Genetic Testing for Familial Cutaneous Malignant Melanoma

Policy # 00206
Original Effective Date: 09/20/2006
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Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers genetic testing for genes associated with familial cutaneous malignant melanoma (CMM) or associated with susceptibility to cutaneous malignant melanoma (CMM) to be investigational.*

Background/Overview
A genetic predisposition to 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-dependent 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 kindreds with 3 or more affected first-degree relatives. Variant detection rates of the CDKN2A gene are generally estimated as 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 as a family 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 1 was diagnosed before age 50 years, or pancreatic cancer occurred in a
first- or second-degree relative, or 1 member had multiple primary melanomas. No widely accepted guidelines for the management of families with hereditary risk of melanoma exist.

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 (FAMMM). 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 cosegregate in FAMMM 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.

Melaris is a commercially available genetic test of the CDKN2A gene.

FDA or Other Governmental Regulatory Approval
U.S. Food and Drug Administration (FDA)
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 Laboratory Improvement Act (CLIA). Melaris (Myriad Genetics, Salt Lake City, UT) and other CDKN2A tests are LDTs and available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. FDA has chosen not to require any regulatory review of this test.

Centers for Medicare and Medicaid Services (CMS)
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.
Rationale/Source
Validation of the clinical use of any diagnostic test focuses on 3 main principles: (1) analytic validity of the test (ie, the technical performance of the test); (2) clinical validity (ie, the diagnostic performance of the test, eg, sensitivity, specificity, and positive and negative predictive values) in different populations of patients and compared with the criterion standard; and (3) clinical utility of the test (ie, how the results of the diagnostic test will be used to improve patient management). Following is a summary of the key literature to date.

GENETIC TESTING IN INDIVIDUALS WITH CUTANEOUS MALIGNANT MELANOMA AND FAMILY HISTORY OF THIS DISEASE

Clinical Context and Test Purpose
The purpose of genetic testing of individuals with CMM and family history of the disease is to identify variants in genes association 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 health outcomes in individuals with 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
Genetic testing for genes associated with CMM.

Comparators
Standard clinical management without genetic testing.

Outcomes
The general outcomes of interest are overall survival (OS), disease-specific survival, test accuracy, and test validity. The potential beneficial outcomes of primary interest would be improvements in OS and disease-specific survival.

Potential harmful outcomes are those resulting from a 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 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 a 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 explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

Analytic Validity
No published data on the analytic validity of genetic testing for genes associated with familial CMM were identified.

Clinical Validity
Clinical validity is related to interpretation of the results of genetic analysis for the individual patient. One issue common to genetic testing for any type of 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.

Interpretation of a negative test is another issue. CDKN2A variants are found in less than half of those with 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.

For example, in a 2011 meta-analysis of 145 genome-wide association studies, 8 independent genetic loci were identified as associated with a statistically significant risk of cutaneous melanoma, including 6 with strong epidemiologic credibility (MC1R, TYR, TYRP1, SLC45A2, ASIP/PIGU/MYH7B, CDKN2A/MTAP). Also, in a 2011 meta-analysis of 20 studies with data from 25 populations, red hair color variants on the MC1R gene were associated with the highest risk of melanoma, but non-red hair color variants also were associated with an increased risk of melanoma. In a 2012 review, Ward et al noted the genetics of melanoma are far from being understood, and “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.”
In 2010, Kanetsky et al conducted a study to describe associations between \(MC1R\) (melanocortin 1 receptor gene) variants and melanoma in a U.S. population and to investigate whether 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, 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 these findings indicated \(MC1R\) genotypes provided information about melanoma risk in those individuals who would not be identified as high risk based on their phenotypes or exposures alone. However, 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 melanosome 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 odds ratio for 1 allele was 2.2 (95% CI, 1.9 to 2.6); the odds ratio for 2 alleles was 5.0 (95% CI, 2.8 to 8.9). In 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. The effects on health outcomes were uncertain.

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 odds ratio for 1 high-risk allele was 1.5 (95% CI, 1.1 to 2.0); the odds ratio for 2 high-risk alleles was 2.5 (95% CI, 1.7 to 3.7). In multivariate logistic regression, 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. 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 (eg, 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 \textit{MC1R} categories defined by the presence of high risk or other alleles. Compared with sibling controls, 2 \textit{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 adjusted analysis. There was no association between other \textit{MC1R} alleles (not considered high risk) and the odds of developing melanoma in unadjusted or adjusted analyses. In 2010, Psaty et al published an article on identifying individuals at high risk for melanoma and emphasized the use of family history.

In 2016, Di Lorenzo et al published a study on 400 patients with CMM who were observed for a 6-year period at an Italian university. Forty-eight patients met the criteria of the Italian Society of Human Genetics (SIGU) for the diagnosis of familial melanoma and were screened for \textit{CDKN2A} and \textit{CDK4} variants. Genetic testing revealed that none of the families carried variants in the \textit{CDK4} gene and only 1 patient harbored the rare \textit{CDKN2A} p.R87W variant. The study did not identify a high variant rate of \textit{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 people, 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 (eg, latitude, sun exposure), could determine the occurrence of melanoma.

\textbf{Section Summary: Clinical Validity}

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 preventative measures. The clinical validity of genetic variants associated with familial CMM is lacking.

\textbf{Clinical Utility}

In 2003 and 2010, 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 be offered only 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.

Although genetic testing for \textit{CDKN2A} variants is recognized as an important research tool, its clinical use will depend on how results of genetic analysis can be used to improve patient management and health.
outcomes. Currently, management of patients considered high risk for malignant melanoma focuses on 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 \textit{CDKN2A} would alter these management recommendations.

\textbf{Affected Individual With a Positive Family History}

If an affected individual tests positive for a \textit{CDKN2A} variant, he/she may be at increased risk for a second primary melanoma compared with the general population. However, limited and protected sun exposure and increased surveillance would be recommended to any patient with a malignant melanoma, regardless of the presence of a \textit{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 \textit{CDKN2A} and \textit{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 \textit{CDKN2A} and pancreatic cancer. One publication (2007) added the cautioned that differences in melanoma risk across geographic regions justify the need for studies in individual countries before counseling should be considered.

\textbf{Direct Evidence}

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Preferred evidence comes from randomized controlled trials (RCTs). No such trials were identified.

\textbf{Chain of Evidence}

A chain of 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.

\textbf{Section Summary: Clinical Utility}

Direct evidence of the clinical utility of genetic testing in individuals with melanoma and a family history of 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.
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GENETIC TESTING IN 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 health outcomes 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
Genetic testing for genes associated with CMM.

Comparators
Standard clinical management without genetic testing.

Outcomes
The general outcomes of interest are OS, disease-specific survival, test accuracy, and test validity. The potential beneficial outcomes of primary interest would be improvements in OS and disease-specific survival.

Potential harmful outcomes are those resulting from a false-positive or false-negative test results. False-positive test results can lead to increased surveillance and preventative 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 melanoma and a 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 explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.
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Analytic Validity
Same as the previous section.

Clinical Validity
For asymptomatic individuals in a family at high risk for developing melanoma, clinical validity is the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in risk assessment for predicting melanoma development in asymptomatic individuals.

In 2009, Yang et al 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. Their analyses identified some candidate genes, such as FAS, BCL7A, CASP14, TRAF6, WRN, IL9, IL10RB, TNFSF8, TNFRSF9, and JAK3, that were 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.

In 2013, Puntervol et al described the phenotype of individuals with CDK4 variants in 17 melanoma families (209 individuals; 62 cases, 106 related controls, 41 unrelated controls). 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 color 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 previously, the clinical significance of this genetic distinction is currently unclear.

Section Summary: Clinical Validity
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 preventative 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.

Clinical Utility
Asymptomatic Individual in a High-Risk Family
If the asymptomatic individual is the first to be tested in the family (ie, no affected relative has been previously tested to define a familial variant), it is very 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, again 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.

In a 2008 study, Aspinwall et al found 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. In 2013, Aspinwall et al reported outcomes for 37 (62%) patients of this cohort who were available for 2-year follow-up. 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 knowledge of test results.

In a 2011 retrospective case-control study, van der Rhee et al sought to determine whether a surveillance program of families with a Dutch founder variant in CDKN2A (the p16-Leiden variant) allowed for 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 unscreened melanoma patients who were found to have the CDKN2A variant and participated in a surveillance program over a 25-year period. Surveillance comprised 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 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 program, and almost half of patients were noncompliant when first diagnosed with melanoma.

In 2013, van der Rhee et al reported on a retrospective case-control study of 21 families with the p16-Leiden founder variant. The purpose of the study was to investigate 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) in first-degree relatives and 2.1 per 1000 person-years (95% CI, 1.2 to 3.8) 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 and 12.9 (95% CI, 7.2 to 23.4) in second-degree relatives. 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 relevance of the finding is uncertain.

Branstrom et al (2012) assessed a survey of self-reported genetic testing perceptions and preventive behaviors in 312 family members with 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.

Section Summary: Clinical Utility
Direct evidence of the clinical utility of genetic testing in asymptomatic individuals in a family at high risk for developing CMM is lacking. 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 cutaneous malignant melanoma and a family history of this disease who receive genetic testing for genes associated with familial cutaneous malignant melanoma, the evidence includes genetic association studies between variants in certain genes and the risk of developing cutaneous melanoma. Relevant outcomes are overall survival, disease-specific survival, test accuracy, and test validity. Data on the analytic validity of testing are lacking. 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 do not change based on genetic variants identified in genes associated with familial cutaneous malignant melanoma, 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 cutaneous malignant melanoma who receive genetic testing for genes associated with familial cutaneous malignant melanoma, the evidence includes genetic association studies between variants in certain genes and the risk of developing cutaneous malignant melanoma. Relevant outcomes are overall survival, disease-specific survival, test accuracy, and test validity. Data on the analytic validity of testing are lacking. 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 cutaneous malignant melanoma focuses on 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 cutaneous malignant melanoma would alter these management recommendations; therefore, clinical utility is lacking. The evidence is insufficient to determine the effects of the technology on health outcomes.
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References


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Policy History

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| 09/06/2006              | Medical Director review |
| 09/20/2006              | Medical Policy Committee approval |
| 10/01/2008              | Medical Director review |
| 10/22/2008              | Medical Policy Committee approval. No change to coverage eligibility. |
| 10/01/2009              | Medical Policy Committee review |
| 10/14/2009              | Medical Policy Committee review |
| 10/14/2010              | Medical Policy Committee review |
| 10/06/2011              | Medical Policy Committee review |
| 10/19/2011              | Medical Policy Implementation Committee approval. Added "familial" to the policy title. Replaced "hereditary" with "familial" in the investigational statement and throughout the policy. |
| 10/11/2012              | Medical Policy Committee review |
| 10/31/2012              | Medical Policy Implementation Committee approval. Coverage eligibility unchanged. |
| 10/03/2013              | Medical Policy Committee review |
| 10/16/2013              | Medical Policy Implementation Committee approval. Coverage eligibility unchanged. |
| 11/06/2014              | Medical Policy Committee review |
| 08/03/2015              | Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed. |
| 10/29/2015              | Medical Policy Committee review |
| 11/16/2015              | Medical Policy Implementation Committee approval. Coverage eligibility unchanged. |
| 11/03/2016              | Medical Policy Committee review |
| 01/01/2017              | Coding update: Removing ICD-9 Diagnosis Codes |

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11/02/2017 Medical Policy Committee review

Next Scheduled Review Date: 11/2018

Coding

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<td>C44.701-C44.799 C44.80-C44.89 C44.90-C44.99 D03.0-D03.9</td>
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*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

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Genetic Testing for Familial Cutaneous Malignant Melanoma

Policy #  00206
Original Effective Date:       09/20/2006
Current Effective Date:       11/15/2017

1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

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