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Medical Policy Manual

Topic: Genetic Testing for Hereditary Breast and/or Ovarian Cancer

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Section: Genetic Testing

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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

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). Identification of patients with BRCA mutations may lead to enhanced screening and/or surveillance that could lead to improved outcomes.

BRCA1, BRCA2 Sequencing

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 causative mutations in BRCA genes in common. 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, 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 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, and research to date has not yet identified other moderate or high-penetrance gene mutations that account for disease in these families. BRCA gene mutations are inherited in an autosomal dominant fashion through either the maternal or paternal lineage (each lineage must be considered separately). 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.

CHEK2

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.

Definitions:

Close blood relatives include first-, second-, and third-degree relatives from the same lineage:

- *First-degree relatives*: parents, siblings, and children of an individual
- *Second-degree relatives*: grandparents, aunts, uncles, nieces, nephews, grandchildren, and half-siblings (siblings with one shared biological parent) of an individual
- *Third-degree relatives:* great-grandparents, great-aunts, great-uncles, great-grandchildren, and first-cousins

Limited family history: includes, but is not limited to, fewer than two first- or second-degree female relatives or female relatives not surviving beyond age 45 in either lineage

Ovarian cancer: for the purposes of this policy, fallopian tube and primary peritoneal cancers are included in the definition of ovarian cancer because ovarian/fallopian tube/primary peritoneal cancers are component tumors of Lynch syndrome

Triple negative breast cancer: a cancer negative for expression of estrogen and progesterone receptors, and for overexpression of HER2 receptors.

Two primary breast cancers: includes bilateral disease, or two or more clearly separate ipsilateral primary tumors.

Note:

The National Comprehensive Cancer Network (NCCN) Guidelines for Genetic/Familial High-Risk Assessment for breast and ovarian cancers includes two sets of criteria: [1]

- Criteria for Further Risk Evaluation

  The objective of these criteria is to identify individuals who are at risk of HBOC Syndrome and should be referred to a cancer genetics professional for further risk evaluation.

- Hereditary Breast and/or Ovarian Cancer Syndrome Testing Criteria

  The objective of these criteria is to identify individuals who should actually be tested for the BRCA mutations.

The following medical policy criteria are based on the NCCN *testing* criteria.

MEDICAL POLICY CRITERIA

In identifying families with a high risk of mutation in the BRCA1 or BRCA 2 gene, including testing for large genomic rearrangements of both BRCA1 AND BRCA2 (BART), both maternal and paternal family histories are important; however, each lineage must be considered separately.

I. Family with a known BRCA1/BRCA2 mutation: Genetic testing for BRCA1 and BRCA2 mutations, including testing for large genomic rearrangements of both BRCA1 AND BRCA2 (BART), may be considered **medically necessary** when the individual is from a family with a known BRCA1/BRCA2 mutation.

II. Personal history of certain cancers (specified in criteria IIA-D): When the family mutation status is unknown, genetic testing for BRCA1 and BRCA2 mutations, including testing for large genomic rearrangements of both BRCA1 AND BRCA2 (BART), may be considered **medically necessary** when any one or more of the following criteria (A-D) is met:

   A. There is a personal history of breast cancer *and* at least one of the following (1-11) is met:

      1. Breast cancer diagnosed at or before age 45

      2. Breast cancer diagnosed at or before age 50 *and* there is:

         a. At least one close blood relative* with breast cancer diagnosed at any age , and/*or*

         b. At least one close blood relative with ovarian* cancer diagnosed at any age

      3. Two primary breast cancers* with the first breast cancer diagnosed at or before age 50;

      4. Triple negative breast cancer* diagnosed at or before age 60

5. Breast cancer is diagnosed at or before age 50 *and* there is an unknown or limited family history*

6. Breast cancer is diagnosed at any age and there are at least two close blood relatives* with breast* cancer diagnosed at any age

7. Breast cancer is diagnosed at any age with at least one close blood relative with breast cancer diagnosed at or before age 50

8. Breast cancer is diagnosed at any age and there are at least one close blood relative* with ovarian* cancer diagnosed at any age

9. Breast cancer is diagnosed at any age with at least two close blood relatives* with pancreatic cancer or aggressive prostate cancer (Gleason score ≥7) at any age

10. There is a close male blood relative* with breast cancer

11. Breast cancer is diagnosed at any age and there is a personal history of ovarian* cancer

12. The provider documents in the clinical record that the member's ethnic background is associated with higher mutation frequency. Examples of such ethnic backgrounds include but are not limited to Ashkenazi Jewish, Norwegian, Dutch, Icelandic descent.

B. There is a personal history of ovarian* cancer

C. There is a personal history of *male* breast cancer

D. There is a personal history of pancreatic cancer or aggressive prostate cancer (Gleason score ≥7) diagnosed at any age *and* two or more close blood relatives* with breast and/or ovarian* and/or pancreatic cancer or aggressive prostate cancer diagnosed at any age.

III. Unknown patient mutation status and no personal history of certain cancers (specified in criteria II): When the family mutation status is unknown, genetic testing for BRCA1 and BRCA2 mutations, including testing for large genomic rearrangements of both BRCA1 AND BRCA2 (BART), may be considered **medically necessary** in patients when either (A) or (B) below is met:

A. There is a first- or second-degree blood relative* meeting any of the criteria in IIA - IID.

B. There is a third-degree blood relative* who meets both (1) and (2) below:

1. Has a history of breast cancer and/or ovarian* cancer *and*

2. Has at least two close blood relatives* with ovarian* cancer and/or breast cancer. *For those close blood relatives with breast cancer*, at least one must be diagnosed at or before age 50.

IV. Genetic testing for BRCA1 and BRCA2 mutations, including testing for large genomic rearrangements of both BRCA1 AND BRCA2 (BART), is considered **not medically necessary** when the criteria in I, II, or III above are not met.

V. Testing for CHEK2 genetic abnormalities (mutations, deletions, etc) is considered **investigational** in cancer-affected and unaffected patients with breast cancer, regardless of family history.

VI. Genetic testing in minors for BRCA1 and BRCA2 mutations, including testing for large genomic rearrangements of both BRCA1 AND BRCA2 (BART), is considered **not medically necessary**.

*See Definitions in the Description section.

POLICY GUIDELINES

As the majority of test results will be negative and uninformative in unaffected family members of potential BRCA mutation families, 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), the 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 or mutations of uncertain significance because the possibility of a causative BRCA mutation is not ruled out.

In patients with breast cancer, ovarian cancer, cancer of the fallopian tube, or primary peritoneal cancer who are from high-risk families without a known BRCA1 or BRCA2 gene and who are not from an ethnic group with known founder mutations, comprehensive BRCA mutation analysis should be performed.

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

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. 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 Medical Policy Criteria).

SCIENTIFIC EVIDENCE

The focus of the scientific evidence review is on the investigational indications only, and is related to the ability of test results to:

- Guide decisions in the clinical setting related to either treatment, management, or prevention, and
- Improve health outcomes as a result of those decisions.

CHEK2 Testing

A number of publications have described the association of cell cycle checkpoint kinase 2 (CHEK2) mutations with hereditary breast cancer. The prevalence of this finding varies greatly by geographic region, being most common in northern and eastern Europe. It has been detected in 4% of early breast cancer patients in the Netherlands, in 2.3% of such patients in Germany, but has been noted to be rare in these patients in Spain or Australia. In the US, this mutation is much less common than BRCA mutations and BRCA rearrangements. For example, in the study by Walsh[2] cited above, 14 (4.7%) of the 300 patients with a positive family history of breast cancer (4 affected relatives) who were negative by standard BRCA testing, were positive for CHECK2 mutations. The low frequency makes evaluation of risk and treatment implications less precise. In general, the risk of breast cancer associated with this mutation is less that that associated with either BRCA1 or BRCA2.

The impact of CHEK2 testing on net health outcome is uncertain as studies report inconsistent findings:

- In a systematic review and meta-analysis authors identified fifteen case-control studies, including 19,621 cases and 27,001 controls in their analysis.[3] Authors reported a significant association found between the CHEK2 I157T variant and increased risk of unselected breast cancer, and early-onset breast cancer. In addition, an even stronger significant association was found between the CHEK2 I157T C variant and increased risk of lobular type breast tumors. Authors concluded the CHEK2 I157T variant may be another important genetic mutation which increases risk of breast cancer, especially the lobular type. The quality of this review was limited; there was no clear rating system of the evidence.
- A meta-analysis by Weischer concluded that for familial breast cancer, the cumulative risk at age 70 years for CHEK2*1100delC mutation was 37% (confidence interval 26% to 56%).[4] This risk is lower than cumulative risk at age 70 of 57% for BRCA1 and 49% for BRCA2. In an accompanying editorial, Offit and Garber raise a number of questions about potential use of this assay.[5] In particular, they raise questions about the breast cancer risk estimates presented in the Weischer study; a number of the questions relate to the variable methods of ascertainment used in the studies in this meta-analysis. They also note that other mutations, such as CHEK2*S428F, are observed in other populations. The varying frequency is mentioned, with the mutation noted in 0.5 – 1.0% of the population in northern and eastern Europe compared with 0.2 – 0.3% in the US. Finally, they raise concerns about the implications of the low penetrance of this mutation. They concluded that on the basis of data available at this time, there is not compelling evidence to justify routine clinical testing for CHECK2 to guide the management of families affected with breast cancer.
- In a meta-analysis by Han and others, investigated the relationship of the CHEK2 I157T variant and the incidence of cancer.[6] In total, 26,336 cases and 44,219 controls from 18 case-control studies were used in the meta-analysis. Authors concluded that the CHEK2 I157T variant was an important cancer gene, which increases cancer risk, especially for breast and colorectal cancer.
- In a meta-analysis, the link between CHEK2 1100delC heterozygote and breast cancer risk was investigated.[7] A total of 29,154 cases and 37,064 controls from 25 case-control studies were identified in this meta-analysis. A significant association was found between CHEK2 1100delC

heterozygote and breast cancer risk. Authors concluded that the CHEK2 1100delC variant could be a potential factor for increased breast cancer risk in Caucasians; however, they suggested that more consideration is needed in order to apply it to allele screening or other clinical work.

- Myszka et al. compared 284 breast- and 113 ovarian cancer patients to 287 healthy Polish women and found that the cancer-affected individuals did not have a higher rate of *CHEK2* mutations.[8]
- Zhang et al. performed a systematic review of candidate-gene association studies of breast cancer risk, identifying more than 1000 published articles. Meta-analysis was performed for a total of 279 genetic variants in 128 genes that were identified by at least three different researchers. Significant associations with the risk of breast cancer were found for 29 variants in 20 genes. The association was strong for 10 variants in six genes, four of which were located in the *CHEK2* gene.[9]
- In their review, Peng et al. identified 87 meta-analyses and pooled analyses which examined the association of 145 candidate gene variants and breast cancer. They found significant association for 46 variants, with odds ratios (OR) ranging from 0.66 to 3.13. The further analysis of ORs (using the method of false-positive report probability) identified ten noteworthy associations, including CHEK2 (*1100delC).[10]

Clinical Practice Guidelines

- National Comprehensive Cancer Network Guidelines (NCCN)
    - The 2014 NCCN Guidelines for Genetic/Familial High-Risk Assessment for breast and ovarian cancer recommend BRCA testing in select individuals as noted in the Medical Policy Criteria above.[11]
    - The NCCN guideline recommends large genomic rearrangement (LGR) testing for all patients undergoing testing for BRCA1 and BRCA2 and considers BART testing as part of comprehensive BRCA testing.
    - According to NCCN guidelines, patients who meet criteria for genetic testing should be tested for mutations in *BRCA1* and *BRCA2*. In patients with a known familial *BRCA* mutation, targeted testing for the specific mutation is recommended. In patients with no known familial *BRCA* mutation, comprehensive testing, including full sequencing and testing for large genomic rearrangements, is recommended; if the affected individual is of Ashkenazi Jewish descent, testing for the three known founder mutations (185delAG and 5182insC in *BRCA1*; 6174delT in *BRCA2*) should be done first.
    - The guidelines do not include recommendations for genotyping low or moderate penetrance susceptibility genes, such as *CHEK2*. NCCN lists CHEK1 and CHEK2 as current genes available within new genetic testing panels. Limitations of panel testing noted in NCCN guidelines include "an unknown percentage of variants of unknown significance, uncertainty of level of risk associated with most of these genes, and lack of clear guidelines on risk management of carriers of some of these mutations."

- U.S. Preventive Services Task Force (USPSTF)[12]

    - The USPSTF recommends that women whose family history is associated with an increased risk for deleterious mutations in BRCA1 or BRCA2 genes be referred for genetic counseling and evaluation for BRCA testing. (Grade B recommendation)
    - The USPSTF recommends against routine referral for genetic counseling or routine BRCA testing for women whose family history is not associated with an increased risk

for deleterious mutations in BRCA1 or BRCA2 genes (Grade D recommendation).

- The American Society of Clinical Oncology (ASCO)[13]

  In 2003, ASCO recommended 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. A 2010 update of the ASCO policy statement recommended that "genetic tests with uncertain clinical utility, including genomic risk assessment, be administered in the context of clinical trials."[14] The *CHEK2*1100delC* variant was cited as a mutation with unproven clinical utility.

Summary

The evidence is sufficient to suggest that knowledge of BRCA1 and BRCA2 mutation status, including genomic rearrangements, may be effective in guiding healthcare decisions in individuals at increased risk of a mutation based on personal and/or family history, and that health outcomes may be improved as a result of those decisions. Therefore, testing high-risk individuals for *BRCA1* and *BRCA2* mutations, including BART, may be considered medically necessary.

The evidence addressing CHEK2 testing is uncertain. It has not been demonstrated that results of CHEK2 testing can effectively guide clinical decision-making or improve net health outcomes; therefore, testing for CHEK2 mutations is considered investigational.

REFERENCES

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CROSS REFERENCES

Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20

CODES	NUMBER	DESCRIPTION
CPT	81211	BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and common duplication/deletion variants in BRCA1 (ie, exon 13 del 3.835kb, exon 13 dup 6kb, exon 14-20 del 26kb, exon 22 del 510bp, exon 8-9 del 7.1kb)
	81212	BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; 185delAG, 5385insC, 6174delT variants
	81213	BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; uncommon duplication/deletion variants
	81214	BRCA1 (breast cancer 1) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and common duplication/deletion variants (ie, exon 13 del 3.835kb, exon 13 dup 6kb, exon 14-20 del 26kb, exon 22 del 510bp, exon 8-9 del 7.1kb)
	81215	BRCA1 (breast cancer 1) (eg, hereditary breast and ovarian cancer)

CODES	NUMBER	DESCRIPTION
		gene analysis; known familial variant
	81216	BRCA2 (breast cancer 2) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis
	81217	BRCA2 (breast cancer 2) (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant
HCPCS	None	