Title: Genetic Testing for Familial Cutaneous Malignant Melanoma (CDKN2A)

Description/Background

GENETICS OF 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 are identified in a single patient; and 3) in the case of 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 main genes involved in CMM susceptibility have now been identified. Cyclin-dependent kinase inhibitor 2A (CDKN2A), located on chromosome 9p21 encodes proteins that act as tumor suppressors. Mutations at this site 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 mutations 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 mutation. Mutations are also infrequent in those with an early age of onset or those with multiple primary melanomas. However, the incidence of CDKN2A mutations increases with a positive family history; CDKN2A mutations will be found in 5% of families with first-degree relatives, rising to 20–40% in kindreds with 3 or more affected first-degree relatives. Mutation detection rates in the CDKN2A gene are generally estimated as 20–25% 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 mutation 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 mutations, have been described. The most pronounced associated malignancy is pancreatic cancer, followed by 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 mutations have been described in families with melanoma and breast cancer, gastrointestinal cancer, pancreatic cancer, or prostate cancer.

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 mutations. 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 since 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 mutations, there were family members with multiple atypical nevi who were noncarriers of the CDKN2A familial mutation. Thus, the nevus phenotype cannot be used to distinguish carriers from noncarriers of CMM susceptibility in these families.

Ward et al (2012) reviewed the literature on germline melanoma susceptibility and concluded that in addition to the 2 rare high-penetrance variants (CDKN2A and CDK4), there are potentially many single nucleotide polymorphisms (SNP) which have small effects and low penetrance. Management

No widely accepted guidelines for the management of families with hereditary risk of melanoma exist. Badenas et al (2012) suggested several parameters to guide genetic testing for melanoma: in countries with a low to medium incidence of melanoma, genetic testing should be offered to families with 2 cases of melanoma or to an individual with 2 primary melanomas (the rule of 2); in countries with high incidence of melanoma, genetic testing should be offered to families with 3 cases of melanoma, or to an individual with 3 primary melanomas (the rule of 3). Delaunay et al (2017) suggested a modification to the recommendations by Badenas et al. In countries with a low to medium incidence of melanoma, Delaunay et al propose that the rule of 2 should guide genetic testing only if there is an individual with melanoma before the age of 40, otherwise the rule of 3 should apply. In a review, In general, individuals with increased risk
of melanoma are educated on prevention strategies such as reducing sun exposure and on skin examination procedures.

**Regulatory Status**

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). Melaris® and other CDKN2A tests are laboratory-developed tests (LDTs). Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, FDA has chosen not to require any regulatory review of this test.

**Medical Policy Statement**

The peer reviewed medical literature has not yet demonstrated the clinical utility of genetic testing for familial cutaneous malignant melanoma. Therefore, this service is experimental/investigational.

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

N/A

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

*Established codes:*

N/A

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

81404

**Rationale**

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.

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 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 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
The current practice being used: 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.
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).

Clinical validity is related to the interpretation of the results of the 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 mutations. For example, mutations in the CDKN2A gene can occur along its entire length, and some of these mutations represent harmless polymorphisms or noncoding mutations. Interpretation will improve as more data accumulate regarding the clinical significance of individual mutations in families with a known hereditary pattern of melanoma. However, the penetrance of a given mutation will also affect its clinical significance, particularly since the penetrance of CDKN2A mutations 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 the penetrance. Bishop et al (2002) estimated that the calculated risk of developing melanoma before age 80 years in carriers of CDKN2A mutations ranges from 58% in Europe to 91% in Australia.

Interpretation of a negative test is another issue. CDKN2A mutations 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. In a survey of individuals considered high risk for melanoma, Branstrom et l (2012) reported that those with variant-negative test results erroneously believed that they had a lower risk of developing melanoma and practiced fewer preventive behaviors.

Observational Studies
CDKN2A and CDK4 Studies
Table 1 summarizes rates of CDKN2A and CDK4 variants detected among patients with melanoma in various countries.

Harland et al (2014) conducted a case control study on patients with melanoma from Australia, Spain, and United Kingdom. CDKN2A variant rates for each of the populations were similar (Table 1). Case-control analyses showed that the strongest predictor of carrying a variant was having multiple primaries odds ratio [OR] = 5.4, 95% confidence interval [CI] = 2.5 to 11.6; and having 3 primaries, OR=32.4, 95% CI=14.7 to 71.2). Another predictor of carrying a variant is having a strong family history of melanoma: having 1 relative, OR = 3.8, 95% CI = 1.9 to 7.5; and having 2 or more relatives, OR = 23.2, 95% CI = 11.3 to 47.6).

Potrony et al (2014) measured the rate of CDKN2A variants among patients in Spain with sporadic multiple primary melanoma (MPM) and familial melanoma. Variant rates are presented in Table 1.
Bruno et al (2016) reported on the multiMEL study, in which genetic testing for CDKN2A and CDK4 variants were performed on 587 consecutive patients with MPM and 587 consecutive patients with single primary melanoma (SPM). Rates of the variants are presented in Table 1. Subgroup analyses by familial versus sporadic melanoma showed that among patients with familial MPM and familial SPM, the mutation rates were 44.4% and 24.6%, respectively, compared with sporadic MPM and sporadic SPM variant rates of 10.8% and 2.1%, respectively.

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 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. This low detection rate compared with other European countries and Australia 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 (e.g., latitude, sun exposure), could determine the occurrence of melanoma.

Mangas et al (2016) measured the rate of CDKN2A variants among individuals considered high risk for melanoma, defined as families with at least 2 cases of melanoma or individuals with multiple melanomas. A total of 57 individuals were tested, 41 of which were considered the index cases. Of the 41, a CDKN2A variant was identified in 4 index cases (Table 1).

Puig et al (2016) conducted genetic testing for CDKN2A variants among patients with melanoma in Latin America and Spain. Table 1 shows the variant rates among patients with familial melanoma. The CDKN2A variant rates were lower among patients in Latin America and Spain with sporadic MPM, 10.0% and 8.5%, respectively.

### Table 1. Presence of CDKN2A and CDK4 Variants in Patients with Melanoma

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>N</th>
<th>Number (%) with CDKN2A or CDK4 Variant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harland (2014)</td>
<td>Patients from Australia with melanoma</td>
<td>596</td>
<td>14 (2.3)</td>
</tr>
<tr>
<td>Harland (2014)</td>
<td>Patients from Spain with melanoma</td>
<td>747</td>
<td>19 (2.5)</td>
</tr>
<tr>
<td>Harland (2014)</td>
<td>Patients from United Kingdom with melanoma</td>
<td>1586</td>
<td>31 (2.0)</td>
</tr>
<tr>
<td>Potrony (2014)</td>
<td>Patients in Spain with sporadic multiple primary melanoma</td>
<td>234</td>
<td>20 (8.5)</td>
</tr>
<tr>
<td>Potrony (2014)</td>
<td>Patients in Spain with familial melanoma</td>
<td>326</td>
<td>46 (14.1)</td>
</tr>
<tr>
<td>Bruno (2016)</td>
<td>Patients in Italy with multiple primary melanoma</td>
<td>587</td>
<td>112 (19.1)</td>
</tr>
<tr>
<td>Bruno (2016)</td>
<td>Patients in Italy with single primary melanoma</td>
<td>587</td>
<td>26 (4.4)</td>
</tr>
<tr>
<td>Di Lorenzo (2016)</td>
<td>Patients in Italy meeting the Italian Society of Human Genetics definition of familial melanoma</td>
<td>48</td>
<td>1 (2.1)</td>
</tr>
<tr>
<td>Mangas (2016)</td>
<td>Patients from southern Switzerland with melanoma</td>
<td>41</td>
<td>4 (9.7)</td>
</tr>
<tr>
<td>Puig (2016)</td>
<td>Patients with familial melanoma from Argentina, Brazil, Chile, Mexico, and Uruguay</td>
<td>109</td>
<td>26 (23.9)</td>
</tr>
<tr>
<td>Puig (2016)</td>
<td>Patients with familial melanoma from Spain (Barcelona and Valencia)</td>
<td>439</td>
<td>62 (14.1)</td>
</tr>
</tbody>
</table>
**MC1R Studies**

Ghiiorzo et al (2012) studied 49 $CDKN2A$-mutation positive and 390 $CDKN2A$-mutation negative Italian patients with cutaneous melanoma. MC1R variants were associated with increased odds of melanoma only in $CDKN2A$-mutation-negative patients in a dose-dependent fashion: OR for one high-risk allele: 1.5 (95% CI: 1.1–2.0); OR for two high-risk alleles: 2.5 (95% CI: 1.7–3.7). In multivariate logistic regression, effects of MC1R variants were statistically significant in most $CDKN2A$ mutation-negative subgroups and few mutation-positive subgroups defined by phenotype (eye and hair color, skin complexion and phototype, presence or absence of freckles or atypical nevi, and 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 mutation-positive (OR: 71.2, 95% CI: 23.0–221.0) and mutation-negative (OR: 5.3, 95% CI: 2.0-14.3) patients, although 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 mutation-positive cases only (OR: 2.44, 95% CI: 1.3–4.5). This finding underscores the significance of nongenetic factors (e.g., sun exposure, and history of severe sunburn) for development of melanoma and the complexity of interpreting a positive family history.

In 2010, Kanetsty and colleagues conducted a study to describe associations of 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), with self-reported phenotypic characteristics and sun exposure information. Logistic regression was used to estimate associations of 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 variant, was associated with increased risk of melanoma (odds ratio [OR]: 1.7; 95% confidence interval [CI]: 1.0-2.8; and OR: 2.2; 95% CI: 1.5-3.0, respectively). However, risk was noted to be stronger in or limited to individuals 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 provide 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 of 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 1,639 melanoma patients (15% familial) and 1,342 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: OR for one allele: 2.2 (95% CI: 1.9–2.6); OR for two alleles: 5.0 (95% CI: 2.8–8.9). 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. Effects on health outcomes are unknown.

Cust et al (2012) classified 565 patients with invasive cutaneous melanoma diagnosed between 18-39 years of age, 518 sibling controls, and 409 unrelated controls into \textit{MC1R} categories defined by presence of high risk or other alleles.\textsuperscript{16} Compared to sibling controls, two \textit{MC1R} high-risk alleles (R151C and R160W) were associated with increased odds of developing melanoma (OR: 1.7 [95% CI: 1.1–2.6] and OR: 2.0 [95% CI: 1.2–3.2], respectively), but these associations were no longer statistically significant in analyses adjusted for pigmentation, nevus count, and sun exposure. Compared to unrelated controls, only the \textit{R151C} high-risk allele was associated with increased odds of developing melanoma in adjusted analysis. There was no association between other \textit{MC1R} allelic categories defined by presence of high risk or other alleles.

\textbf{Multiple Gene Study}

Cust et al (2018) used data from 2 large case-control studies to assess the incremental contribution of gene variants to risk prediction models using traditional phenotype and environmental factors.\textsuperscript{43} Data from 1035 cases and controls from an Australian study and 1460 cases and controls from a United Kingdom study were used in the analyses. The logistic regression models contained the following variables: presence of 45 single nucleotide polymorphisms (among 21 genes); family history of melanoma; hair color; nevus density; nonmelanoma skin cancer; blistering sunburn as a child; sunbed use; freckling as an adult; eye color; and sun exposure hours on weekends and vacation. When polygenic risk scores were added to the model with traditional risk factors, the area under the receiving operator curve (AUC) increased by 2.3\% for the Australia population and 2.8\% for the United Kingdom population. The \textit{MC1R} gene variants, which are related to pigmentation, were responsible for most of the incremental improvement in the risk prediction models.

\textbf{Systematic Reviews}

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 (\textit{MC1R}, \textit{TYR}, \textit{TYRP1}, \textit{SLC45A2}, \textit{ASIP/PIGU/MYH7B}, \textit{CDKN2A}/\textit{MTAP}).\textsuperscript{10}

Williams et al (2011) conducted a literature search through October 2009 and identified 20 studies providing data on 25 populations to include in a meta-analysis of \textit{MC1R} variants and melanoma. The meta-analysis found red hair color variants on the \textit{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.\textsuperscript{11}

\textbf{Section Summary: Clinically Valid}

Studies measuring \textit{CDKN2A} and \textit{CDK4} variants among patients with melanoma report rates between 2\% and 24\%, depending on the country of origin, type of melanoma (familial or sporadic) and number of primaries. 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 mutations is recognized as an important research tool, its clinical use will depend on how the results of the genetic analysis can be used to improve patient management. Currently, management of patients considered at 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 CDKN2A would alter these management recommendations.

If an affected individual tests positive for a CDKN2A mutation, the individual may be at increased risk for a second primary melanoma compared to the general population. Limited and protected sun exposure and increased surveillance would be recommended to any patient with a malignant melanoma, regardless of the presence of a CDKN2A mutation. However, a positive result will establish a mutation, thus permitting targeted testing for the rest of the family. In addition, a positive mutation in an affected family member increases the likelihood of its clinical significance if detected in another family member. However, a negative test is not interpretable, as a negative result does not necessarily indicate a decreased risk for melanoma.

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. 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 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. Patients with melanoma, regardless of variant status, will receive instructions on recurrence preventive measures in regards to sun avoidance techniques.
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.

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).

In 2009, Yang et al conducted a study to identify modifier genes for CMM in CMM-prone families with or without CDKN2A mutations. 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-positive families (BCL7A and IL9), while some were stronger in CDKN2A-negative families (BCL2L1). The authors considered these findings supportive of the hypothesis that common genetic polymorphisms 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, Puntervoll et al published a description of the phenotype of individuals with CDK4 mutations in 17 melanoma families (209 individuals; 62 cases, 106 related controls, and 41 unrelated controls). The incidence of atypical nevi was higher in those with CDK4 mutations (70% in melanoma patients; 75% in unaffected individuals) than in those without CDK4 mutations (27%; p<0.001). The distribution of eye color or hair color was not statistically different between CDK4 mutation-positive individuals (with or without melanoma) and mutation-negative family members. The authors conclude that “it is not possible to distinguish CDK4 melanoma families from those with CDKN2A mutation based on phenotype.” As noted previously, 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 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.

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 the target mutation), it is difficult to interpret the clinical significance of a mutation, as described. The likelihood of clinical significance is increased if the identified mutation is the same as one reported in other families, although the issue of
penetrance is a confounding factor. If the unaffected individual has the same mutation 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, regardless of whether the patient has undergone genetic testing.

**Prospective Studies**

In a 2008 study, Aspinwall et al found short-term change in behavior among a small group of patients without melanoma who were positive for the CDKN2A mutation.\(^{24}\) In this prospective study of 59 members of a CDKN2A mutation-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 mutation 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.\(^{26}\) In 2013, Aspinwall et al reported outcomes for 37 patients (62%) of this cohort who were available for 2-year follow-up.\(^{25}\) 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 knowledge of test results.

Borroni et al (2017) offered CDKN2A variant testing and counseling to patients with familial atypical mole/multiple melanoma syndrome.\(^{28}\) Of the 19 unrelated patients with 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 (9 females, 6 males; median age, 25 years; range, 11-79 years) 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.

Aspinwall et al (2018) compared potential informational and motivational benefits from genetic testing for melanoma among individuals from high risk families who were variant-positive (n=28), variant-negative (n=41), and unknown carrier status (n=45).\(^{44}\) High risk individuals were defined as those related to a patient with a known CDKN2A variant or those with a significant family history of melanoma (>3 cases) but no identified variant. All participants received genetic counseling, which included a risk estimate of developing melanoma during their lifetime. Outcomes, measured after 1 month and 1 year follow-up, included: feeling informed and prepared to manage risk; motivation to reduce sun exposure; motivation to perform screening; and negative/positive emotions about melanoma risk. Individuals who were tested (both variant-positive and variant negative) reported feeling significantly more informed and prepared to manage risk compared to those not tested. All participants had low negative emotions concerning melanoma risk.

**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 variant in CDKN2A (the p16-
Leiden variant) allowed for earlier identification of melanomas. Characteristics of 40 melanomas identified in 35 unscreened index patients (before heredity was diagnosed) were compared with 226 melanomas identified in 92 relatives of those 35 melanoma patients who were 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 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 mutation. 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 rate was 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. In comparison with the general population in the Netherlands, overall standardized morbidity ratio for melanoma was 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 conclude that surveillance of second- (as well as first-) degree relatives from very high-risk melanoma families is justified based on these findings, it is unclear whether these findings apply to families without or with other CDKN2A mutations. Further, because increased sun protection and surveillance are recommended for any member of a high-risk family, clinical relevance of the finding is uncertain.

Dalmasso et al (2018) conducted a retrospective case-control study to determine if there was an association between CDKN2A variants and survival among patients with melanoma. From consecutive patients with the diagnosis of melanoma and genetic testing data from a single hospital, 106 variant-positive cases and 199 variant-negative controls, matched by age and sex, were included in the analyses. The overall rate of deaths in both groups was 17%. Melanoma-specific mortality was 10.8% in the variant-positive group and 7.8% in the variant-negative group. There were no statistically significant differences in overall or melanoma-specific survival between the 2 groups.

### Table 2. Relevance Gaps

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcomes</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspinwall (2008)²⁴</td>
<td>2.No comparison group-all patients knew test results</td>
<td>1.Self-reported prevention behaviors; no health outcomes such as development of melanoma or survival</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

b Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.

c Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.

d Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).

e Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true positives, true negatives, false positives, false negatives cannot be determined).

Table 3. Study Design and Conduct Gaps

<table>
<thead>
<tr>
<th>Study</th>
<th>Selectiona</th>
<th>Blindingb</th>
<th>Test Deliveryc</th>
<th>Selective Reportingd</th>
<th>Data Completenesse</th>
<th>Statisticalf</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspinwall (2008)24 and (2013)25,26</td>
<td>3.33% dropout by 1 month follow-up (58 at baseline; 39 at 1 month)</td>
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</tr>
</tbody>
</table>

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

a Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., convenience).

b Blinding key: 1. Not blinded to results of reference or other comparator tests.

c Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.


e Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data. f Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported.

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 1 had an outcome of melanoma occurrence. None of the carriers developed melanoma, but the sample
size was small and the duration of follow-up may not have been long enough to detect disease development. 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 measuring prevalence of variants in certain genes among those with cutaneous malignant melanoma. Relevant outcomes are overall survival, disease-specific survival, test accuracy, and test validity. Limitations with clinical validity include difficulties with mutation variant interpretations, variable penetrance of a given mutation, and residual risk with a negative mutation. Currently, management of melanoma patients, which involves surveillance and education on sun avoidance behaviors, does 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. 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.

**Ongoing and Unpublished Clinical Trials**
Some currently unpublished trials that might influence this review are listed in Table 4.

**Table 4. Summary of Key Trials**

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT00339222</td>
<td>Family study of melanoma in Italy</td>
<td>1600</td>
<td>NR</td>
</tr>
<tr>
<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>
</tr>
<tr>
<td>NCT00591500</td>
<td>A model of genetic susceptibility: melanoma</td>
<td>4082</td>
<td>July 2020</td>
</tr>
<tr>
<td>NCT00849407</td>
<td>Genetic risk factors and acquired oncogenic mutations of melanoma</td>
<td>2000</td>
<td>Dec 2020</td>
</tr>
<tr>
<td>NCT00450593</td>
<td>Studies of familial melanoma</td>
<td>5000</td>
<td>Dec 2020</td>
</tr>
</tbody>
</table>

NCT: national clinical trial
SUPPLEMENTAL INFORMATION

PRACTICE GUIDELINES AND POSITION STATEMENTS

**Melanoma Genetics Consortium**
In 2002, Melanoma Genetics Consortium, comprising familial melanoma researchers from North America, Europe and Australia, indicated that genetic testing for melanoma susceptibility should not be offered outside of a research setting.\(^3\)

**American Society of Clinical Oncology**
In a 2002 American Society of Clinical Oncology (ASCO) publication, Kefford et al noted the sensitivity and specificity of tests for \(CDKN2A\) mutations are not fully known.\(^3\) Because interpreting genetic tests is difficult and because test results do not alter patient management, the Kefford publication indicated \(CDKN2A\) genetic testing should be performed only in clinical trials for several reasons including: a low likelihood of finding mutations in known melanoma susceptibility genes, uncertainty about the functionality and phenotypic expression of the trait among mutation carriers, and the lack of proven melanoma prevention and surveillance strategies. Additionally, it was noted all patients with risk factors for cutaneous melanoma should follow programs of sun protection and skin surveillance, not just those patients considered to be high risk due to family history.

In 2003\(^3\) and 2010,\(^3\) 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.\(^3\) ASCO recommends that “genetic tests with uncertain clinical utility, including genomic risk assessment, be administered in the context of clinical trials.”

**American Academy of Dermatology**
In 2019, the American Academy of Dermatology published guidelines for the care and management of primary cutaneous melanoma.\(^4\) There was a single recommendation related to genetic testing, which was directed to pregnant women: "Referral for genetic counseling and possible germline genetic testing for select patients with cutaneous melanoma" - strength of recommendation: C; level of evidence: III. The Work Group explained that "there is no strong evidence that genetic evaluation is either harmful or helpful.”

**National Comprehensive Cancer Network**
Current National Comprehensive Cancer Network guidelines for cutaneous melanoma (v.1.2019) 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.”\(^3\)
Government Regulations
National:
There is no national Medicare coverage determination on this topic.

Local:
There is no local Medicare coverage determination on this topic.

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

Related Policies

Genetic Testing and Counseling

References


The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through February 2019, the date the research was completed.
## Joint BCBSM/BCN Medical Policy History

<table>
<thead>
<tr>
<th>Policy Effective Date</th>
<th>BCBSM Signature Date</th>
<th>BCN Signature Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>3/1/13</td>
<td>12/11/12</td>
<td>12/31/12</td>
<td>Joint policy established</td>
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<tr>
<td>3/1/14</td>
<td>12/10/13</td>
<td>1/6/14</td>
<td>Routine maintenance. Deleted procedure code 88299; added CPT code 81404. Updated rationale and references.</td>
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<tr>
<td>7/1/16</td>
<td>4/19/16</td>
<td>4/19/16</td>
<td>Routine maintenance. Updated references and rationale.</td>
</tr>
<tr>
<td>7/1/17</td>
<td>4/18/17</td>
<td>4/18/17</td>
<td>Routine maintenance of non-covered service. No change in policy status.</td>
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<tr>
<td>7/1/18</td>
<td>4/17/18</td>
<td>4/17/18</td>
<td>Routine policy maintenance, updated rationale, added references #18, 30 and 35. No change in policy status.</td>
</tr>
<tr>
<td>7/1/19</td>
<td>4/16/19</td>
<td></td>
<td>Routine policy update, added references 43, 44 and 46. No change in policy status.</td>
</tr>
</tbody>
</table>

Next Review Date: 2nd Qtr, 2020
## BLUE CARE NETWORK BENEFIT COVERAGE
**POLICY: GENETIC TESTING FOR FAMILIAL CUTANEOUS MALIGNANT MELANOMA (CDKN2A)**

### I. Coverage Determination:

<table>
<thead>
<tr>
<th>Plan Type</th>
<th>Coverage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commercial HMO (includes Self-Funded groups unless otherwise specified)</td>
<td>Not covered.</td>
</tr>
<tr>
<td>BCNA (Medicare Advantage)</td>
<td>Not covered.</td>
</tr>
<tr>
<td>BCN65 (Medicare Complementary)</td>
<td>Coinsurance covered if primary Medicare covers the service.</td>
</tr>
</tbody>
</table>

### II. Administrative Guidelines:

N/A