Policy Statement

Genetic testing for genes associated with familial cutaneous malignant melanoma or associated with susceptibility to cutaneous malignant melanoma is considered investigational.

Policy Guidelines

Genetics Nomenclature Update

The Human Genome Variation Society (HGVS) nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society’s nomenclature is recommended by the Human Variome Project, the HUman Genome Organization (HUGO), and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) 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>
<thead>
<tr>
<th>Previous Definition</th>
<th>Updated Definition</th>
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<tr>
<td>Mutation variant</td>
<td>Disease-associated change in the DNA sequence</td>
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<tr>
<td>Variant</td>
<td>Change in the DNA sequence</td>
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<tr>
<td>Familial variant</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
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<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
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<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
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<tr>
<td>Likely pathogenic</td>
<td>Likely disease-causing change in the DNA sequence</td>
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<tr>
<td>Variant of uncertain significance</td>
<td>Change in DNA sequence with uncertain effects on disease</td>
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<tr>
<td>Likely benign</td>
<td>Likely benign change in the DNA sequence</td>
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<tr>
<td>Benign</td>
<td>Benign change in the DNA sequence</td>
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ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

Genetic Counseling

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.
CPT code 81404 includes:

- CDKN2A (cyclin-dependent kinase inhibitor 2A) (e.g., CDKN2A-related cutaneous malignant melanoma, familial atypical mole-malignant melanoma syndrome), full gene sequence

Testing for CDK4 would be reported with the following code:

- 81479: Unlisted molecular pathology procedure

Cutaneous melanoma is the third most common type of skin cancer, but the most lethal. Some cases of cutaneous malignant melanoma are familial. Potential genetic markers for this disease are being evaluated in affected individuals with a family history of the disease and in unaffected individuals in a high-risk family.

Related Policies

- N/A

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates [e.g., Federal Employee Program (FEP)] prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

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. Melaris® (Myriad Genetics) and other CDKN2A tests 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 has chosen not to require any regulatory review of this test.

Rationale

Background

Cutaneous Malignant Melanoma

A genetic predisposition to cutaneous malignant melanoma (CMM) is suspected in specific clinical situations: (1) melanoma has been diagnosed in multiple family members; (2) multiple primary melanomas have been identified in a single patient; and (3) early age of onset. A positive family history of melanoma is the most significant risk factor; it is estimated that approximately 10% of melanoma cases report a first- or second-degree relative with melanoma. Although some of the familial risk may be related to shared environmental factors, 3 principal genes involved in CMM susceptibility have been identified. Cyclin-dependent kinase inhibitor 2A (CDKN2A), located on chromosome 9p21, encodes proteins that act as tumor suppressors.
Variants in this gene can alter the tumor suppressor function. The second gene, cyclin-independent kinase 4 (CDK4), is an oncogene located on chromosome 12q13 and has been identified in about 6 families worldwide. A third gene, not fully characterized, maps to chromosome 1p22.

The incidence of CDKN2A disease-associated variants in the general population is very low. For example, it is estimated that in Queensland, Australia, an area with a high incidence of melanoma, only 0.2% of all patients with melanoma will harbor a CDKN2A disease-associated variant. Variants are also infrequent in those with an early age of onset or those with multiple primary melanomas. However, the incidence of CDKN2A disease-associated variants increases with a positive family history; CDKN2A disease-associated variants will be found in 5% of families with first-degree relatives, rising to 20% to 40% in patients with 3 or more affected first-degree relatives. Variant detection rates of the CDKN2A gene are generally estimated to be 20% to 25% in hereditary CMM but can vary between 2% and 50% depending on the family history and population studied. Validated clinical risk prediction tools to assess the probability that an affected individual carries a germline CDKN2A disease-associated variant are available.

Familial CMM has been described in families in which either 2 first-degree relatives are diagnosed with melanoma or a family with 3 melanoma patients, irrespective of the degree of relationship. Others have defined familial CMM as having at least 3 (first-, second-, or third-degree) affected members or 2 affected family members in which at least one was diagnosed before age 50 years, or pancreatic cancer occurred in a first- or second-degree relative or 1 member had multiple primary melanomas. Other malignancies associated with familial CMM, specifically those associated with CDKN2A variants, have been described. The most pronounced associated malignancy is pancreatic cancer. Other associated malignancies include other gastrointestinal malignancies, breast cancer, brain cancer, lymphoproliferative malignancies, and lung cancer. It is also important to recognize that other cancer susceptibility genes may be involved in these families. In particular, germline BRCA2 gene variants have been described in families with melanoma and breast cancer, gastrointestinal cancer, pancreatic cancer, or prostate cancer.

CMM can occur either with or without a family history of multiple dysplastic nevi. Families with both CMM and multiple dysplastic nevi have been referred to as having familial atypical multiple mole and melanoma syndrome. This syndrome is difficult to define because there is no agreement on a standard phenotype, and dysplastic nevi occur in up to 50% of the general population. Atypical or dysplastic nevi are associated with an increased risk for CMM. Initially, the phenotypes of atypical nevi and CMM were thought to co-segregate in familial atypical multiple mole and melanoma syndrome families, leading to the assumption that a single genetic factor was responsible. However, it was subsequently shown that, in families with CDKN2A variants, some family members with multiple atypical nevi were noncarriers of the CDKN2A familial variant. Thus, the nevus phenotype cannot be used to distinguish carriers from noncarriers of CMM susceptibility in these families.

Some common allele(s) are associated with increased susceptibility to CMM but have low-to-moderate penetrance. One gene of moderate penetrance is the melanocortin 1 receptor gene (MC1R). Variants in this gene are relatively common and have low penetrance for CMM. This gene is associated with fair complexion, freckles, and red hair, all risk factors for CMM. Variants in MC1R also modify the CMM risk in families with CDKN2A variants.

Management
No widely accepted guidelines for the management of families with hereditary risk of melanoma exist. Melaris is a commercially available genetic test of the CDKN2A gene.

Literature Review
Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome.
That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Testing Individuals with Cutaneous Malignant Melanoma and Family History of this Disease

Clinical Context and Test Purpose

The purpose of genetic testing of individuals with cutaneous malignant melanoma (CMM) and family history of the disease is to identify variants in genes associated with familial CMM to inform management decisions and potentially inform the decision to test asymptomatic family members for variants associated with familial CMM.

The question addressed in this evidence review is: Does genetic testing improve the net health outcome in individuals with melanoma and a family history of melanoma?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is individuals with CMM and a family history of the disease.

Interventions
The test being considered is genetic testing for gene variants associated with CMM.

Comparators
The following practices are currently being used; standard clinical management without genetic testing.

Outcomes
The potential beneficial outcomes of primary interest would be improvements in overall survival and disease-specific survival.

Potential harmful outcomes are those resulting from false-positive or false-negative test results. False-positive test results can lead to unnecessary clinical management changes or unnecessary cascade testing for asymptomatic family members. False-negative test results can lead to the absence of clinical management changes or lack of testing for asymptomatic family members.

Timing
The primary outcomes of interest are the initiation and frequency of monitoring and short-term and long-term survival.

Setting
Patients with melanoma and family history may be referred from primary care to a dermatologist or medical geneticist for investigation and management. Referral for genetic counseling is important for the explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

Simplifying Test Terms
There are 3 core characteristics for assessing a medical test. Whether imaging, laboratory, or other, all medical tests must be:
- Technically reliable
- Clinically valid
- Clinically useful.
Because different specialties may use different terms for the same concept, we are highlighting the core characteristics. The core characteristics also apply to different uses of tests, such as diagnosis, prognosis, and monitoring treatment.

Diagnostic tests detect presence or absence of a condition. Surveillance and treatment monitoring are essentially diagnostic tests over a time frame. Surveillance to see whether a condition develops or progresses is a type of detection. Treatment monitoring is also a type of detection because the purpose is to see if treatment is associated with the disappearance, regression, or progression of the condition.

Prognostic tests predict the risk of developing a condition in the future. Tests to predict response to therapy are also prognostic. Response to therapy is a type of condition and can be either a beneficial response or adverse response. The term predictive test is often used to refer to response to therapy. To simplify terms, we use prognostic to refer to both predicting a future condition or to predicting a response to therapy.

**Technically Reliable**

Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review, and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

**Clinically Valid**

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

One issue common to genetic testing for any cancer susceptibility is determining the clinical significance of individual variants. For example, variants in the CDKN2A gene can occur along its entire length, and some of these variants are benign. Interpretation will improve as more data accumulate on the clinical significance of individual variants in families with a known hereditary pattern of melanoma. However, the penetrance of a given variant will also affect its clinical significance, particularly because the penetrance of CDKN2A variants may vary with ethnicity and geographic location. For example, exposure to sun and other environmental factors, as well as behavior and ethnicity, may contribute to penetrance. Bishop et al (2002) estimated that the calculated risk of developing melanoma before age 80 years in carriers of CDKN2A variants ranged from 58% in Europe to 91% in Australia.9

Interpretation of a negative test is another issue. CDKN2A variants are found in less than half of those with a strong family history of melanoma. Therefore, additional melanoma predisposition genes are likely to exist, and patients with a strong family history with normal test results must not be falsely reassured that they are not at increased risk.1

For example, in a meta-analysis of 145 genome-wide association studies, Chatzinassiou et al (2011) identified 8 independent genetic loci as associated with a statistically significant risk of cutaneous melanoma, including 6 with strong epidemiologic credibility (MC1R, TYR, TYRP1, SLC45A2, ASP/PIGU/MYH7B, CDKN2A/MTAP).10 Also, in a meta-analysis of 20 studies with data from 25 populations, Williams et al (2011) found red hair color variants on the MC1R gene to be associated with the highest risk of melanoma, but non-red hair color variants also were associated with an increased risk of melanoma.11 In a review, Ward et al (2012) noted that, for melanoma, “it is likely a large number of single-nucleotide polymorphisms (SNPs), each with a small effect and low penetrance, in addition to the small number of large effect, high-penetrance SNPs, are responsible for CMM [cutaneous malignant melanoma] risk.”12

Kanetsky et al (2010) described the associations between MC1R (melanocortin 1 receptor gene) variants and melanoma in a U.S. population and investigated whether the genetic risk is
modified by pigmentation characteristics and sun exposure. The study population included melanoma patients (n=960) and controls (n=396) who self-reported phenotypic characteristics and sun exposure information. Logistic regression was used to estimate associations between high- and low-risk MC1R variants and melanoma, overall and within phenotypic and sun exposure groups. Carriage of 2 low-risk or any high-risk MC1R variants was associated with increased risk of melanoma (low-risk odds ratio [OR], 1.7; 95% confidence interval [CI], 1.0 to 2.8; high-risk OR=2.2; 95% CI, 1.5 to 3.0). However, the risk was noted to be stronger in or limited to people with protective phenotypes and limited sun exposure, such as those who tanned well after repeated sun exposure (OR=2.4), had dark hair (OR=2.4), or had dark eyes (OR=3.2). The authors concluded that MC1R genotypes provided information about melanoma risk in those individuals who would not be identified as high risk based on their phenotypes or exposures alone. How this information impacts patient care and clinical outcomes is unknown.

Two subsequent studies in southern European populations examined further the association between MC1R variants and melanoma. Ibarrola-Villava et al (2012) conducted a case-control study in 3 sample populations from France, Italy, and Spain. Susceptibility genotypes in 3 genes involved in pigmentation processes were examined in 1639 melanoma patients (15% familial) and 1342 controls. MC1R variants associated with red hair color were successfully genotyped in 85% of cases and 93% of controls. (Two other genes not associated with familial cutaneous melanoma—TYR, which encodes a tyrosinase, and SLC45 A2, which encodes a melanosomal enzyme—also were studied.) In univariate logistic regression analysis, MC1R red hair color variants were significantly associated with the odds of developing melanoma in a dose-dependent fashion: the OR for 1 allele was 2.2 (95% CI, 1.9 to 2.6); the odds for 2 alleles was 5.0 (95% CI, 2.8 to 8.9). In an analysis stratified by self-reported phenotype, these variants were statistically associated with increased odds of melanoma not only in individuals with fair phenotype (eye, hair, and skin color) but also in those with dark/olive phenotype. The authors suggested that MC1R genotyping to identify elevated risk in southern European patients considered not at risk based on phenotype alone warranted further investigation.

Ghiorzo et al (2012) studied 49 CDKN2A variant-positive and 390 CDKN2A variant-negative Italian patients with cutaneous melanoma. MC1R variants were associated with increased odds of melanoma only in CDKN2A variant-negative patients in a dose-dependent fashion: the OR for 1 high-risk allele was 1.5 (95% CI, 1.1 to 2.0); the odds for 2 high-risk alleles was 2.5 (95% CI, 1.7 to 3.7). In multivariate logistic regression, the effects of MC1R variants were statistically significant in most CDKN2A variant-negative subgroups and a few variant-positive subgroups defined by phenotype (eye and hair color, skin complexion and phototype, presence or absence of freckles or atypical nevi, total nevus count), sun exposure, and history of severe sunburn. In contrast, first-degree family history of cutaneous melanoma increased the odds of developing melanoma in both variant-positive (OR=71.2; 95% CI, 23.0 to 221.0) and variant-negative (OR=5.3; 95% CI, 2.0 to 14.3) patients, although the uncertainty in the estimates of association was considerable. The family history of cutaneous nevi (at least 1 first-degree relative with >10 nevi and/or atypical nevi) increased the odds of melanoma in variant-positive cases only (OR=2.44; 95% CI, 1.3 to 4.5). This finding underscores the significance of nongenetic factors (e.g., sun exposure, history of severe sunburn) for development of melanoma and the complexity of interpreting a positive family history.

Cust et al (2012) classified 565 patients with invasive CMM diagnosed between 18 and 39 years of age, 518 sibling controls, and 409 unrelated controls into MC1R categories defined by the presence of high-risk or other alleles. Compared with sibling controls, 2 MC1R high-risk alleles (R151C, R160W) were associated with increased odds of developing melanoma (R151C OR=1.7; 95% CI, 1.1 to 2.6; R160W OR=2.0; 95% CI, 1.2 to 3.2), but these associations were no longer statistically significant in analyses adjusted for pigmentation, nevus count, and sun exposure. Compared with unrelated controls, only the R151C high-risk allele was associated with increased odds of developing melanoma in the adjusted analysis. There was no association between other MC1R alleles (not considered high risk) and the odds of developing melanoma in unadjusted or adjusted analyses.
Di Lorenzo et al (2016) observed 400 patients with CMM for a 6-year period at an Italian university.17 Forty-eight patients met the criteria of the Italian Society of Human Genetics for the diagnosis of familial melanoma and were screened for CDKN2A and CDK4 variants. Genetic testing revealed that none of the families carried variants in the CDK4 gene and only 1 patient harbored the rare CDKN2A p.R87W variant. The study did not identify a high variant rate of CDKN2A in patients affected by familial melanoma or multiple melanomas. This difference could be attributed to different factors, including the genetic heterogeneity of the Sicilian population. It is likely that, as in the Australian populations, the inheritance of familial melanoma in this island of the Mediterranean Sea is due to intermediate-/low-penetrance susceptibility genes, which, together with environmental factors (e.g., latitude, sun exposure), could determine the occurrence of melanoma.

**Section Summary: Clinically Valid**

Studies have indicated that the clinical sensitivity of genetic testing for genes associated with familial CMM is difficult to ascertain due to differences in gene penetrance, variant interpretation, study populations, sun exposure, and preventive measures. These studies have not provided evidence that there is a clinically valid association between genetic variants and familial CMM.

**Clinically Useful**

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

**Direct Evidence**

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

Although genetic testing for CDKN2A variants is recognized as an important research tool, its clinical use will depend on how results of the genetic analysis can be used to improve patient management and health outcomes. Currently, management of patients considered high risk for malignant melanoma focuses on the reduction of sun exposure, use of sunscreens, vigilant cutaneous surveillance of pigmented lesions, and prompt biopsy of suspicious lesions. Presently, it is unclear how genetic testing for CDKN2A would alter these management recommendations.

If an affected individual tests positive for a CDKN2A variant, he/she may be at increased risk for a second primary melanoma compared with the general population. Limited and protected sun exposure and increased surveillance would be recommended to any patient with malignant melanoma, regardless of the presence of a CDKN2A variant. However, a positive result will establish a familial variant, thus permitting targeted testing in the rest of the family. Additionally, a positive variant in an affected family member increases the likelihood of its clinical significance if detected in another family member. As described earlier, a negative test is not interpretable.

Published data on genetic testing of the CDKN2A and CDK4 genes have focused on the underlying genetics of hereditary melanoma, identification of variants in families at high risk of melanoma, and risk of melanoma in those harboring these variants. Other studies have focused on the association between CDKN2A and pancreatic cancer.18-20 One publication (2007) cautioned that differences in melanoma risk across geographic regions justifies the need for studies in individual countries before counseling should be considered.21

**Chain of Evidence**

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.
Currently, no inferences can be drawn about the usefulness of testing individuals with melanoma who have a family history of the disease.

**Section Summary: Clinically Useful**
Direct evidence of the clinical utility of genetic testing in individuals with melanoma and a family history of the disease is lacking. While genetic variants associated with increased risk for developing melanoma have been identified, changes in clinical management and improved health outcomes as a result of genetic testing for individuals with melanoma is uncertain.

**Testing Asymptomatic Individuals in a Family at High Risk of Developing Melanoma**

**Clinical Context and Test Purpose**
The purpose of genetic testing of asymptomatic individuals in a family at high risk of developing CMM is to identify variants in genes associated with melanoma for increased surveillance to potentially detect disease at an earlier, more treatable stage.

The question addressed in this evidence review is: Does genetic testing improve the net health outcome in asymptomatic individuals in a family at high risk of developing CMM?

The following PICOTS were used to select literature to inform this review.

**Patients**
The relevant population of interest is asymptomatic individuals in a family at high risk of developing CMM.

**Interventions**
The test being considered is genetic testing for gene variants associated with CMM.

**Comparators**
The following practices are currently being used: standard clinical management without genetic testing.

**Outcomes**
The potential beneficial outcomes of primary interest would be improvements in overall survival and disease-specific survival.

Potential harmful outcomes are those resulting from false-positive or false-negative test results. False-positive test results can lead to increased surveillance and preventive measures. False-negative test results can lead to an erroneous perception of lower risk, fewer preventive measures, and absence of increased surveillance.

**Timing**
The primary outcomes of interest are the initiation and frequency of monitoring and use of preventive measures.

**Setting**
Patients with suspected melanoma and family history may be referred from primary care to a dermatologist or medical geneticist for investigation and management. Referral for genetic counseling is important for the explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

**Technically Reliable**
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review, and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.
**Clinically Valid**
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Yang et al (2009) conducted a study to identify modifier genes for CMM in CMM-prone families with or without CDKN2A variants. Investigators genotyped 537 individuals (107 CMM) from 28 families (19 CDKN2A-positive, 9 CDKN2A-negative) for genes involved in DNA repair, apoptosis, and immune response. Analyses identified some candidate genes, such as FAS, BCL7A, CASP14, TRAF6, WRN, IL9, IL10RB, TNFSF8, TNFRSF9, and JAK3, associated with CMM risk; after correction for multiple comparisons, IL9 remained significant. The effects of some genes were stronger in CDKN2A variant-positive families (BCL7A, IL9), and some were stronger in CDKN2A-negative families (BCL2L1). The authors considered these findings supportive of the hypothesis that common genetic variants in DNA repair, apoptosis, and immune response pathways may modify the risk of CMM in CMM-prone families, with or without CDKN2A variants.

Puntervoll et al (2013) described the phenotype of individuals with CDK4 variants in 17 melanoma families (209 individuals; 62 cases, 106 related controls, 41 unrelated controls). The incidence of atypical nevi was higher in those with CDK4 variants (70% in melanoma patients vs 75% in unaffected individuals) than in those without CDK4 variants (27%; p<0.001). The distribution of eye or hair color did not differ statistically between CDK4 variant-positive individuals (with or without melanoma) and variant-negative family members. The authors concluded that “it is not possible to distinguish CDK4 melanoma families from those with CDKN2A variants based on phenotype.” As noted, the clinical significance of this genetic distinction is currently unclear.

**Section Summary: Clinically Valid**
Studies have indicated that the clinical sensitivity of genetic testing for genes associated with familial CMM is difficult to ascertain due to differences in gene penetrance, variant interpretation, study populations, sun exposure, and preventive measures. For asymptomatic individuals in a family at high risk for developing melanoma, identification of genetic variants provides minimal value in risk assessment due to the multifactorial nature of disease development and progression.

**Clinically Useful**
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

**Direct Evidence**
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

If the asymptomatic individual is the first to be tested in the family (i.e., no affected relative has been previously tested to define a familial variant), it is difficult to interpret the clinical significance of a variant, as described. The likelihood of clinical significance is increased if the identified variant is the same as that reported in other families, although the issue of penetrance is a confounding factor. If the asymptomatic individual has the same variant as an affected relative, then the patient is at high risk for melanoma. However, it is unclear how this would affect the management of the patient. Increased sun protection and surveillance are recommended for any patient in a high-risk family.

**Prospective Studies**
Aspinwall et al (2008) reported on the short-term change in behavior among a small group of patients without melanoma who tested positive for the CDKN2A variant. In this prospective
study of 59 members of a CDKN2A variant–positive pedigree, behavioral assessments were made at baseline, immediately after CDKN2A test reporting and counseling, and at 1-month follow-up (42 participants). Across multiple measures, test reporting caused CDKN2A disease–associated variant carriers without a melanoma history to improve to the level of adherence reported by participants with a melanoma history. CDKN2A-positive participants without a melanoma history reported greater intention to obtain total body skin examinations, increased intentions and adherence to skin self-examination recommendations, and increased number of body sites examined at 1 month. Aspinwall et al (2013) reported on outcomes for 37 (62%) patients of this cohort with 2-year follow-up. Of the cohort available, 27 were unaffected noncarriers, 15 were unaffected carriers, and 18 were affected carriers. Anxiety, depression, and cancer-specific worry declined over 2 years, although baseline values were low and the declines are of uncertain clinical significance. Adherence to annual total body skin examinations and monthly skin self-examinations varied by carrier status; however, without a comparison group, it is not possible to attribute any change in adherence to the knowledge of test results.

Branstrom et al (2012) assessed a survey of self-reported genetic testing perceptions and preventive behaviors in 312 family members with an increased risk of melanoma. Fifty-three percent had been diagnosed with melanoma, and 12% had a positive susceptibility genetic test. The study indicated that a negative test might be associated with an erroneous perception of lower risk and fewer preventive measures.

Borroni et al (2017) evaluated asymptomatic individuals with family members diagnosed with primary cutaneous melanoma (PCM) and a CDKN2A variant who underwent genetic testing and counseling. Of the 19 unrelated patients with PCM and a CDKN2A variant, 40 clinically healthy relatives were tested. Fifteen of the 40 relatives tested positive for the same variant as the relative with PCM. The 15 relatives underwent a complete dermatologic examination with dermoscopy. During a mean follow-up of 37 months (range, 4-53 months), none of the relatives developed PCM.

Retrospective Studies
In a retrospective case-control study, van der Rhee et al (2011) sought to determine whether a 25-year surveillance program of families with a Dutch founder mutation in CDKN2A (the p16-Leiden variant) permitted earlier identification of melanomas. Characteristics of 40 melanomas identified in 35 unscreened patients (before heredity was diagnosed) were compared with 226 melanomas identified in 92 relatives of those 35 melanoma patients who were later found to have the CDKN2A variant. Surveillance consisted of a minimum of an annual total skin evaluation, which became more frequent if melanoma was diagnosed. Melanomas diagnosed during surveillance were found to have a significantly lower Breslow program, and almost half of the patients were noncompliant when first diagnosed with melanoma. Thickness (median thickness, 0.50 mm) than melanomas identified in unscreened patients (median thickness, 0.98 mm), signifying earlier identification with surveillance. However, only 53% of melanomas identified in the surveillance group were detected on regular screening appointments. Additionally, there was no correlation between length of screening intervals (for intervals <24 months) and melanoma tumor thickness at the time of diagnosis. The authors also noted that, despite understanding the importance of surveillance, patient noncompliance was still observed in the surveillance.

Van der Rhee et al (2013) reported on a retrospective case-control study of 21 families with the p16-Leiden founder mutation. This study investigated the yield of surveillance of first- and second-degree relatives of patients with melanoma (n=14 families) or with melanoma and pancreatic cancer (n=7 families). Overall, melanoma incidence rates were 9.9 per 1000 person-years (95% CI, 7.4 to 13.3 person-years) in first-degree relatives and 2.1 per 1000 person-years (95% CI, 1.2 to 3.8 person-years) in second-degree relatives. Compared with the general Dutch population, overall standardized morbidity ratios for melanoma were 101.0 (95% CI, 55.9 to 182.3) in first-degree relatives (observed, 45; expected, 0.76) and 12.9 (95% CI, 7.2 to 23.4) in second-
degree relatives (observed, 11; expected, 0.53). Although the authors concluded that surveillance of second- (as well as first-) degree relatives from very high risk melanoma families were justified based on these findings, it is unclear whether these findings apply to families without or with other CDKN2A variants. Further, because increased sun protection and surveillance are recommended for any member of a high-risk family, the clinical utility of the finding is uncertain.

**Chain of Evidence**
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

No inferences can be drawn on the usefulness of testing asymptomatic individuals in a family at high-risk of developing CMM.

**Section Summary: Clinically Useful**
Direct evidence of the clinical utility of genetic testing in asymptomatic individuals in a family at high risk for developing CMM is lacking. Among the prospective studies, only one had an outcome of melanoma occurrence. None of the carriers developed melanoma, but the sample size was small. While familial variants associated with increased risk for developing melanoma have been identified, changes in clinical management and improved health outcomes as a result of genetic testing for asymptomatic individuals is uncertain.

**Summary of Evidence**
For individuals who have CMM and a family history of this disease who receive genetic testing for genes associated with familial CMM, the evidence includes genetic association studies correlating variants in certain genes and the risk of developing cutaneous melanoma. Relevant outcomes are overall survival, disease-specific survival, test accuracy, and test validity. Limitations with clinical validity include difficulties with variant interpretations, variable penetrance of a given variant, and residual risk with a benign variant. Currently, management of melanoma patients does not change based on genetic variants identified in genes associated with familial CMM, therefore, clinical utility is lacking. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are asymptomatic and in a family at high-risk of developing CMM who receive genetic testing for genes associated with familial CMM, the evidence includes genetic association studies correlating variants in certain genes and the risk of developing CMM. Relevant outcomes are overall survival, disease-specific survival, test accuracy, and test validity. Limitations with clinical validity include difficulties with variant interpretations, variable penetrance of a given variant, and residual risk with a benign variant. Currently, management of patients considered high-risk for CMM focuses on the reduction of sun exposure, use of sunscreens, vigilant cutaneous surveillance of pigmented lesions, and prompt biopsy of suspicious lesions. It is unclear how genetic testing for variants associated with increased risk of CMM would alter these management recommendations; therefore, clinical utility is lacking. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Supplemental Information**

**Practice Guidelines and Position Statements**

**American Society of Clinical Oncology**
In an American Society of Clinical Oncology (ASCO) publication, Kefford et al (2002) noted that the sensitivity and specificity of tests for CDKN2A variants are not fully known. Because interpreting genetic tests is difficult and because test results do not alter patient management, ASCO recommended that CDKN2A genetic testing should be performed only in clinical trials, for several reasons, including a low likelihood of finding disease-associated variants in known melanoma susceptibility genes, uncertainty about the functionality and phenotypic expression of the trait among disease-associated variant carriers, and lack of proven melanoma prevention strategies.
and surveillance strategies. Additionally, it was noted that all individuals with risk factors for cutaneous melanoma should follow programs of sun protection and skin surveillance, not just those considered high risk due to family history.

In 2003\(^{32}\) and 2010,\(^{33}\) the American Society of Clinical Oncology issued policy statements on genetic and genomic testing for cancer susceptibility. Both statements recommended that, outside of a research setting, genetic testing for cancer susceptibility should only be offered when the following 3 criteria are met: (1) the individual being tested has a personal or family history suggestive of an underlying hereditary component; (2) the genetic test can be adequately interpreted; and (3) test results will guide diagnosis and management.

In 2010, ASCO updated its policy statement on genetic and genomic testing for cancer susceptibility.\(^{33}\) ASCO recommended that “genetic tests with uncertain clinical utility, including genomic risk assessment, be administered in the context of clinical trials.”

**American Academy of Dermatology**

In 2011, the American Academy of Dermatology published guidelines on the management of primary cutaneous melanoma.\(^{34}\) The use of genetic testing in patients diagnosed with cutaneous malignant melanoma or asymptomatic patients with family history of the disease was not addressed.

**National Comprehensive Cancer Network**

Current National Comprehensive Cancer Network guidelines for melanoma (v.1.2018) have added under Common Follow-Up Recommendations for All Patients: “consider referral to a genetics counselor for p16/CDKN2A mutation [variant] testing in the presence of 3 or more invasive melanomas or a mix of invasive melanoma and pancreatic cancer diagnoses in an individual or family. Testing for other genes that can harbor melanoma-predisposing mutations (e.g., CDK4, TERT, MITF, and BAP1) may be warranted.”\(^{35}\)

**U.S. Preventive Services Task Force Recommendations**

Not applicable.

**Medicare National Coverage**

There is no national coverage determination. 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 1.

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**Table 1. Summary of Key Trials**

<table>
<thead>
<tr>
<th>NCTNo.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<tr>
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<td></td>
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<tr>
<td>NCT00339222</td>
<td>Family Study of Melanoma in Italy</td>
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<td>NCT00040352</td>
<td>Clinical, Laboratory, and Epidemiologic Characterization of Individuals and Families at High Risk of Melanoma</td>
<td>3000</td>
<td>NR</td>
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<td>NCT00591500</td>
<td>A Model for Genetic Susceptibility: Melanoma</td>
<td>4082</td>
<td>Jul 2018</td>
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<tr>
<td>NCT00849407</td>
<td>Genetic Risk Factors and Acquired Oncogenic Mutations of Melanoma</td>
<td>2000</td>
<td>Dec 2020</td>
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<tr>
<td>NCT00450593</td>
<td>Studies of Familial Melanoma</td>
<td>5000</td>
<td>Dec 2020</td>
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</table>

NCT: national clinical trial.

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**References**


**Documentation for Clinical Review**

- No records required
Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

IE
The following services may be considered investigational.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>CPT®</td>
<td>81404</td>
<td>Molecular Pathology Procedure Level 5</td>
</tr>
<tr>
<td></td>
<td>81479</td>
<td>Unlisted molecular pathology procedure</td>
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<tr>
<td>HCPCS</td>
<td>None</td>
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<tr>
<td>ICD-10 Procedure</td>
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Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
<th>Reason</th>
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<tbody>
<tr>
<td>04/01/2016</td>
<td>BCBSA Medical Policy adoption</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>05/01/2017</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>05/01/2018</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
</tbody>
</table>

Definitions of Decision Determinations

Medically Necessary: A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.
Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.