022	Medical Policy Committee review
03/09/2022	Medical Policy Implementation Committee approval. Title changed from "Genetic Testing for BRCA1 or BRCA2 for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers" to "Germline Genetic Testing for BRCA1 or BRCA2 for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers". Revised the "When Services May Be Eligible for Coverage" section.

Next Scheduled Review Date: 03/2023

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2021 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of

descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	0102U, 0103U, 0129U, 0138U, 81162, 81163, 81164, 81165, 81166, 81167, 81212, 81215, 81216, 81217, 81432, 81433 Delete code effective 4/1/2022: 0172U
HCPCS	No codes
ICD-10 Diagnosis	C50.011-C50.029, C50.111-C50.129, C50.211-C50.229, C50.311-C50.329, C50.411-C50.429, C50.511-C50.529, C50.611-C50.629, C50.811-C50.829, C50.911-C50.929, C56.1-C56.9, C79.60-C79.62, C79.81, D05.00-D05.02, D50.10-D50.12, D05.80-D05.82, D05.90-D05.92, D07.30-D07.39, Z80.3, Z80.41, Z80.8-Z80.9, Z85.3, Z85.43 Add code eff 10/1/2021: C79.63

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

Policy # 00047
Original Effective Date: 05/13/2003
Current Effective Date: 04/11/2022

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and 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 that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.