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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.

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.[1]

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.[2]

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

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 **PICOs** were used to select literature to inform this review.

Populations

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

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.[3,] However, the incidence of *CDKN2A* disease-associated variants increases with a positive family history;*CDKN2A* disease-associated variants will be found in 5% of families with first-degree relatives, rising to 20% to 40% in patients with 3 or more affected first-degree relatives.[4,] Variant detection rates of the *CDKN2A* gene are generally estimated to be 20% to25% in hereditary cutaneous malignant melanoma 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.[5,6,]

Interventions

Genetic testing for genes associated with CMM. Referral for genetic counseling is important for the explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

In 2012, Badenas et al 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 a 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).[7,] In 2017, Delaunay et al suggested a modification to the recommendations by Badenas et al (2012). In countries with a low to medium incidence of melanoma, Delaunay et al (2017) proposed 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.[8,]

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.

Review of Evidence

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 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.[3,4] 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.[9]

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.[3] 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.[10]

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.[11] *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.[12] 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).[13] 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.[14] 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.[15] 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.[16] 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.

Artomov et al (2017) assessed the rate of rare genetic variants including *CDKN2A* among patients with familial cutaneous melanoma (n=273) in the United States and Greece.[17] A validation set utilizing case-matched European controls against data obtained from The Cancer Genome Atlas melanoma cohort (n=379) confirmed statistically significant association for the *CDKN2A* variant (p=0.009).

Gironi et al (2018) conducted genetic testing in Italian families prone to cutaneous melanoma to elucidate distinctive clinical and histological features of melanomas in *CDKN2A* mutation carriers.[18] Three hundred patients with cutaneous melanoma (CM) were enrolled and interviewed about their personal and family history of CM and other cancers. Specifically, patients were eligible for genotyping if they had a histologically proven diagnosis of 1 or more CM and met at least 1one of the following inclusion criteria: 1) CM diagnosis at ≤ 40 years of

age; 2) MPM; 3) family history of CM; and/or 4) Personal and/or family history of non-cutaneous cancers suggestive of familial cancer syndrome related to germline mutations of CDKN2A, CDK4, MITF, and BAP1 genes. Genotyping revealed 100 patients with wildtype (WT)CDKN2A genes and 32 patients with CDKN2A variants that were subsequently analyzed according to histological and clinical features. The WT group did not significantly differ from the CDKN2A mutation-positive group with respect to photo type (p=-0.759), number of total common melanocytic nevi (p=0.131). However, a personal history of previously excised dysplastic nevi was more frequent among CDKN2A variant-positive patients compared to WT (62.5% vs. 26%; p<0.001). A positive family history of CM and/or pancreatic cancer was detected in 90.6% of mutation-positive patients compared to 37% of the WT group (p<0.001). This significance was maintained for CM or pancreatic cancer, individually (78.1% vs. 29%; p<0.001 and 34.4% vs. 10%; p<0.001). There were 54 (41%) patients in this study with at least 1 family member with a history of CM. Among these patients, 25/54 (46.3%) carried a CDKN2A germline mutation. There were 21 (16%) of patients with a family history of pancreatic cancer. Among these patients, 11/21 (52.4%) carried a CDKN2A germline mutation. Patients with a CDKN2A germline mutation developed a statistically significant higher number of MPMs compared to the WT group (mean, 1.88 vs. 1.18; p<0.001). However, while most patients in both genotype groups developed 2 primary melanomas (61% CDKN2A, 87.5% WT), 3 or 4 MPMs were observed more frequently in patients with a CDKN2A mutation. All CDKN2A carriers were found to develop superficial spreading melanomas whereas WT patients generated mostly nodular melanomas or lentigo maligna and lentigo maligna melanomas (p=0.006). There was no significant difference in CDKN2A status with respect to meeting inclusion criteria for sentinel node biopsy (15.6% CDKN2A, 22% WT; p=0.302). Additionally, 0/5 (0%) patients who underwent the procedure with a CDKN2A variant showed metastases compared to 4/22 (18.2%) of WT patients.

De Simone et al (2020) conducted a retrospective review of melanoma predisposition variants (e.g., CDKN2A, CDK4) in 888 patients with melanoma from Central Italy.[19] Overall, the study included 309 patients with multiple primary melanomas, 435 patients with familial melanoma, and 144 cases with both multiple primary melanomas and familial melanoma. Table 1 summarizes the CDKN2A variant rate, which includes variants of unknown significance.

Pissa et al (2021) conducted genetic testing for CDKN2A variants among 403 Swedish families between 2015-2020.[20] Included families had 3 or more cases of melanoma and/or pancreatic cancer, 2 melanomas in first-degree relatives with the youngest case occurring before age 55, or individuals with 3 or more multiple primary melanomas, with the first occurring before age 55. A total of 33 families (8.2%) were found to have CDKN2A pathogenic variants. Frequencies of CDKN2A pathogenic variants ranged from 0.9% in families with only 2 melanomas to 43.2% in families with 3 or more melanoma cases and pancreatic cancer. The frequency of CDKN2A variants ranged from 2.1% to 16.5% in families where the youngest case occurred after age 55 or before age 35 (p=.04). Families with CDKN2A pathogenic variants had a higher rate of melanoma-related mortality (37.6% versus 10.0%; p<.001). The authors concluded that these findings may help inform selection criteria to guide genetic testing for familial melanoma.

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

Study	Population	N	Number (%) with *CDKN2A* or *CDK4* Variant
Harland (2014)	Patients from Australia with melanoma	596	14 (2.3)
Harland (2014)	Patients from Spain with melanoma	747	19 (2.5)
Harland (2014)	Patients from United Kingdom with melanoma	1586	31 (2.0)
Potrony (2014)	Patients in Spain with sporadic multiple primary melanoma	234	20 (8.5)
Potrony (2014)	Patients in Spain with familial melanoma	326	46 (14.1)
Bruno (2016)	Patients in Italy with multiple primary melanoma	587	112 (19.1)
Bruno (2016)	Patients in Italy with single primary melanoma	587	26 (4.4)
Di Lorenzo (2016)	Patients in Italy meeting the Italian Society of Human Genetics definition of familial melanoma	48	1 (2.1)
Mangas (2016)	Patients from southern Switzerland with melanoma	41	4 (9.7)
Puig (2016)	Patients with familial melanoma from Argentina, Brazil, Chile, Mexico, and Uruguay	109	26 (23.9)
Puig (2016)	Patients with familial melanoma from Spain (Barcelona and Valencia)	439	62 (14.1)
Artomov (2017)	Patients with familial cutaneous melanoma from the United States (Boston) and Greece (Athens)	273	5 (1.8)
Gironi (2018)	Patients with cutaneous melanoma from Italy meeting criteria for a familial cancer syndrome related to melanoma-susceptibility genes	134	32 (23.8)
De Simone et al (2020)	Patients with cutaneous melanoma from Central Italy, including patients with multiple primary melanomas and/or histories of familial melanoma	888	98 (11.0)[1]
Pissa et al (2021)	Families with cutaneous melanoma from Sweden, including families with multiple cases of melanoma and/or pancreatic cancer and young age at incidence	403[b]	33 (8.2%)[b]

[1] Includes variants of unknown significance.
[b] Based on familial incidence.

MC1R Studies

Ghiorzo et al (2012) studied 49 *CDKN2A*-mutation positive and 390 *CDKN2A*-mutation negative Italian patients with cutaneous melanoma.[21] *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 photo type, 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.[22] 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.[23] 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 *MC1R* categories defined by presence of high risk or other alleles.[24] Compared to sibling controls, two *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 *R151C* high-risk allele was associated with increased odds of developing melanoma in adjusted analysis. There was no association between other *MC1R* alleles (not considered high risk) and odds of developing melanoma in unadjusted or adjusted analyses.

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.[25] 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 *MC1R* gene variants, which are related to pigmentation, were responsible for most of the incremental improvement in the risk prediction models.

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 (*MC1R, TYR, TYRP1, SLC45A2, ASIP/PIGU/MYH7B, CDKN2A/MTAP*).[26]

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 *MC1R* variants and melanoma. The meta-analysis 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.[27]

Section Summary: Clinically Valid

Studies measuring *CDKN2A* and *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.

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.[28]

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: Testing Individuals with Cutaneous Malignant Melanoma and Family History of this Disease
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 **PICOs** were used to select literature to inform this review.

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

Familial cutaneous malignant melanoma has been described in families in which either 2 first-degree relatives are diagnosed with melanoma or a family with 3 melanoma patients, irrespective of the degree of relationship.[29,] Others have defined familial cutaneous malignant melanoma 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.[30,] Other malignancies associated with familial cutaneous malignant melanoma, 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.

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

Interventions
Genetic testing for genes associated with CMM.

Patient referral for genetic counseling is important for the explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

In 2012, Badenas et al 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 a 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).[7,] In 2017, Delaunay et al suggested a modification to the recommendations by Badenas et al (2012). In countries with a low to medium incidence of melanoma, Delaunay et al (2017) proposed 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.[8,]

Comparators
The following practice is currently being used: standard clinical management without genetic testing. Personal and family history are used to guide melanoma screening decisions. For individuals in a family at high risk of melanoma, regular skin checks by trained health care providers, skin self-exams, and counseling on sun protective practices are recommended. Given the overlap between genetic susceptibility for melanoma and other cancers, there may be relevant recommendations for screening of other cancers (e.g., pancreatic, breast, colon).

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.

The primary outcomes of interest are clinician directed changes in patient management including the initiation and frequency of monitoring and use of preventive measures.

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).

Review of Evidence
In 2009, Yang et al conducted a study to identify modifier genes for CMM in CMM-prone families with or without *CDKN2A* mutations.[31] 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).[32] 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.

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.

Several studies, described below, have reported changes in self- or objectively reported changes in sun protective behaviors and attitudes as a result genetic counseling and/or test reporting. However, no inferences can be drawn on the usefulness of testing asymptomatic individuals in a family at high-risk of developing cutaneous malignant melanoma as studies have not yet addressed improvements in key health outcomes and changes in clinician-directed patient management.

Systematic Reviews
Primiero et al (2021) published 2 systematic reviews evaluating the impact of genetic testing in familial melanoma on primary and secondary preventative behaviors and psychosocial outcomes and attitudes.[33,34] Eight studies evaluating sun-protective behaviors were identified. Authors concluded that genetic testing has a modestly positive impact on sun-protective behaviors (e.g., sunscreen use, sun-protective clothing, avoiding sun exposure and tanning) in high-risk individuals. These improvements were observed regardless of mutation carrier status, although higher adherence was observed in carriers. Twelve studies evaluating psychosocial outcomes and behaviors were identified. The authors found that generalized distress does not appear to be impacted by testing outcomes, carrier status, or personal history. However, melanoma-specific distress was associated with carrier status and/or personal history. Genetic

risk assessment was not found to impact participants' perceived risk of subsequent melanomas.

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.[35] 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. In 2013, Aspinwall et al reported outcomes for 37 patients (62%) of this cohort who were available for 2-year follow-up.[36,37] 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.[38] 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).[39] 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.

Stump et al (2018) provided genetic test reporting and counseling for melanoma risk in pediatric patients to assess effects on sun-protective behaviors and psychological harms.[40] Patients aged 10-15 with a parent with a *CDKN2A/p16* mutation, no personal history of melanoma, and no previous genetic testing for melanoma were eligible for the study. Twenty children enrolled and 2 withdrew prior to the 1-month follow-up visit, resulting in 18 participants from 11 families. Measures of protective behavior and distress were collected at baseline, 1

week, 1 month, and 1 year. Participants and their mothers were individually interviewed regarding the psychological and behavioral impact of genetic testing. *CDKN2A* carriers (n=9) and non-carriers (n=9) both reported significantly fewer sunburns and a greater proportion reported sun protection adherence between baseline and 1 year; results did not vary by mutation status. Anxiety symptoms were low post-disclosure, whereas depressive symptoms and cancer worry decreased.

Stump et al (2020) investigated whether genetic counseling and test reporting for CDKN2A carrier status promoted objective reductions in sun exposure.[41] Participants were recruited from two types of pedigrees: families with an identified CDKN2A mutation and families with a similar melanoma history but no identified CDKN2A mutation. Subjects from CDKN2A-positive families were derived from 3 kindreds, and accounted for 32 carriers and 46 noncarriers. No-test control subjects (n=50) were derived from 9 CDKN2A-negative families. The daily standard erythemal dose (SED; J/m^2) of ultraviolet radiation (UVR) exposure was measured with a wrist-worn, battery-powered dosimeter over three 27-day periods. Complete dosimetry data was available for 75.8% of participants, with missing data due to technical issues, device loss, or device damage. The average number of days coded as "not worn" ranged from 7-10 days in each assessment period. Both carriers and no-test controls exhibited a significant decrease in UVR dose at 1 year compared to baseline ($P < 0.01$). No change from baseline was noted for noncarriers at any timepoint. However, these outcomes do not account for the use of sunscreen or sun-protective clothing. Skin pigmentation was assessed via reflectance spectroscopy, yielding a Melanin Index (MI) score in which higher scores represent greater melanin content. Measurements from the face and wrist were standardized to measurements obtained from non-exposed sites to account for differences in skin tone. Data from patients using artificial tanning products within a week of testing were excluded. Only carriers exhibited a significant decrease in skin pigmentation at the wrist at 1 year ($P < 0.001$). However, no corresponding changes in facial pigmentation were detected for any group. Both carriers and no-test controls self-reported fewer sunburns than non-carriers ($P < 0.05$). Noncarriers did not demonstrate changes in any measure of UVR exposure; however, daily UVR exposure was higher among noncarriers compared to no-test controls at baseline ($P = 0.03$). Despite the incorporation of propensity score matching in their statistical methods, the authors acknowledge that they cannot exclude yet-to-be identified confounding factors driving between-group differences in their non-equivalent control study design. The study did not assess key health outcomes such as melanoma incidence.

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.[42] 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.[43] 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.[44] 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. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-up[e]
Aspinwall (2008) and (2013)			2.No comparison group-all patients knew test results	1.Self-reported prevention behaviors; no health outcomes such as development of melanoma or survival	
Borroni (2017)			2. No comparison group		1.Follow-up of 37.5 months may not be long to detect disease development
Aspinwall (2018)				1.Self-reported prevention behaviors; no health outcomes such as development of melanoma or survival	1.Follow-up of 1 year not adequate for clinical outcomes

Stump (2018)	1. Parental history of *CDKN2A/p16* mutation required but only 45.5% of families reported as having a parent with a prior melanoma diagnosis			1. Self-reported prevention behaviors; no health outcomes such as development of melanoma or survival	1. Follow-up of 1 y not adequate for clinical outcomes
Stump et al (2020)			2. Non-equivalent comparison group	1. Physiologic measures are not validated surrogates for key health outcomes such as development of melanoma or survival	1. Follow-up of 1 y not adequate for clinical outcomes

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

Study	Selection[a]	Blinding[b]	Test Delivery[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Aspinwall (2008) and (2013)		1. Patients aware of test results			3.33% dropout by 1 month follow-up (58 at baseline; 39 at 1 month)	
Borroni (2017)		1.No discussion of blinding				
Aspinwall (2018)		1.Patients aware of test results				
Stump (2018)		1.Blinding not described		1.Not registered		1.Other; small sample size
Stump et al (2020)	2. Selection not random	1. Blinding not described		1. Not registered	3. 25% of participants had incomplete dosimetry data	1. Other: cannot exclude selection bias despite propensity score matching

The evidence limitations stated in this table are those notable in the current review; this is not a comprehensive limitations 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.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[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.

Section Summary: Testing Asymptomatic Individuals in a Family at High-Risk of Developing Cutaneous Malignant Melanoma

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 that the technology results in an improvement in the net health outcome.

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. Some guidelines recommend specific screening intervals and modalities for *CDKN2A* carriers; therefore, clinical utility is lacking. The evidence is insufficient to determine that the technology results in an improvement in the net 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

NCT No.	Trial Name	Planned Enrollment	Completion Date

Ongoing			
NCT00040352	Clinical, laboratory, and epidemiologic characterization of individuals and families at high risk of melanoma	3000	NR
NCT00591500	A model of genetic susceptibility: melanoma	4082	July 2020
NCT00849407	Genetic risk factors and acquired oncogenic mutations of melanoma	2000	Dec 2020 (unknown)
NCT00450593	Studies of familial melanoma	5000	Dec 2020
NCT00445783	Melanoma family case-control study protocol	3700	Dec 2020
NCT00591500	A model for genetic susceptibility: melanoma	4082	Jul 2021
NCT02645149[a]	Molecular Profiling and Matched Targeted Therapy for Patients With Metastatic Melanoma (MatchMel)	1000	Dec 2028
Unpublished			
NCT00339222	Family study of melanoma in Italy	1708	Jan 2020 (completed)

NCT: national clinical trial
[a] Denotes industry-sponsored or cosponsored trial

SUPPLEMENTAL INFORMATION

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

PRACTICE GUIDELINES AND POSITION STATEMENTS
Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

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.[47] 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[48] and 2010,[49] 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.[49] ASCO recommends that "genetic tests with uncertain clinical utility, including genomic risk assessment, be administered in the context of clinical trials."

In 2015, the ASCO commissioned another update to its policy statement on genetic and genomic testing for cancer susceptibility.[50] The ASCO "affirms that it is sufficient for cancer risk assessment to evaluate genes of established clinical utility that are suggested by the patient's personal and/or family history."

American Academy of Dermatology
In 2019, the American Academy of Dermatology published guidelines for the care and management of primary cutaneous melanoma.[45] 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." Criteria for cancer risk genetic counseling with possible multigene testing for patients with cutaneous melanoma include:
- A family history of invasive cutaneous melanoma or pancreatic cancer (>3 affected members on 1 side of the family)
- Multiple primary invasive cutaneous melanomas (>3), including 1 early-onset tumor (at age <45 years)
- A family history of mesothelioma, meningioma, and/or uveal melanoma and >1 melanocytic *BAP1* mutated atypical intradermal tumor (MBAIT)
- >2 MBAITs

These 2019 guidelines are similar to standards previously established by the International Melanoma Genetics Consortium in 2009.[46]

National Comprehensive Cancer Network
Current National Comprehensive Cancer Network guidelines for cutaneous melanoma (v.1.2024) have added under Common Follow-up Recommendations for All Patients:[52]

- "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, and/or astrocytoma diagnoses in an individual or family.
- "Multigene panel testing that includes CDKN2A is also recommended for patients with invasive cutaneous melanoma who have a first-degree relative diagnosed with pancreatic cancer."
- Testing for other genes that can harbor melanoma-predisposing mutations (e.g., *MC1R, CDK4, TERT, MITF*, PTEN, and *BAP1*) may be warranted."

Current (v.3.2024) NCCN guidelines for genetic/familial high-risk assessment in breast, ovarian, and pancreatic cancer state that Comprehensive skin examination by a dermatologist, supplemented with total body photography and dermoscopy is recommended biannually .[53]

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

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through March 2024, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
3/1/13	12/11/12	12/31/12	Joint policy established
3/1/14	12/10/13	1/6/14	Routine maintenance. Deleted procedure code 88299; added CPT code 81404. Updated rationale and references.
7/1/15	4/24/15	5/8/15	Routine maintenance. Updated references and rationale.
7/1/16	4/19/16	4/19/16	Routine maintenance. Updated references and rationale.
7/1/17	4/18/17	4/18/17	Routine maintenance of non-covered service. No change in policy status.
7/1/18	4/17/18	4/17/18	Routine policy maintenance, updated rationale, added references #18, 30 and 35. No change in policy status.
7/1/19	4/16/19		Routine policy update, added references 43, 44 and 46. No change in policy status.
7/1/20	4/14/20		Routine policy maintenance. No change in policy status.
7/1/21	4/20/21		Routine policy maintenance, added references #22 and 39. No change in policy status.
7/1/22	4/19/22		Routine policy maintenance, added references # 23, 34 and 35. No change in policy status.
7/1/23	4/18/23		Routine policy maintenance. No change in policy status. Vendor managed: N/A. (ds)
7/1/24	4/16/24		Routine policy maintenance, some of description section incorporated into rationale section, references reorganized. No change in policy status. Vendor managed: N/A (ds)

Next Review Date: 2nd Qtr. 2025

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: GENETIC TESTING FOR FAMILIAL CUTANEOUS MALIGNANT MELANOMA
(CDKN2A)

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Not covered.
BCNA (Medicare Advantage)	see government section.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

N/A