



Louisiana

Genetic Testing for Familial Cutaneous Malignant Melanoma

Policy # 00206

Original Effective Date: 09/20/2006

Current Effective Date: 11/21/2018

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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

CUTANEOUS MALIGNANT MELANOMA

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

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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.

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.

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) 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)

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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

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

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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 both to 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.

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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.

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.

For example, in a meta-analysis of 145 genome-wide association studies, Chatzinasiou 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*, *ASIP/PIGU/MYH7B*, *CDKN2A/MTAP*). 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."

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

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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 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 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 (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 *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

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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. 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 (eg, 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

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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. 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.

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.

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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

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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 (ie, 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

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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 for 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

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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.

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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.

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09/06/2006 Medical Director review

09/20/2006 Medical Policy Committee approval

10/01/2008 Medical Director review

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10/22/2008	Medical Policy Committee approval. No change to coverage eligibility.
10/01/2009	Medical Policy Committee review
10/14/2009	Medical Policy Implementation Committee approval. No change to coverage eligibility.
10/14/2010	Medical Policy Committee review
10/20/2010	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
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
11/21/2014	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
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
11/16/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
11/02/2017	Medical Policy Committee review
11/15/2017	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/08/2018	Medical Policy Committee review
11/21/2018	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
Next Scheduled Review Date:	11/2019

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	81404
HCPCS	No codes
ICD-10 Diagnosis	C43.0 C43.10-C43.12 C43.20-C43.22 C43.30-C43.39
	C43.4 C43.51-C43.59 C43.60-C43.62 C43.70-C43.72
	C43.8-C43.9 C44.00-C44.09 C44.101-C44.199 C44.201-C44.299
	C44.300-C44.399 C44.40-C44.49 C44.500-C44.599 C44.601-C44.699
	C44.701-C44.799 C44.80-C44.89 C44.90-C44.99 D03.0-D03.9

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- 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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