
Medical Policy



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***Current Policy Effective Date: 1/1/20**
(See policy history boxes for previous effective dates)

Title: Genetic Testing for CHEK2 Mutations for Breast Cancer

Description / Background

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 (e.g., 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.¹ 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.²

For the majority of cancer susceptibility genes, most of the evidence on breast cancer risk relates to protein-truncating variants (e.g., nonsense substitutions, frame shift small insertions or deletions, and variants affecting splicing). However, the risk associated with the large majority of missense variants remains unknown.¹

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.³ 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.

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Improvement Act (CLIA). Lab tests for CHEK2 mutations are available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of these tests.

Medical Policy Statement

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 experimental/investigational. It has not been scientifically demonstrated to improve patient clinical outcomes.

Inclusionary and Exclusionary Guidelines (Clinically based guidelines that may support individual consideration and pre-authorization decisions)

N/A

CPT / HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

N/A

Other codes (investigational, not medically necessary, etc.):

G0452

81479

Rationale

Literature that describes the analytic validity, clinical validity, and clinical utility of genetic testing for CHEK2 mutations was sought.

Analytic Validity

Analytic validity is the technical accuracy of the test in detecting a mutation that is present or in excluding a mutation that is absent. Published data on the analytic validity of CHEK2 individual mutation testing are not identified.

Clinical Validity

Risk of Developing Breast Cancer in an Individual with a CHEK2 Mutation

For genetic susceptibility to cancer, clinical validity can be established if the variant that the test is intended to identify are associated with disease risk, and if so, if these risks are well quantified.¹ Most of the studies assessing risk of breast cancer associated with CHEK2 are population-based and family-based case control studies.

A 2015 article in the New England Journal of Medicine by Easton et al reported that the magnitude of relative risk of breast cancer associated with CHEK2 truncating mutations is likely to be moderate and unlikely to be high.² On the basis of 2 large case-control analyses, the authors calculated an estimated relative risk of breast cancer associated with CHEK2 mutations of 3.0 (90% confidence interval [CI], 2.6 to 3.5), and an absolute risk of 29% by age 80 years.

A 2012 meta-analysis by Yang et al examined the risk of breast cancer in Caucasians with the CHEK2 1100delC variant.⁴ A total of 25 case-control studies conducted in Europe, and North and South America published in 16 articles were analyzed, with a total of 29,154 breast cancer cases and 37,064 controls. Of the cases, 13,875 patients had unselected breast cancer, 7945 had familial breast cancer, and 5802 had early-onset breast cancer. In total, 391 of the cases had a CHEK2 1100delC mutation (1.3%) and 164 of the controls (0.4%). The association between CHEK2 1100delC and breast cancer risk was significant (odds ratio [OR], 2.75; 95% CI, 2.25 to 3.36). By subgroup, the OR and CI were 2.33 (1.79 to 3.05) for unselected, 3.72 (2.61 to 5.31) for familial, and 2.78 (2.28 to 3.39) for early-onset breast cancer, respectively.

In 2011, Cybulski et al reported on the risk of breast cancer in women with a CHEK2 mutation with and without a family history of breast cancer.² A total of 7494 BRCA1-negative breast cancer patients and 4346 controls were genotyped for the 4 CHEK2 founder mutations. A truncating mutation was present in 227 patients (3.0%) and in 37 controls (0.8%; OR=3.6; 95% CI, 2.6 to 5.1). The OR was higher for women with a first- or second-degree relative with breast cancer (OR=5.0; 95% CI, 3.3 to 7.6) than for women with no family history (OR=3.3; 95% CI, 2.3 to 4.7), and if both a first- and second-degree relative were affected with breast cancer, the OR was 7.3 (95% CI, 3.2 to 16.8). The authors estimated the lifetime risk of breast cancer for carriers of CHEK2 truncating mutations to be 20% for a woman with no affected relative, 28% for a woman with 1 second-degree relative affected, 34% for a woman with 1 first-degree relative affected, and 44% for a woman with both a first- and second-degree relative affected.

In 2008 Weischer et al performed a meta-analysis of studies on CHEK2 1100delC heterozygosity and the risk of breast cancer among patients with unselected (including the general population), early-onset (<51 years of age) and familial breast cancer.⁵ The analysis identified prospective cohort and case-control studies on CHEK2 1100delC and the risk of breast cancer published before March 2007. Inclusion criteria were women with unilateral breast cancer who did not have a known multicancer syndrome, Northern or Eastern European descent, availability for CHEK2 genotyping, BRCA1 and BRCA2 mutation-negative or unknown status, and breast cancer-free women as controls. The meta-analysis included 16 studies with 26,488 patient cases and 27,402 controls. Using fixed-effect models, for CHEK2 1100delC heterozygotes versus noncarriers, the aggregated OR for breast cancer was 2.7 (95% CI, 2.1 to 3.4) and 2.4 (95% CI, 1.8 to 3.2), respectively, for CHEK2 1100delC

heterozygotes versus noncarriers in studies of patients with unselected breast cancer, 2.6% (95% CI, 1.3 to 5.5) versus 2.7 (95% CI, 1.3 to 5.6), respectively, for early-onset breast cancer, and 4.8 (95% CI, 3.3 to 7.2) versus 4.6 (95% CI, 3.1 to 6.8), respectively, for familial breast cancer.

In summary, studies 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*- and *BRCA2*-negative patients, it is relatively rare, and risk estimates, which have been studied in population- and family-based case controls, are subject to bias and overestimation.

Prognosis of Breast Cancer in an Individual With a *CHEK2* Mutation

Studies on survival differences between breast cancer patients with and without *CHEK2* mutations have shown differing results. Breast cancer patients with *CHEK2* mutations may have worse prognosis than non-carriers.

A 2014 study by Huzarski et al estimated the 10-year survival rate for patients with early-onset breast cancer, with and without *CHEK2* mutations.⁶ Patients were consecutively identified women with invasive breast cancer diagnosed at or below the age of 50, between 1996 and 2007, in 17 hospitals throughout Poland. Patients were tested for 4 founder mutations in the *CHEK2* gene after diagnosis, and their medical records were used to retrieve tumor characteristics and treatments received. Dates of death were retrieved from a national registry. A total of 3592 women were eligible for the study, of whom 487 (13.6%) carried a *CHEK2* mutation (140 with truncating mutations, 347 with missense mutations). Mean follow-up was 8.9 years. Ten-year survival for *CHEK2* mutation carriers was similar to noncarriers, at 78.8% (95% CI, 74.6% to 83.2%) and 80.1% (95% CI, 78.5% to 81.8%), respectively. After adjusting for other prognostic features, the hazard ratio comparing carriers of the missense mutation and noncarriers was similar, as for carriers of a truncating mutation and noncarriers.

A 2014 study by Kriege et al compared breast cancer outcomes in patients with and without *CHEK2* mutations.⁷ Different study cohorts were combined to compare 193 carriers to 4529 non-carriers. Distant disease-free survival and breast cancer-specific survival were similar in the first 6 years after diagnosis. After 6 years, both distant disease-free survival and breast cancer-specific survival were worse in *CHEK2* carriers (multivariate HRs 2.65 (95% CI 1.79 to 3.93) and 2.05 (95% CI 1.41-2.99)). No interaction between *CHEK2* status and adjuvant chemotherapy was observed.

In 2012, Weischer et al reported on breast cancer associated with early death, breast cancer-specific death and the increased risk of a second breast cancer (defined as a contralateral tumor) in *CHEK2* mutation carriers and noncarriers in 25,571 white women of Northern and Eastern European descent who had invasive breast cancer, using data from 22 studies participating in the Breast Cancer Association Consortium conducted in 12 countries.⁷ The 22 studies included 30,056 controls. Data were reported on early death in 25,571 women, breast cancer-specific death in 24,345 and a diagnosis of a second breast cancer in 25,094. Of the 25,571 women, 459 (1.8%) were *CHEK2* 1100delC heterozygous and 25,112 (98.2%) were noncarriers. Median follow-up was 6.6 years, over which time 124 (27%) deaths, 100 (22%) breast cancer-specific deaths, and 40 (9%) second breast cancers among *CHEK2*

1100delC mutation carriers were observed. Corresponding numbers among noncarriers were 4864 (19%), 2732 (11%), and 607 (2%), respectively. At the time of diagnosis, CHEK2 mutation carriers versus noncarriers were on average 4 years younger ($p < 0.001$) and more often had a positive family history ($p < 0.001$). Multifactorially adjusted hazard ratios for CHEK2 versus noncarriers were 1.43 (95% CI, 1.12 to 1.82; log-rank $P = .004$) for early death and 1.63 (95% CI, 1.24 to 2.15; log-rank $P < .001$) for breast cancer-specific death.

Clinical Utility

Clinical utility refers to how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

Risk of Developing Breast Cancer in an Individual with a CHEK2 Mutation

Identifying a person with a genetic mutation that confers a high risk of developing cancer could lead to changes in clinical management and improved health outcomes. There are well-defined clinical guidelines on the management of patients who are identified as having a high-risk hereditary cancer syndrome. Changes in clinical management could include modifications in cancer surveillance, specific risk-reducing measures (e.g., prophylactic surgery), and treatment guidance (e.g., avoidance of certain exposures). In addition, other at-risk family members could be identified.

On the other hand, identifying mutations that have moderate penetrance is of limited clinical utility. Clinical management guidelines for patients found to have one of these mutations are not well defined. Patients who have a family and personal history consistent with hereditary breast cancer already meet criteria for more intensive breast cancer screening.⁹ A positive test may not change the risk of breast cancer sufficiently to warrant more aggressive preventive intervention. In addition, there is a potential for harm, in that the diagnosis of a moderate-risk mutation may lead to undue psychological stress and unnecessary prophylactic surgical intervention.

Prognosis of Breast Cancer in an Individual With a CHEK2 Mutation

Despite some studies showing potentially poorer outcomes of breast cancer patients who have CHEK2 mutations, it is unclear how such knowledge would be used to alter the treatment of such a patient. No evidence is available to support the clinical utility of genetic testing for CHEK2 mutations in breast cancer patients to guide patient management. There is not a strong indirect chain of evidence supporting CHEK2 testing in breast cancer patients.

Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov did not identify any ongoing or unpublished trials that would likely influence this review.

SUMMARY OF EVIDENCE

For individuals who are asymptomatic, with or without a family history of breast cancer, for breast cancer risk assessment who receive genetic testing for CHEK2 mutations, the evidence includes population and family-based case control studies. Relevant outcomes are overall survival, test accuracy and validity, morbid events, resource utilization, and treatment-related morbidity. Studies 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, however, risk

estimates 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 established guidelines for high-risk patients. Clinical management recommendations for breast cancer-associated genes with moderate penetrance, such as *CHEK2*, are not standardized, nor is it known if testing for *CHEK2* mutations will lead to changes in patient management or improved health outcomes. Patients being considered for testing already meet criteria for increased intensity of breast cancer screening. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have breast cancer who receive genetic testing for *CHEK2* mutations, the evidence includes retrospective and prospective cohort studies. Relevant outcomes are overall survival, disease-specific survival, morbid events, resource utilization, and treatment-related morbidity. Studies have shown that breast cancer may occur earlier in individuals with a *CHEK2* mutation versus those without. Studies have shown inconsistent results as to whether a *CHEK2* mutation in an individual with breast cancer is associated with increased risk of early death or breast cancer specific death. There are no specific treatment recommendations for individuals with breast cancer based on the presence of a *CHEK2* mutation. It has not been investigated whether testing for *CHEK2* mutations will lead to changes in management of breast cancer that result in improved health outcomes, nor is there a strong indirect chain of evidence supporting *CHEK2* testing in breast cancer patients. The evidence is insufficient to determine the effects of the technology on health outcomes.

SUPPLEMENTAL INFORMATION

PRACTICE GUIDELINES AND POSITION STATEMENTS

National Comprehensive Cancer Network

National Comprehensive Cancer Network guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian (v.1.2018) state “The panel recommends annual mammogram for women with a mutated *CHEK2* gene beginning at 40 years of age, with consideration of annual breast MRI. There is no data on the benefit of risk-reducing mastectomy for women with *CHEK2* mutations.”

American Society of Clinical Oncology

In a 2010 policy statement update on genetic and genomic testing for cancer susceptibility, the American Society of Clinical Oncology (ASCO) stated that testing for high-penetrance mutations in appropriate populations has clinical utility in that they inform clinical decision making and facilitate the prevention or amelioration of adverse health outcomes but that genetic testing for intermediate-penetrance mutations are of uncertain clinical utility because the cancer risk associated with the mutation is generally too small to form an appropriate basis for clinical decision making.¹⁰ ASCO recommends that genetic tests with uncertain clinical utility (low-to-moderate penetrance mutations) be administered in the context of clinical trials.

In 2015, the ASCO recommendations were updated. ASCO asserts that providers with particular expertise in cancer risk assessment should be involved in ordering and interpreting multi-gene panels that include genes of uncertain clinical utility and genes not suggested by the patient’s personal and/or family history. Further, ASCO encourages research to delineate the optimal use of panel-based testing, development of evidence-based practice guidelines as data emerges, and education of providers on the challenges of using these tests.

Government Regulations

National:

There is no NCD on this topic.

Local:

There is no WPS LCD on this topic.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Genetic Testing-Assays of Genetic Expression to Determine the Prognosis of Breast Cancer Patients.
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References

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2. Cybulski C, Wokolorczyk D, Jakubowska A, et al. Risk of breast cancer in women with a CHEK2 mutation with and without a family history of breast cancer. *J Clin Oncol*. Oct 1 2011;29(28):3747-3752. PMID 21876083
3. Tung N, Battelli C, Allen B, et al. Frequency of mutations in individuals with breast cancer referred for BRCA1 and BRCA2 testing using next-generation sequencing with a 25-gene panel. *Cancer*. Jan 1 2015;121(1):25-33. PMID 25186627
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8. Weischer M, Nordestgaard BG, Pharoah P, et al. CHEK2*1100delC heterozygosity in women with breast cancer associated with early death, breast cancer-specific death, and increased risk of a second breast cancer. *J Clin Oncol*. Dec 10 2012;30(35):4308-4316. PMID 23109706
9. National Comprehensive Cancer Network (NCCN). NCCN guidelines Genetic/Familial High Risk Assessment: Breast and Ovarian (V2.2018). Accessed August 2019.

10. Robson ME, Storm CD, Weitzel J, et al. American Society of Clinical Oncology policy statement update: genetic and genomic testing for cancer susceptibility. *J Clin Oncol*. Feb 10 2010;28(5):893-901. PMID 20065170
11. Blue Cross Blue Shield Association, "Genetic Testing for CHEK2 Mutations for Breast Cancer", Medical Policy Reference Manual, Policy #2.04.133, original policy date, August 2015, last review date, July 2016. Archived 2016.
12. HAYES Medical Technology Directory, "CHEK2-Related Susceptibility to Breast Cancer", Lansdale, PA: HAYES, Inc., April 2015, archived July 2016; outdated.

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through August 2019, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
1/1/16	10/13/15	11/5/15	Joint policy established
1/1/17	10/11/16	10/11/16	Routine policy maintenance, no change in policy status.
1/1/18	10/19/17	10/19/17	Routine policy maintenance, no change in policy status.
1/1/19	10/16/18	10/16/18	Routine policy maintenance, no change in policy status.
1/1/20	10/15/19		Policy to be replaced by new policy "Moderate Penetrance Variants Associated with Breast Cancer". No change in status.

Next Review Date:
with a new policy.

This policy is no longer subject to review. It has been replaced

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: GENETIC TESTING FOR CHEK2 MUTATIONS FOR BREAST CANCER

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	N/A
BCNA (Medicare Advantage)	See government section.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.