

2.04.44 Germline Genetic Testing for Familial Cutaneous Malignant Melanoma (CDKN2A, CDK4)

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Section:	2.0 Medicine	Page:	Page 1 of 25

Policy Statement

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

NOTE: Refer to [Appendix A](#) to see the policy statement changes (if any) from the previous version.

Policy Guidelines

Genetics Nomenclature Update

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

The American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology - "pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"- to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

Genetic Counseling

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic

testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Hereditary Cancer Syndromes and Screening Recommendations

Genetic susceptibility for melanoma can be a component in other hereditary cancer syndromes and therefore risk assessment and screening guidelines related to other cancers may be relevant to consider. NCCN v.2.2023 guidelines for genetic/familial high-risk assessment in breast, ovarian, and pancreatic cancer recommend comprehensive skin examination by a dermatologist supplemented with biannual total body photography and dermoscopy for *CDKN2A* variant carriers. The publication referenced in the guidelines to support the recommendation is a review article that does not provide evidence that biannual total body photography and dermoscopy improves outcomes.

Coding

The following CPT code has been **revised**: CPT code 81404 includes:

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

Testing for *CDK4* would be reported with the following code:

- **81479**: Unlisted molecular pathology procedure

Description

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

Related Policies

- N/A

Benefit Application

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

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

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Melaris® (Myriad Genetics) and other *CDKN2A* tests are available under the auspices of the CLIA. Laboratories that offer laboratory-developed tests must be licensed by the CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

Rationale

Background

Genetics of Cutaneous Malignant Melanoma

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

The incidence of *CDKN2A* disease-associated variants in the general population is very low. For example, it is estimated that in Queensland, Australia, an area with a high incidence of melanoma, only 0.2% of all patients with melanoma will harbor a *CDKN2A* disease-associated variant. Variants are also infrequent in those with an early age of onset or those with multiple primary melanomas.¹ 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.² Variant detection rates of the *CDKN2A* gene are generally estimated to be 20% to 25% 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.^{3,4}

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.⁵ 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.⁶ 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.

Some common allele(s) are associated with increased susceptibility to cutaneous malignant melanoma but have low-to-moderate penetrance. One gene of moderate penetrance is the melanocortin 1 receptor gene (*MCR1*). Variants in this gene are relatively common and have low penetrance for cutaneous malignant melanoma. This gene is associated with fair complexion, freckles, and red hair, all risk factors for cutaneous malignant melanoma. Variants in *MCR1* also modify the cutaneous malignant melanoma risk in families with *CDKN2A* variants.⁷

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 to co-segregate in familial atypical multiple mole and melanoma syndrome families, leading to the assumption that a single genetic factor was responsible. However, it was subsequently shown that, in families with *CDKN2A* variants, some family members with multiple atypical nevi were noncarriers of the *CDKN2A* familial variant. Thus, the nevus phenotype cannot be used to distinguish carriers from noncarriers of cutaneous malignant melanoma susceptibility in these families.

In 2012, Ward et al 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 which have small effects and low penetrance.⁸

Management

No widely accepted guidelines for the management of families with hereditary risk of melanoma exist.⁹ 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).¹⁰ 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.¹¹

In general, individuals with increased risk of melanoma are educated on prevention strategies such as reducing sun exposure and on skin examination procedures.

Literature Review

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

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

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

Testing Individuals with Cutaneous Malignant Melanoma and Family History of this Disease Clinical Context and Test Purpose

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

asymptomatic family members for variants associated with familial cutaneous malignant melanoma.

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

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with cutaneous malignant melanoma 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% to 25% 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

The test being considered is genetic testing for gene variants associated with cutaneous malignant melanoma.

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. In individuals with melanoma, surveillance and follow-up decisions are guided by the individual's melanoma staging.

Outcomes

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

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

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

One issue common to genetic testing for any cancer susceptibility is determining the clinical significance of individual variants. For example, variants in the *CDKN2A* gene can occur along its entire length, and some of these variants are benign. Interpretation will improve as more data accumulate on the clinical significance of individual variants in families with a known hereditary pattern of melanoma. However, the penetrance of a given variant will also affect its clinical significance, particularly because the penetrance of *CDKN2A* variants may vary with ethnicity and geographic location.^{3,4} For example, exposure to sun and other environmental factors, as well as behavior and ethnicity, may contribute to penetrance. In 2002, Bishop et al estimated that the calculated risk of developing melanoma before age 80 years in carriers of *CDKN2A* variants ranged from 58% in Europe to 91% in Australia.⁹

Interpretation of a negative test is another issue. *CDKN2A* variants are found in less than half of those with a strong family history of melanoma. Therefore, additional melanoma predisposition genes are likely to exist, and patients with a strong family history with normal test results must not be falsely reassured that they are not at increased risk.³ In a survey of individuals considered high-risk for melanoma, Branstrom et al (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 the 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; 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 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 multiple primary melanoma and 587 consecutive patients with single primary melanoma.¹³ Rates of the variants are presented in Table 1. Subgroup analyses by familial versus sporadic melanoma showed that among patients with familial multiple primary melanoma and familial single primary melanoma, the mutation rates were 44.4% and 24.6%, respectively, compared with sporadic multiple primary melanoma and sporadic single primary melanoma variant rates of 10.8% and 2.1%, respectively.

Di Lorenzo et al (2016) observed 400 patients with cutaneous malignant melanoma for a 6-year period at an Italian university.¹⁴ Forty-eight patients met the criteria of the Italian Society of Human Genetics for the diagnosis of familial melanoma and were screened for *CDKN2A* and *CDK4* variants. Genetic testing revealed that none of the families carried variants in the *CDK4* gene and only 1 patient harbored the rare *CDKN2A* p.R87W variant (Table 1). 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 populations, the

inheritance of familial melanoma in this island of the Mediterranean Sea is due to intermediate-/low-penetrance susceptibility genes, which, together with environmental factors (e.g., latitude, sun exposure), could determine the occurrence of melanoma.

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 multiple primary melanoma, 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 a statistically significant association for the *CDKN2A* variant ($p=.009$).

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 were enrolled and interviewed about their personal and family history of cutaneous melanoma and other cancers. Specifically, patients were eligible for genotyping if they had a histologically proven diagnosis of 1 or more cutaneous melanoma and met at least 1 of the following inclusion criteria: 1) cutaneous melanoma diagnosis at ≤ 40 years of age; 2) multiple primary melanoma; 3) family history of cutaneous melanoma; 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 *CDKN2A* genes and 32 patients with *CDKN2A* variants that were subsequently analyzed according to histological and clinical features. The wildtype group did not significantly differ from the *CDKN2A* mutation-positive group with respect to phototype ($p=.759$) or number of total common melanocytic nevi ($p=.131$). However, a personal history of previously excised dysplastic nevi was more frequent among *CDKN2A* variant-positive patients compared to wildtype (62.5% vs. 26%; $p<.001$). A positive family history of cutaneous melanoma and/or pancreatic cancer was detected in 90.6% of mutation-positive patients compared to 37% of the wildtype group ($p<.001$). This significance was maintained for cutaneous melanoma or pancreatic cancer, individually (78.1% vs. 29%; $p<.001$ and 34.4% vs. 10%; $p<.001$). There were 54 (41%) patients in this study with at least 1 family member with a history of cutaneous melanoma. Among these patients, 25/54 (46.3%) carried a *CDKN2A* germline mutation. There were 21 (16%) 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 multiple primary melanomas compared to the wildtype group (mean, 1.88 vs. 1.18; $p<.001$). However, while most patients in both genotype groups developed 2 primary melanomas (61% *CDKN2A*, 87.5% wildtype), 3 or 4 multiple primary melanomas were observed more frequently in patients with a *CDKN2A* mutation. All *CDKN2A* carriers were found to develop superficial spreading melanomas whereas wildtype patients generated mostly nodular melanomas or lentigo maligna and lentigo maligna melanomas ($p=.006$). There was no significant difference in *CDKN2A* status with respect to meeting inclusion criteria for sentinel node biopsy (15.6% *CDKN2A*, 22% wildtype; $p=.302$). Additionally, 0/5 (0%) patients who underwent the procedure with a *CDKN2A* variant showed metastases compared to 4/22 (18.2%) of wildtype 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* Variants in Patients with Melanoma

Study	Population	N	Number (%) with <i>CDKN2A</i> variants
Harland et al (2014) ¹¹	Patients from Australia with melanoma	596	14 (2.3)
Harland et al (2014) ¹¹	Patients from Spain with melanoma	747	19 (2.5)
Harland et al (2014) ¹¹	Patients from United Kingdom with melanoma	1586	31 (2.0)
Potrony et al (2014) ¹²	Patients in Spain with sporadic multiple primary melanoma	234	20 (8.5)
Potrony et al (2014) ¹²	Patients in Spain with familial melanoma	326	46 (14.1)
Bruno et al (2016) ¹³	Patients in Italy with multiple primary melanoma	587	112 (19.1)
Bruno et al (2016) ¹³	Patients in Italy with single primary melanoma	587	26 (4.4)
Di Lorenzo et al (2016) ¹⁴	Patients in Italy meeting the Italian Society of Human Genetics definition of familial melanoma	48	1 (2.1)
Mangas et al (2016) ¹⁵	Patients from southern Switzerland with melanoma	41	4 (9.7)
Puig et al (2016) ¹⁶	Patients with familial melanoma from Argentina, Brazil, Chile, Mexico, and Uruguay	109	26 (23.9)
Puig et al (2016) ¹⁶	Patients with familial melanoma from Spain (Barcelona and Valencia)	439	62 (14.1)
Artomov et al (2017) ¹⁷	Patients with familial cutaneous melanoma from the United States (Boston) and Greece (Athens)	273	5 (1.8)
Gironi et al (2018) ¹⁸	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) ¹⁹	Patients with cutaneous melanoma from Central Italy, including patients with multiple primary melanomas and/or histories of familial melanoma	888	98 (11.0) ^a
Pissa et al (2021) ²⁰	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

^a Includes variants of unknown significance.

^b Based on familial incidence.

MC1R Studies

Ghiorzo et al (2012) studied 49 *CDKN2A* variant-positive and 390 *CDKN2A* variant-negative Italian patients with cutaneous melanoma.²¹ *MC1R* (melanocortin 1 receptor gene) variants were associated with increased odds of melanoma only in *CDKN2A* variant-negative patients in a dose-dependent fashion: the OR for 1 high-risk allele was 1.5 (95% CI, 1.1 to 2.0); the odds for 2 high-risk alleles was 2.5 (95% CI, 1.7 to 3.7). In multivariate logistic regression, the effects of *MC1R* variants were statistically significant in most *CDKN2A* variant-negative subgroups and a few variant-positive subgroups defined by phenotype (eye and hair color, skin complexion and phototype, presence or absence of freckles or atypical nevi, total nevus count), sun exposure, and history of severe sunburn. In contrast, first-degree family history of cutaneous melanoma increased the odds of developing melanoma in both variant-positive (OR, 71.2; 95% CI, 23.0 to 221.0) and variant-negative (OR, 5.3; 95% CI, 2.0 to 14.3) patients, although the uncertainty in the estimates of association was considerable. The family history of cutaneous nevi (at least 1 first-degree relative with >10 nevi and/or atypical nevi) increased the odds of melanoma in variant-positive cases only (OR, 2.44; 95% CI, 1.3 to 4.5). This finding underscores the significance of nongenetic factors (e.g., sun exposure, history of severe sunburn) for development of melanoma and the complexity of interpreting a positive family history.

Kanetsky et al (2010) described the associations between *MC1R* variants and melanoma in a U.S. population and investigated whether the genetic risk is modified by pigmentation characteristics and sun exposure.²² The study population included melanoma patients (n=960) and controls (n=396) who self-reported phenotypic characteristics and sun exposure information. Logistic regression was used to estimate associations between high- and low-risk *MC1R* variants and melanoma, overall and within phenotypic and sun exposure groups. Carriage of 2 low-risk, or any high-risk *MC1R* variants, was associated with increased risk of melanoma (low-risk OR, 1.7; 95% CI, 1.0 to 2.8; high-risk OR, 2.2; 95% CI, 1.5 to 3.0). However, the risk was noted to be stronger in or limited to people with protective phenotypes and limited sun exposure, such as those who tanned well after repeated sun exposure (OR, 2.4), had dark hair (OR, 2.4), or had dark eyes (OR, 3.2). The authors concluded that *MC1R* genotypes provided information about melanoma risk in those individuals who would not be identified as high-risk based on their phenotypes or exposures alone. How this information impacts patient care and clinical outcomes are unknown.

Two subsequent studies in southern European populations examined further the association between *MC1R* variants and melanoma. In 2012, Ibarrola-Villava et al 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 1342 controls. *MC1R* variants associated with red hair color were successfully genotyped in 85% of cases and 93% of controls. (Two other genes not associated with familial cutaneous melanoma- *TYR*, which encodes a tyrosinase, and *SLC45A2*, which encodes a melanosome enzyme were also studied). In univariate logistic regression analysis, *MC1R* red hair color variants were significantly associated with the odds of developing melanoma in a dose-dependent fashion: the OR for 1 allele was 2.2 (95% CI, 1.9 to 2.6); the odds for 2 alleles was 5.0 (95% CI, 2.8 to 8.9). In an analysis stratified by self-reported phenotype, these variants were statistically associated with increased odds of melanoma not only in individuals with fair phenotype (eye, hair, and skin color) but also in those with dark/olive phenotype. The authors suggested that *MC1R* genotyping to identify elevated risk in southern European patients considered not at risk based on phenotype alone warranted further investigation.

Cust et al (2012) classified 565 patients with invasive cutaneous malignant melanoma diagnosed between 18 and 39 years of age, 518 sibling controls, and 409 unrelated controls into *MC1R* categories defined by the presence of high-risk or other alleles.²⁴ Compared with sibling controls, 2 *MC1R* high-risk alleles (R151C, R160W) were associated with increased odds of developing melanoma (R151C OR, 1.7; 95% CI, 1.1 to 2.6; R160W OR, 2.0; 95% CI, 1.2 to 3.2), but these associations were no longer statistically significant in analyses adjusted for pigmentation, nevus count, and sun exposure. Compared with unrelated controls, only the R151C high-risk allele was associated with increased odds of developing melanoma in the adjusted analysis. There was no association between

other *MC1R* alleles (not considered high-risk) and the odds of developing melanoma in unadjusted or adjusted analyses.

Multiple Gene Study

Cust et al (2018) used the 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 1,035 cases and controls from an Australian study and 1,460 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 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 epidemiological 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 cutaneous malignant melanoma 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 cutaneous malignant melanoma.

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, more effective therapy, or avoid unnecessary therapy or 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 (RCTs).

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

If an affected individual tests positive for a *CDKN2A* variant, the individual may be at increased risk for a second primary melanoma compared with the general population. However, limited and protected sun exposure and increased surveillance would be recommended to any patient with malignant melanoma, regardless of the presence of a *CDKN2A* variant. A positive result would establish a familial variant and permit targeted testing in the rest of the family. A positive variant 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 justify 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 the disease is lacking. While genetic variants associated with increased risk for developing melanoma have been identified, changes in clinical management and improved health outcomes as a result of genetic testing for individuals with melanoma is uncertain. Patients with melanoma, regardless of variant status, will receive instructions on recurrence preventive measures in regards to sun avoidance techniques.

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

Clinical Context and Test Purpose

The purpose of genetic testing of asymptomatic individuals in a family at high-risk of developing cutaneous malignant melanoma is to identify variants in genes associated with melanoma for increased surveillance to potentially detect disease at an earlier, more treatable stage.

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

The following PICO was 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 cutaneous malignant melanoma.

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 to co-segregate in familial atypical multiple mole and melanoma syndrome families, leading to the assumption that a single genetic factor was responsible. However, it was subsequently shown that, in families with *CDKN2A* variants, some family members with multiple atypical nevi were noncarriers of the *CDKN2A* familial variant. Thus, the nevus phenotype cannot be used to distinguish carriers from noncarriers of cutaneous malignant melanoma susceptibility in these families.

Interventions

The test being considered is genetic testing for gene variants associated with cutaneous malignant melanoma.

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

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

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

Yang et al (2009) conducted a study to identify modifier genes for cutaneous malignant melanoma in cutaneous malignant melanoma-prone families with or without *CDKN2A* variants.³¹ Investigators genotyped 537 individuals (107 cutaneous malignant melanoma) from 28 families (19 *CDKN2A*-positive, 9 *CDKN2A*-negative) for genes involved in DNA repair, apoptosis, and immune response. Analyses identified some candidate genes, such as *FAS*, *BCL7A*, *CASP14*, *TRAF6*, *WRN*, *IL9*, *IL10RB*, *TNFSF8*, *TNFRSF9*, and *JAK3*, associated with cutaneous malignant melanoma risk; after correction for multiple comparisons, *IL9* remained significant. The effects of some genes were stronger in *CDKN2A* variant-positive families (*BCL7A*, *IL9*), and some were stronger in *CDKN2A*-negative families (*BCL2L1*). The authors considered these findings supportive of the hypothesis that common genetic variants in DNA repair, apoptosis, and immune response pathways may modify the risk of cutaneous malignant melanoma in cutaneous malignant melanoma-prone families, with or without *CDKN2A* variants.

Punternvoll et al (2013) described the phenotype of individuals with *CDK4* variants in 17 melanoma families (209 individuals; 62 cases, 106 related controls, 41 unrelated controls).³² The incidence of atypical nevi was higher in those with *CDK4* variants (70% in melanoma patients vs. 75% in unaffected individuals) than in those without *CDK4* variants (27%; $p < .001$). The distribution of eye or hair color did not differ statistically between *CDK4* variant-positive individuals (with or without melanoma) and variant-negative family members. The authors concluded that "it is not possible to distinguish *CDK4* melanoma families from those with *CDKN2A* variants based on phenotype." As noted, the clinical significance of this genetic distinction is currently unclear.

Section Summary: Clinically Valid

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

Clinically Useful

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

If the asymptomatic individual is the first to be tested in the family (ie, no affected relative has been previously tested to define a familial variant), it is difficult to interpret the clinical significance of a variant, as described. The likelihood of clinical significance is increased if the identified variant is the same as that reported in other families, although the issue of penetrance is a confounding factor. If the asymptomatic individual has the same variant as an affected relative, then the patient is at high-risk for melanoma.

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 of 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. While some guidelines recommend specific melanoma screening intervals and modalities for *CDKN2A* variant carriers, these screening strategies have not been demonstrated to improve health outcomes in *CDKN2A* carriers.

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

Aspinwall et al (2008) reported on the short-term change in behavior among a small group of patients without melanoma who tested positive for the *CDKN2A* variant.³⁵ In this prospective study of 59 members of a *CDKN2A* variant-positive pedigree, behavioral assessments were made at baseline, immediately after *CDKN2A* test reporting and counseling, and at 1-month follow-up (42 participants). Across multiple measures, test reporting caused *CDKN2A* disease-associated variant carriers without a melanoma history to improve to the level of adherence reported by participants with a melanoma history. *CDKN2A*-positive participants without a melanoma history reported greater intention to obtain total body skin examinations, increased intentions and adherence to skin self-examination recommendations, and increased number of body sites examined at 1 month. In 2013, Aspinwall et al reported on outcomes for 37 (62%) patients of this cohort with 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 the knowledge of test results.

Borroni et al (2017) offered *CDKN2A* variant testing and counseling to patients with familial atypical mole/multiple melanoma syndrome.³⁸ Variants were identified in 19 of the 92 patients. 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 primary cutaneous melanoma. The 15 relatives underwent a complete dermatologic examination with dermoscopy. During a mean follow-up of 37 months (range, 4 to 53 months), none of the relatives developed primary cutaneous melanoma.

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 to 15 years 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 2 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 erythral dose (SED; J/m²) 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 to 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 ($p < .01$). 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 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 ($p < .001$). 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 ($p < .05$). 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 ($p = .03$). Despite the incorporation of propensity score matching in their statistical methods, the authors acknowledged 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 mutation in *CDKN2A* (the p16-Leiden variant) permitted 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 later found to have the *CDKN2A* variant. Surveillance consisted of a minimum of an annual total skin evaluation, which became more

frequent if melanoma was diagnosed. Melanomas diagnosed during surveillance were found to have a significantly lower Breslow thickness (median thickness, 0.50 mm) than melanomas identified in unscreened index 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 with surveillance recommendations still occurred van der Rhee et al (2013) reported on a retrospective case-control study of 21 families with the *CDKN2A* p16-Leiden founder mutation.⁴³ This study investigated the yield of surveillance of first- and second-degree relatives of patients with melanoma (n=14 families) or with melanoma and pancreatic cancer (n=7 families). Overall, melanoma incidence rates were 9.9 per 1000 person-years (95% CI, 7.4 to 13.3 person-years) in first-degree relatives and 2.1 per 1000 person-years (95% CI, 1.2 to 3.8 person-years) in second-degree relatives. Compared with the general Dutch population, overall standardized morbidity ratios for melanoma were 101.0 (95% CI, 55.9 to 182.3) in first-degree relatives (observed, 45; expected, 0.76) and 12.9 (95% CI, 7.2 to 23.4) in second-degree relatives (observed, 11; expected, 0.53). Although the authors concluded that surveillance of second- (as well as first-) degree relatives from very high-risk melanoma families were justified based on these findings, it is unclear whether these findings apply to families without or with other *CDKN2A* variants. Further, because increased sun protection and surveillance are recommended for any member of a high-risk family, the clinical utility of the finding is uncertain.

Dalmaso 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. Relevance, design, and conduct limitations of selected studies are summarized in Tables 2 and 3.

Table 2. Study Relevance Limitations

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Follow-Up ^e
Aspinwall et al (2008) ³⁵ , and (2013) ^{36,37}			2. No comparison group	1. Self-reported prevention behaviors; no health outcomes such as development of melanoma or survival	
Borroni et al (2017) ³⁸			2. No comparison group		1. Follow-up of 37.5 months not sufficient for clinical outcomes
Aspinwall et al (2018) ³⁹				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 et al (2018) ⁴⁰	1. Parental history of <i>CDKN2A/p16</i> mutation			1. Self-reported prevention	1. Follow-up of 1 year not

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Follow-Up ^e
	required but only 45.5% of families reported as having a parent with a prior melanoma diagnosis			behaviors; no health outcomes such as development of melanoma or survival	adequate for clinical outcomes
Stump et al (2020) ⁴¹		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 year not adequate for clinical outcomes

The study limitations 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.; 5 Enrolled study populations do not reflect relevant diversity

^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 Limitations

Study	Selection ^a	Blinding ^b	Test Delivery ^c	Selective Reporting ^d	Data Completeness ^e	Statistical ^f
Aspinwall et al (2008) ³⁵ , and (2013) ^{36,37}		1. Patients aware of test results			3. 33% dropout by 1 month follow-up (58 at baseline; 39 at 1 month)	
Borroni et al (2017) ¹⁰		1. Blinding not described				
Aspinwall et al (2018) ³⁹		1. Patients aware of test results				
Stump et al (2018) ⁴⁰		1. Blinding not described		1. Not registered		1. Other: small sample size
Stump et al (2020) ⁴¹	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 study limitations 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 (ie, 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 with 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 cutaneous malignant melanoma is lacking. Among the prospective studies, only one had an outcome of melanoma occurrence. None of the carriers developed melanoma, but the sample size was small and the duration of follow-up may not have been sufficient to detect disease development. While familial variants associated with increased risk for developing melanoma have been identified, net benefit of changes in clinical management a result of genetic testing for asymptomatic individuals is uncertain.

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 Academy of Dermatology

In 2019, the American Academy of Dermatology published guidelines for the care and management of primary cutaneous melanoma.⁴⁵ Referral for genetic counseling and possible germline genetic testing for select patients with cutaneous melanoma was recommended for consideration with a level III C grade of evidence. 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

American Society of Clinical Oncology

In an American Society of Clinical Oncology (ASCO) publication, Kefford et al (2002) noted that the sensitivity and specificity of tests for *CDKN2A* variants are not fully known.⁴⁷ Because interpreting genetic tests is difficult and because test results do not alter patient management, ASCO recommended that *CDKN2A* genetic testing should be performed only in clinical trials, for several reasons. These include a low likelihood of finding disease-associated variants in known melanoma susceptibility genes, uncertainty about the functionality and phenotypic expression of the trait among disease-associated variant carriers, and lack of proven melanoma prevention and surveillance strategies. Additionally, it was noted that all individuals with risk factors for cutaneous

melanoma should follow programs of sun protection and skin surveillance, not just those considered high-risk due to family history.

In 2003,⁴⁸ and 2010,⁴⁹ ASCO 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 recommended that "genetic tests with uncertain clinical utility, including genomic risk assessment, be administered in the context of clinical trials."

In 2015, ASCO commissioned another update to its policy statement on genetic and genomic testing for cancer susceptibility.⁵⁰ 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."

National Comprehensive Cancer Network

Current (v.1.2023) National Comprehensive Cancer Network (NCCN) guidelines for cutaneous melanoma include the following follow-up recommendations:⁵¹

- "Consider genetic counseling referral for *p16/CDKN2A* mutation [variant] testing in the presence of 3 or more invasive melanomas, or a mix of invasive melanoma, pancreatic cancer, and/or astrocytoma diagnoses in an individual or family."
- "Multigene panel testing that includes *CDKN2A* is 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*, *BRCA2*, and *BAP1*] may be warranted."

Current (v.2.2023) NCCN guidelines for genetic/familial high-risk assessment in breast, ovarian, and pancreatic cancer state that for *CDKN2A* mutation carriers "Comprehensive skin examination by a dermatologist, supplemented with total body photography and dermoscopy is recommended biannually".⁵²

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 4.

Table 4. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
<i>Ongoing</i>			
NCT00040352	Clinical, Laboratory, and Epidemiologic Characterization of Individuals and Families at High Risk of Melanoma	3000	NR (recruiting)
NCT00849407	Genetic Risk Factors and Acquired Oncogenic Mutations of Melanoma	2000	Dec 2020 (unknown)

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT00450593	Studies of Familial Melanoma	5000	Dec 2020 (unknown)
NCT00445783	Melanoma Family Case-Control Study Protocol	3700	Dec 2020 (unknown)
NCT00591500	A Model for Genetic Susceptibility: Melanoma	4082	Jul 2023 (ongoing)
NCT02645149 ^a	Molecular Profiling and Matched Targeted Therapy for Patients With Metastatic Melanoma (MatchMel)	1000	Dec 2028 (recruiting)
<i>Unpublished</i>			
NCT00339222	Family Study of Melanoma in Italy	1708	Jun 2020 (completed)

NCT: national clinical trial; NR: not reported.

^a Denotes industry-sponsored or cosponsored trial.

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Documentation for Clinical Review

- No records required

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	81345	TERT (telomerase reverse transcriptase) (e.g., thyroid carcinoma, glioblastoma multiforme) gene analysis, targeted sequence analysis (e.g., promoter region)
	81404	Molecular Pathology Procedure Level 5
	81479	Unlisted molecular pathology procedure
HCPCS	None	

Policy History

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

Effective Date	Action
04/01/2016	BCBSA Medical Policy adoption
05/01/2017	Policy revision without position change
05/01/2018	Policy revision without position change
02/01/2019	Coding update
06/01/2019	Policy revision without position change
05/01/2020	Annual review. No change to policy statement. Literature review updated.
01/01/2021	Coding update
05/01/2021	Annual review. No change to policy statement. Literature review updated.
06/01/2022	Annual review. No change to policy statement. Literature review updated.

Effective Date	Action
05/01/2023	Annual review. No change to policy statement. Policy guidelines and literature review updated. Policy title changed from Genetic Testing for Familial Cutaneous Malignant Melanoma to current one.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

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

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

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

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

Appendix A

POLICY STATEMENT	
BEFORE	AFTER
	Blue font: Verbiage Changes/Additions
Genetic Testing for Familial Cutaneous Malignant Melanoma 2.04.44	Germline Genetic Testing for Familial Cutaneous Malignant Melanoma (CDKN2A, CDK4) 2.04.44
Policy Statement: Genetic testing for genes associated with familial cutaneous malignant melanoma or associated with susceptibility to cutaneous malignant melanoma is considered investigational .	Policy Statement: I. Genetic testing for genes associated with familial cutaneous malignant melanoma or associated with susceptibility to cutaneous malignant melanoma is considered investigational .