Genetic Testing for Breast and Ovarian Cancer

Description of Procedure or Service

Hereditary breast and ovarian cancer (HBOC) syndrome describes the familial cancer syndromes that are related to mutations in the BRCA genes (BRCA1 located on chromosome 17q21 and BRCA2 located on chromosome 13q12-13). Families with HBOC syndrome have an increased susceptibility to breast cancer occurring at a young age, bilateral breast cancer, male breast cancer, ovarian cancer at any age, cancer of the fallopian tube, and primary peritoneal cancer as well as other cancers, such as prostate cancer, pancreatic cancer, gastrointestinal cancers, melanoma, and laryngeal cancer.

Several genetic syndromes with an autosomal dominant pattern of inheritance that feature breast cancer have been identified. Of these, hereditary breast and ovarian cancer (HBOC) and some cases of hereditary site-specific breast cancer have in common causative mutations in BRCA 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, and 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, 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 policy, both will be referred to collectively as hereditary breast and/or ovarian cancer.

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

Related Policies:
Genetic Cancer Susceptibility Panels Using Next Generation Sequencing

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.
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BCBSNC will provide coverage for Genetic Testing for Breast and Ovarian Cancer when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

Members must have benefits for the anticipated surgery and meet the guidelines for the testing to be covered.

When Genetic Testing for Breast and Ovarian Cancer is covered

Patients with Cancer
Genetic testing for BRCA1 and BRCA2 mutations in cancer-affected individuals may be medically necessary under any of the following circumstances:

1. Individual from a family with a known BRCA1 or BRCA2 variant
2. Personal history of breast cancer and ≥1 of the following:
   • Diagnosed age ≤45 years
   • 2 primary breast cancers when 1st breast cancer diagnosis occurred age ≤50 years
   • Diagnosed age ≤50 years AND:
     o One or more ≥1 1st-, 2nd-, or 3rd-degree relative with breast cancer at any age, pancreatic cancer or prostate cancer, or
     o Unknown or limited family history
   • Diagnosed age ≤60 years with a triple negative (ER–, PR–, HER2–) breast cancer
   • Diagnosed any age AND ≥1 1st-, 2nd-, or 3rd-degree relative with breast cancer diagnosed ≤50 years
   • Diagnosed any age AND ≥2 1st-, 2nd-, or 3rd-degree relatives with breast cancer at any age
   • Diagnosed any age AND ≥1 1st-, 2nd-, or 3rd-degree relative with epithelial ovarian/fallopian tube/primary peritoneal cancer
   • Diagnosed any age AND ≥2 1st-, 2nd-, or 3rd-degree relatives with pancreatic cancer or prostate cancer at any age
   • 1st-, 2nd-, or 3rd-degree male relative with breast cancer
   • Ethnicity associated with deleterious founder mutations, eg, Ashkenazi Jewish descent
3. Personal history of epithelial ovarian/fallopian tube/primary peritoneal cancer
4. Personal history of male breast cancer
5. Personal history of pancreatic cancer or prostate cancer at any age AND 1 or more 1st-, 2nd-, or 3rd-degree relatives with either of the following: For pancreatic cancer, if Ashkenazi Jewish ancestry, additional affected relatives are not needed.
   • Breast cancer ≤50
   • Ovarian/fallopian tube or primary peritoneal cancer at any age
   • Personal history of pancreatic or prostate cancer at any age AND 2 or more 1st-, 2nd-, or 3rd-degree relatives with breast, pancreatic or prostate cancer at any age. For pancreatic cancer, if Ashkenazi Jewish ancestry, no additional affected relative is needed.

Patients without cancer (see Policy Guidelines: Testing unaffected individuals)
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Genetic testing for \textit{BRCA1} and \textit{BRCA2} variants of cancer-unaffected individuals may be considered \textbf{medically necessary} under any of the following circumstances:

1. Individual from a family with a known \textit{BRCA1}/\textit{BRCA2} mutation
2. 1st- or 2nd-degree blood relative meeting any criterion listed above for Patients with Cancer
3. 3rd-degree blood relative with breast cancer and/or ovarian/fallopian tube/primary peritoneal cancer AND \geq 2 1st-, 2nd-, or 3rd-degree relatives with breast cancer (\geq 1 at age \leq 50 years) and/or ovarian/fallopian tube/primary peritoneal cancer

For the purpose of familial assessment, 1st-, 2nd-, and 3rd-degree relatives are blood 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.

For the purpose of familial assessment, prostate cancer is defined as Gleason score \geq 7.

Testing for Ashkenazi Jewish or other founder mutation(s) should be performed first (see Policy Guidelines: High risk ethnic groups).

**Note:** “Generally, genetic testing for a particular disease should be performed once per lifetime; however, there are rare instances in which testing may be performed more than once in a lifetime (eg, previous testing methodology is inaccurate or a new discovery has added significant relevant mutations for a disease).”

\textbf{When Genetic Testing for Breast and Ovarian Cancer is not covered}

Unless they meet the criteria above, genetic testing either for those affected by breast, ovarian, fallopian tube, or primary peritoneal cancer or for unaffected individuals, including those with a family history of pancreatic cancer, is considered \textbf{investigational}.

Genetic testing in minors for \textit{BRCA1} and \textit{BRCA2} variants is considered \textbf{investigational}.

\textbf{Policy Guidelines}

The Policy Statements above are based on current guidelines from the National Comprehensive Cancer Network (NCCN).

NCCN guidelines for genetic counseling have counseling services divided into pre-test and post-test categories. The pre-test counseling requirements include:
- Collection of a comprehensive family history (close blood relatives include first, second and third degree relatives on each side of the family);
- Evaluation of a patient’s cancer risk;
- Generation of a differential diagnosis and education of the patient on inheritance patterns, penetrance, variable expressivity and the possibility of genetic heterogeneity.

Post-test counseling includes:
- Providing results along with their significance and impact and recommended medical management options;
- Informing and testing at-risk family members;
- Providing available resources such as disease specific support groups and research studies.
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Current U.S. Preventive Services Task Force (USPSTF) guidelines recommend screening women with any family and/or personal history of breast, ovarian, tubal, or peritoneal cancer. Women with positive screening results should receive genetic counseling and, if indicated after counseling, BRCA testing. (Grade 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)
- FHS-7

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

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

**High-risk ethnic groups:** Testing in 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 the 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 mutation be found in an affected family member(s), DNA from the unaffected family member can be tested specifically for the same mutation of the affected family member without having to sequence the entire gene. Interpreting the 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 mutation, but leads to difficulties in interpreting negative test results (uninformative negative) or mutations 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. This is 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 felt to be sufficient justification for BRCA testing.

For individuals who have cancer or a personal or family cancer history and meet criteria suggesting a risk of hereditary breast and ovarian cancer syndrome who receive genetic testing for a BRCA1 or BRCA2 variant, the evidence includes a TEC Assessment and studies of variant prevalence and cancer...
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risk. Relevant outcomes are overall survival, disease-specific survival, test accuracy and 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 overall survival. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable codes: 81162, 81211, 81212, 81213, 81214, 81215, 81216, 81217, G0452

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

MEDLINE database search from 1/97 through 7/97

Consultant Review, August 1997

Plan Medical Director Review, August 1997


Medical Policy Advisory Group 12/2/1999


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Senior Medical Director Review - 2/2009


Senior Medical Director – 9/2010


Medical Director 1/2012


Medical Director 4/2013


Senior Medical Director – 1/2014


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Senior Medical Director – 4/2014


Specialty Matched Consultant Advisory Panel 8/2017


Specialty Matched Consultant Advisory Panel 8/2018

Policy Implementation/Update Information

<table>
<thead>
<tr>
<th>Date</th>
<th>Description</th>
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<tbody>
<tr>
<td>8/97</td>
<td>Original policy: Investigational</td>
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<tr>
<td>6/98</td>
<td>Reviewed: changed from investigational to medically necessary in cases where the member is considering prophylactic surgery and will be using the results of genetic testing as a decision factor. The member must meet the criteria for genetic testing. Recommended by MPAG.</td>
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<tr>
<td>6/99</td>
<td>Reformatted, Description of Procedure or Service changed, Medical Term Definitions added.</td>
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12/99 Reaffirmed, Medical Policy Advisory Group

3/01 Codes 83890-83906, 83912 added to policy.


4/04 Individual CPT codes listed for CPT code ranges 83890-83906 under Billing/Coding section.

8/12/04 Added HCPCS codes S3818, S3819, S3820, S3822, S3823 to Billing/Coding section.

9/23/04 Revised Description of Procedure or Service section. Revised When Covered section to include those with early onset breast cancer, members of high-risk populations without an affected family member, and included ovarian cancer in #1. Removed from When Not Covered section, “unaffected individuals from potentially high risk populations (e.g. Ashkenazi Jewish descent)".


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3/16/09 Reviewed with Senior Medical Director 2/19/09. Reworded the "When Covered" section and added three additional indications. "A. Genetic testing of cancer-affected individuals may be medically necessary under any of the following circumstances: 1.) Women who are affected with breast or ovarian cancer and are from families with a high risk of BRCA1 or BRCA2 mutation as defined in the Policy Guidelines, OR; 2.) Women affected with early onset breast or ovarian cancer, or with breast or ovarian cancer and multiple primary cancers, or with bilateral breast or ovarian cancer, but who do not have a known family history of breast or ovarian cancer, OR; 3.) Women affected with both breast and ovarian cancer, OR; 4.) Men affected with breast cancer at any age, OR; 5.) Those affected with breast or ovarian cancer and who are from an ethnic background, e.g., Ashkenazi Jewish descent, associated with deleterious founder mutations. B. Genetic testing of unaffected adults may be considered medically necessary under any of the following circumstances: 1.) Unaffected individuals (male or female) from families with a known BRCA1 or BRCA2 mutation, OR; 2.) Unaffected individuals from families with a high risk of BRCA1 or BRCA2 mutation based on a family history (See Policy Guidelines), where it is not possible to test an affected family member for a mutation, OR; 3.) Unaffected individuals in populations at risk for specific founder mutations due to ethnic background, e.g., Ashkenazi Jewish descent, with one or more relatives with breast or ovarian cancer at any age." Added to the "Policy Guidelines" section: "The American College of Medical Genetics recommends that "early onset" breast or ovarian cancer be considered cancers that occur in patients age 45 or younger." Policy returned to active review status. References added. (btw)

10/12/09 Specialty Matched Consultant Advisory Panel review 8/28/09. Description revised. No change to policy statement. Reformatted wording in the "When Not Covered"
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section, no change to intent. Added information under "Policy Guidelines" to indicate; "1. The US Preventative Services Task Force (USPSTF) recommends the following in identifying families with a high risk for mutation in the BRCA1 and BRCA2 gene, both the maternal and paternal family histories are important and each lineage must be considered separately. For non-Ashkenazi Jewish women, high risk includes the following: a. Three or more first or second degree relative with breast cancer regardless of age at diagnosis, or b. Two first-degree relatives with breast cancer, one of whom was diagnosed at age 50 years or younger, or c. Combination of both breast and ovarian cancer among first- and second degree relatives, or d. First degree relative with bilateral breast cancer, or e. A combination of two or more first or second degree relatives with ovarian cancer regardless of age at diagnosis, or f. A first or second degree relative with both breast and ovarian cancer at any age, or g. A history of breast cancer in a male relative." and "6. The American Society of Clinical Oncology (ASCO) recommends that cancer predisposition testing be offered when 1) the person has a strong family history of cancer or very early age of onset of disease, 2) the test can be adequately interpreted, and 3) the results will influence the medical management of the patient or family member." References added. (btw)

6/22/10 Policy Number(s) removed (amw)

10/26/10 Added the following information to the “Description” section; “CHEK2 (cell cycle checkpoint kinase2) is also involved with DNA repair and human cancer predisposition like BRCA1 and BRCA2. CHEK2 is normally activated in response to DNA double-stranded breaks. CHEK2 regulates the function of BRCA1 protein in DNA repair and also exerts critical roles in cell cycle control and apoptosis. The CHEK2 mutation, 1100delC in exon 10 has been associated with familial breast cancers.” Added “fallopian tube and primary peritoneal cancer” as additional BRCA-associated malignancies to assess when obtaining the family history throughout policy as appropriate. Reformatted the “When Covered” and “When Not Covered” section. Added “C. Testing for genomic rearrangements of the BRCA1 and BRCA2 genes may be considered medically necessary when: criteria for BRCA testing are met, and testing for point mutations is negative, and there are 3 or more family members (one lineage) affected with breast, ovarian, fallopian tube, or primary peritoneal cancer, or there is a risk of a BRCA mutation of at least 10%. (See Policy Guidelines)” to the “When Covered” section. Added “C. Testing for CHEK2 genetic abnormalities (mutations, deletions, etc.) is considered investigational in patients with breast cancer regardless of the family history.” To the “When Not Covered” section. Added the following to the “Policy Guidelines” section; “For the purposes of this policy, an individual with a history of breast, ovarian, fallopian tube, or primary peritoneal cancer is considered to be from a family with a high risk of BRCA1 or BRCA2 mutation” when one or more of the high risk criteria below are met.” “Please Note: The US Preventative Services Task Force (USPSTF) recommendations for identifying families at high risk for mutation in the BRCA1 and BRCA2 gene applies to women without breast, ovarian, fallopian tube, or primary peritoneal cancer. In situations where the woman has breast, ovarian, fallopian tube, or primary peritoneal cancer, the family is considered at high risk for mutation if the overall family history (one lineage) including the affected individual meets the criteria below.” “7. Comprehensive mutation analysis currently includes sequencing the coding regions and intron/exon splice sites as well as tests to detect common large deletions and rearrangements that can be missed with sequence analysis alone. However, current routine laboratory testing for genomic rearrangement is more limited than the criteria noted in the policy statement; automatic testing is specified for those with a risk of BRCA mutation of at least 30%. In addition, prior to August 2006, testing for large deletions and rearrangements was not performed, thus some patients with familial breast cancer who had negative BRCA testing prior to this time may consider repeat testing for the rearrangements.” “8. Based on data available at this time, there is no compelling evidence to justify routine clinical testing for CHECK2 to guide the
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management of families affected with breast cancer.” Reviewed with Senior Medical Director 9/27/10. References added. (btw)

1/24/12 Specialty Matched Consultant Advisory Panel review August 29, 2011. No change to policy statement. “Policy Guidelines” updated to include NCCN guidelines. Added the following new 2012 CPT codes to the “Billing/Coding” section: 81211, 81212, 81213, 81214, 81215, 81216, and 81217. (btw)

3/30/12 Deleted HCPCS codes S3818, S3819, S3820, S3822, S3823 from Billing/Coding Section. (btw)

9/4/12 Specialty Matched Consultant Advisory Panel review 8/15/2012. No change to policy intent. Reference added. (btw)

1/15/13 Removed the following deleted codes from the Billing/Coding section; 83890, 83891, 83892, 83893, 83894, 83896, 83897, 83898, 83901, 83902, 83903, 83904, 83905, 83906, 83912. Added HCPCS code G0452 to Billing/Coding section. Description section updated. Under the When Covered section, A#2, removed “with both breast cancer and either” from statement. A#3 reworded from “Women who do not have a known family history of breast, epithelial ovarian, fallopian tube, or primary peritoneal cancer…” Changed A#3d. from “epithelial ovarian/fallopian tube/primary peritoneal cancer at any age,” to “two or more close blood relatives with pancreatic cancer any age” Removed “and either” from C#2. Removed C#3 “(a) there are 3 or more family members (one lineage) affected with breast, ovarian, fallopian tube, primary peritoneal cancer, or (b) there is a risk of a BRCA mutation of at least 10%. (See Policy Guidelines)” Updated Policy Guidelines. Reference added. Medical Director review 12/18/2012. (btw)

4/16/13 Revised Policy Guidelines in regards to NCCN testing criteria; From “7. Family history only: • Close blood relative meeting any of the above criteria in #2 above” to “7. Family history only: • Close blood relative meeting any of the criteria in #1-6 above.” (btw)

9/10/13 Removed “epithelial ovarian, fallopian tube, or primary peritoneal” from A.5. in the When Covered section. Updated Policy Guidelines section. Updated NCCN testing criteria based on the current 2013 version. Specialty Matched Consultant Advisory Panel review 8/21/2013. No change to policy intent. Reference added. (btw)

1/28/14 Minor revisions to Description and Policy Guidelines section. Senior Medical Director review 1/13/14. Reference added. (btw)

5/13/14 Policy statement revised to reflect the most recent NCCN guidelines. Policy Guidelines section updated to reflect current U.S. Preventive Services Task Force (USPSTF) guidelines. No change to policy intent. Senior Medical Director review 4/18/2014. References added. (btw)

9/9/14 Specialty matched consultant advisory panel review 8/26/2014. No changes to policy statement. (lpr)

1/13/15 Reference added. Minor revisions to Policy Guidelines. No changes to policy intent. (lpr)

5/26/15 Added the following statement under “When Covered” section: Note: “Generally, genetic testing for a particular disease should be performed once per lifetime; however, there are rare instances in which testing may be performed more than once in a lifetime (eg,
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previous testing methodology is inaccurate or a new discovery has added significant relevant mutations for a disease.” No change to policy intent. (lpr)

7/1/15 Under “Policy Guidelines” section added a statement to include pre and post test counseling components per NCCN 2015 guidelines: pre-test counseling includes: Collection of a comprehensive family history (close blood relatives include first, second and third degree relatives on each side of the family); evaluation of a patient’s cancer risk; generation of a differential diagnosis and education of the patient on inheritance patterns, penetrance, variable expressivity and the possibility of genetic heterogeneity. Post-test counseling includes: providing results along with their significance and impact and recommended medical management options; informing and testing at-risk family members; providing available resources such as disease specific support groups and research studies. Also added “and/or personal history” to the statement “Current U.S. Preventive Services Task Force (USPSTF) guidelines recommend screening women with any family and/or personal history of breast, ovarian, tubal, or peritoneal cancer.” under Policy Guidelines. Sr. Medical Director review 6/2015. (lpr)

10/1/15 Specialty Matched Consultant Advisory Panel review 8/2015. References added. (lpr)

12/30/15 Added CPT code 81162 to the Billing/Coding section effective 1/1/2016. Reference added. (lpr)

9/30/16 Updated Description and Policy Guidelines sections. Reference added. Specialty Matched Consultant Advisory Panel review 8/31/2016. No change to policy statement. (lpr)

12/30/16 Reference added. No change to policy intent. (lpr)

9/15/17 Specialty Matched Consultant Advisory Panel review 8/30/2017. No change to policy statement. (lpr)

12/29/17 Updated Policy Guidelines section. “Mutations” changed to “Variants” throughout the policy. Under “When Covered” section: updated #2, bullet 3; and updated #5, all 3 bullets to reflect changes to NCCN recommendations. Reference added. (lpr)

9/28/18 Specialty Matched Consultant Advisory Panel review 8/2018. No change to policy statement. (lpr)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.