Medical Policy

Genetic Testing for CHEK2 Mutations for Breast Cancer

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Policy Number: 741
BCBSA Reference Number: 2.04.133
NCD/LCD: N/A

Related Policies
- Genetic Testing for Hereditary Breast and/or Ovarian Cancer Syndrome, #245
- Genetic Cancer Susceptibility Panels Using Next Generation Sequencing, #574
- Genetic Testing for PALB2 Mutations, #722

Policy

Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity
Medicare HMO BlueSM and Medicare PPO BlueSM Members

Genetic testing for CHEK2 mutations in patients with breast cancer or for cancer risk assessment in patients with or without a family history of breast cancer is considered INVESTIGATIONAL.

Prior Authorization Information
Pre-service approval is required for all inpatient services for all products.
See below for situations where prior authorization may be required or may not be required.
Yes indicates that prior authorization is required.
No indicates that prior authorization is not required.
N/A indicates that this service is primarily performed in an inpatient setting.

<table>
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<th>Outpatient</th>
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<td>Commercial PPO and Indemnity</td>
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<td>Medicare HMO BlueSM</td>
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CPT Codes / HCPCS Codes / ICD Codes
Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.
Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

CPT Codes
There are no specific CPT codes.

Description
Cancer predisposing genes can be categorized by the risk of developing a particular type of cancer if there is a pathogenic mutation identified in one of these genes. The risk of breast cancer, defined in terms of disease incidence, is relative to the general population and may be categorized as being of high, moderate or low penetrance. Cancer syndromes that are associated with highly penetrant genes have established clinical management guidelines for patients who have been identified as having a pathogenic mutation in one of these genes (eg, BRCA), and it has been established that increased surveillance and risk-reducing interventions lead to improved patient outcomes. However, for gene mutations that confer a moderate risk of developing cancer, clinical management guidelines are lacking, and it is unknown whether identifying mutations in these non-highly-penetrant genes will lead to improved patient outcomes or to overtreatment and harm.

Hereditary Breast Cancer
Breast cancer can be classified as sporadic, familial, or hereditary. Sporadic breast cancer accounts for 70% to 75% of cases and is thought to be due to nonhereditary causes. Familial breast cancer, in which there are more cases within a family than statistically expected, but with no specific pattern of inheritance, accounts for 15% to 25% of cases. Hereditary breast cancer accounts for 5% to 10% of cases and is characterized by well-known susceptibility genes with apparently autosomal dominant transmission. Mutations in the BRCA1/2 genes are responsible for up to half of the heritable mutations in breast cancer.

Mutations associated with breast cancer vary in their penetrance. Highly penetrant mutations in the BRCA1, BRCA2, TP53, and PTEN genes may be associated with a relative risk of breast cancer higher than 4 times the general population, with a lifetime absolute risk ranging from 40% to 85%.

Other mutations, including CHEK2, may be associated with moderate penetrance and a relative risk of breast cancer of 2 to 4. Absolute risks are more strongly influenced by other risk factors for breast cancer, including family history of breast cancer and age at menopause. In the case of a rare variant conferring a relative risk of 2 to 4, the corresponding absolute risks of breast cancer have been estimated to be approximately 18% and 32%, respectively, by the time the patient reached 80 years of age, however, absolute risk of breast cancer has been reported to be higher in mutation carriers with a strong family history of breast cancer. Although CHEK2 mutations account for approximately one-third of mutations identified in BRCA-negative patients, mutations in CHEK2 and any one of the other genes that have been recognized as breast cancer susceptibility genes, are rare, making accurate estimates of risk less precise.

An accurate and comprehensive family history of cancer is essential for identifying people who may be at risk for inherited breast cancer and should include a 3-generation family history with information on both maternal and paternal lineages.

CHEK2
CHEK2 (checkpoint kinase 2) is activated in response to DNA double-strand breakage and plays a role in cell cycle control, DNA repair and apoptosis.

In 2002, a single recurrent truncating mutation in the CHEK2 gene (1100delC) was first reported as a cause of breast cancer, and studies have since confirmed this. The incidence of CHEK2 mutations varies widely among populations. It is most prevalent in Eastern and Northern Europe, where the population
frequency of the 1100delC allele ranges from 0.5% to 1.4%; the allele is less frequent in North America and virtually absent in Spain and India.

Although most of the data for truncating CHEK2 variants are limited to the 1100delC variant, 3 other founder variants of CHEK2 (IVS2+1G>A, del5395, I157T) have been associated with breast cancer in Eastern Europe. IVS2+1G>A and del5395 are protein-truncating mutations, and I157T is a missense variant. The truncating mutations are associated with breast cancer in the Slavic populations of Poland, Belarus, Russia, and the Czech Republic. The I157T variant has a wider geographic distribution, and has been reported to be associated with breast cancer in Poland, Finland, Germany, and Belarus.

For the majority of cancer susceptibility genes, most of the evidence on breast cancer risk relates to protein-truncating variants (eg, nonsense substitutions, frameshift small insertions or deletions, and variants affecting splicing). However, the risk associated with the large majority of missense variants remains unknown.

In 2015, Tung et al assessed the frequency of pathogenic mutations among patients with breast cancer who were referred for BRCA1/2 testing, performed at 1 large reference laboratory. The study included 2 cohorts. Cohort 1 consisted of 1781 patients referred for BRCA1/2 testing between November 2012 and April 2013. A total of 241 (13.5%) individuals were found to have a mutation in at least 1 of the 25 genes tested, 162 in BRCA1/2, and 76 in at least one of the other genes. Of the mutation-positive, BRCA1/2-negative patients, the most common mutation identified was in CHEK2 (n=29), accounting for approximately one-third of the additional mutations identified in BRCA-negative patients, and 12% of mutations overall. The second cohort consisted of 377 samples from patients who were referred to Beth Israel Deaconess Medical Center for genetic testing between 1998 and 2013 and had previously tested negative for BRCA1/2. Mutations were identified in additional genes in 14 women, of which CHEK2 was the most frequent (n=5), comprising approximately 33% of mutations identified in mutation-positive, BRCA-negative patients.

**Summary**
Published data on the analytic validity of CHEK2 individual mutation testing are not identified.

Published data on the clinical validity of testing for CHEK2 mutations have shown that a CHEK2 mutation is of moderate penetrance and confers a risk of breast cancer of 2 to 4 times that of the general population; this risk appears to be higher in patients who also have a strong family history of breast cancer. Although the CHEK2 mutation appears to account for approximately one-third of mutations identified in BRCA1/2-negative patients, it is relatively rare, and accurate risk estimates, which have been studied in population- and family-based case controls, are subject to bias and overestimation. Further studies are needed to determine whether some patients with a CHEK2 mutation have a risk that is similar to the risk with a high-penetrance mutation and who would be best managed according to the guidelines for high-risk patients.

No evidence is available to support the clinical utility of genetic testing for CHEK2 mutations to guide patient management.

**Policy History**

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<td>8/2016</td>
<td>New references added from BCBSA National medical policy.</td>
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**Information Pertaining to All Blue Cross Blue Shield Medical Policies**
Click on any of the following terms to access the relevant information:
- Medical Policy Terms of Use
- Managed Care Guidelines
- Indemnity/PPO Guidelines
- Clinical Exception Process
Medical Technology Assessment Guidelines

References