

Genetic Testing for Cutaneous Malignant Melanoma

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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Genetic markers for cutaneous malignant melanoma (CMM) are being evaluated in those with a family history of the disease and to estimate risk for those who do not have family history of CMM.

MEDICAL POLICY CRITERIA

Genetic testing for variants associated with hereditary cutaneous malignant melanoma or associated with susceptibility to cutaneous malignant melanoma is considered **investigational**.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

1. [Genetic and Molecular Diagnostic Testing](#), Genetic Testing, Policy No. 20
2. [Gene Expression Profiling for Melanoma](#), Genetic Testing, Policy No. 29

BACKGROUND

GENETICS OF CUTANEOUS MALIGNANT MELANOMA

A genetic predisposition to cutaneous malignant melanoma (CMM) is suspected in specific clinical situations:

- Melanoma has been diagnosed in multiple close blood relatives;
- Multiple primary melanomas are identified in a single patient; and
- 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. Hereditary melanoma, caused by single gene disorder accounts for about half of these.^[1]

Multiple genes associated with high risk for melanoma have been identified:

- *CDKN2A*, located on chromosome 9p21, encodes proteins that act as tumor suppressors. Mutations at this site can alter the tumor suppressor function.
- *CDK4* is an oncogene located on chromosome 12q13. *CDK4* is a rare cause of hereditary melanoma than *CDKN2A* and is phenotypically similar.
- *BAP1*, which is located on 3p21, encodes a protein that acts as a tumor suppressor, and is associated with both cutaneous and uveal melanoma.
- *POT1*, located on 7q31.33 is associated with cutaneous melanoma and other cancers. Germline *POT1* variants have been identified in fewer than 100 families.

Additional genes that may be associated with CMM include genes involved in defined tumor syndromes in which melanoma risk may be increased (e.g., *PTEN*), and variants that suggest increased risk, but low-to-intermediate melanoma penetrance (e.g., *MITF*, *MC1R*).^[1-3]

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 variants. Variants are also infrequent in those with an early age of onset or those with multiple primary melanomas.^[4] However, the incidence of *CDKN2A* mutations increases with a positive family history; *CDKN2A* disease-associated variants will be found in 5% of families with first-degree relatives, rising to 20–40% in kindreds with three or more affected first-degree relatives.^[5] Variant detection rates in the *CDKN2A* gene are generally estimated as 20–25% in hereditary CMM but can vary between 2% and 50%, depending on the family history and population studied.

Hereditary CMM has been described as a family in which either two first-degree relatives are diagnosed with melanoma or a family with three melanoma patients, irrespective of the degree of relationship.^[6] Others have defined hereditary CMM as having at least three (first-, second-, or third-degree) affected members or two affected family members in which at least one was diagnosed before age 50 years, or pancreatic cancer occurred in a first- or second-degree relative, or one member had multiple primary melanomas.^[7]

Other malignancies are associated with hereditary CMM. Pathogenic *CDKN2A* variants in particular are associated with an increased risk for pancreatic cancer. Uveal melanoma is the most common cancer associated with *BAP1* tumor predisposition syndrome (TPD). *BAP1* variants are also associated with cutaneous melanoma, renal cell carcinoma and mesothelioma. The incidence of de novo *BAP1* variants is not known, penetrance is incomplete, and manifestations vary within affected families.^[2] Core cancers associated with

POT1-TPD are cutaneous melanoma, chronic lymphocytic leukemia, angiosarcoma and glioma. The penetrance and complete phenotype of *POT1* pathogenic variants are not well understood.^[3]

Hereditary forms of CMM can occur either with or without a family history of multiple dysplastic nevi. Families with both CMM and multiple dysplastic nevi have been referred to as having familial atypical multiple mole and melanoma syndrome (FAMMM). This syndrome is difficult to define since there is no agreement on a standard phenotype, and dysplastic nevi occur in up to 50% of the general population. Atypical or dysplastic nevi are associated with an increased risk for CMM. Initially, the phenotypes of atypical nevi and CMM were thought to co-segregate in FAMMM families, leading to the assumption that a single genetic factor was responsible. However, it was subsequently shown that in families with *CDKN2A* variants, there were family members with multiple atypical nevi who were non-carriers of the *CDKN2A* familial variant. *CDK4* variants are detected in fewer than one percent of patients with FAMMM syndrome.^[8] Thus, the nevus phenotype cannot be used to distinguish carriers from non-carriers of CMM susceptibility in these families.

MANAGEMENT

No widely accepted guidelines for the management of families with hereditary risk of melanoma exist.^[9] Badenas (2012) suggested several parameters to guide genetic testing for melanoma: in countries with a low to medium incidence of melanoma, genetic testing should be offered to families with two cases of melanoma or to an individual with two primary melanomas (the rule of two); in countries with high incidence of melanoma, genetic testing should be offered to families with three cases of melanoma, or to an individual with three primary melanomas (the rule of three).^[10] Delaunay (2017) suggested a modification to the recommendations by Badenas. In countries with a low to medium incidence of melanoma, Delaunay propose that the rule of two should guide genetic testing only if there is an individual with melanoma before the age of 40, otherwise the rule of three 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.

EVIDENCE SUMMARY

Human Genome Variation Society (HGVS) nomenclature^[12] is used to describe variants found in DNA and serves as an international standard. It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term “variant” is used to describe a change in a DNA or protein sequence, replacing previously-used terms, such as “mutation.” Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

Validation of the clinical use of any genetic test focuses on three main principles:

- The analytic validity of the test, which refers to the technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent;
- The clinical validity of the test, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and

- The clinical utility of the test, which describes how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

ANALYTIC VALIDITY

No published data on the analytic validity of genetic testing for variants associated with cutaneous malignant melanoma were identified.

CLINICAL VALIDITY

Clinical validity is related to interpretation of the results of genetic analysis for the individual patient. One issue common to genetic testing for any type of cancer susceptibility, is determining the clinical significance of individual variants. For example, variants in the *CDKN2A* gene can occur along its entire length, and some of these variants represent benign variants. Interpretation will improve as more data accumulate regarding 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.^[4, 5] For example, exposure to sun and other environmental factors, as well as behavior and ethnicity may contribute to penetrance. Bishop 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.^[13]

Interpretation of a negative test is another issue. Melanoma incidence has steadily increased since 1975. Potential reasons include increased exposure to ultraviolet radiation, increased skin cancer detection, and increased longevity.^[14] *CDKN2A* and other germline variants associated with high risk for melanoma are relatively uncommon. Family history of melanoma can be associated with other shared heritable traits (e.g., fair skin, red hair), as well as shared environmental exposures. Therefore, patients with a strong family history and normal genetic test results must not be falsely reassured that they are not at increased risk.^[4]

Simonin-Wilmer (2023) published a population-based study comparing *POT1* assessment of 2928 melanoma cases to 3298 controls, all of European ancestry.^[15] Forty-three *POT1* protein-altering variants were identified. The variants were divided into three groups. Group 1 included 14/43 variants deemed pathogenic. Group 2 included 4/43 variants that were possibly pathogenic, and the remaining 25/43 variants were in Group 3. In the study, 126 cases and 149 controls had a Group 3 variant ($p=0.66$), indicating no increased risk for melanoma. For Groups 1 and 2 combined, nearly twice as many cases as controls had Group 1 or 2 variants, but the difference was not statistically significant ($p=0.096$). The authors concluded that about 0.5% of melanoma cases have a pathogenic *POT1* variant.

Bruno (2022) published a prospective study of multi-gene panel testing related to melanoma involving 940 cutaneous melanoma index cases from 1044 Italian families.^[16] The panel included the *CDKN2A*, *CDK4*, *BAP1*, *POT1*, *ACD*, *TERF2IP*, *MITF*, and *ATM* genes. The panel test revealed 89 variants, with 52 occurring on the *CDKN2A* gene. Intermediate risk *MITF* (18) or *ATM* (10) variants were detected in 28 tests. Other gene variants the panel test detected were *CDK4* (1), *BAP1* (5), and *POT1* (4). The presence of pancreatic cancer in the proband and/or family increased the likelihood of detecting a variant, especially in *CDKN2A* (15/52) and *ATM* (4/10). Participants older than 60 years at melanoma diagnosis had fewer detectable variants [odds ratio (OR)=0.13, $p=0.008$].

De Simone (2020) conducted a retrospective review of melanoma predisposition variants (e.g., *CDKN2A*, *CDK4*) in 888 patients with melanoma from central Italy.^[17] 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. Patients were divided in two clinical categories: "low significance" and "high significance" based on personal and family history. In the sample, 128 patients (72% belonging to the "high significance" category, 28% belonging to the "low significance" category) were found to carry a DNA change defined as pathogenic, likely pathogenic, variant of unknown significance (VUS)-favoring pathogenic or VUS.

Cust (2018) used data from two large case-control studies to assess the incremental contribution of gene variants to risk prediction models using traditional phenotype and environmental factors.^[18] 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.

Gironi (2018) conducted genetic testing in Italian families prone to cutaneous melanoma to elucidate distinctive clinical and histological features of melanomas in *CDKN2A* mutation carriers.^[19] 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 one or more CM and met at least one of the following inclusion criteria: 1) CM diagnosis at less than or equal to 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 phototype ($p=0.759$) or 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 (NMs) or lentigo maligna and lentigo maligna

melanomas (LM-LMMs) ($p=0.006$). 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.

Artomov (2017) assessed the rate of rare genetic variants including *CDKN2A* among patients with familial cutaneous melanoma (CM, $n=273$) in the United States and Greece.^[20] Eleven genes that exhibited borderline association ($p<0.0001$) were independently validated using The Cancer Genome Atlas melanoma cohort ($n=379$) and a matched set of 3563 European controls with *CDKN2A* ($p=0.009$), *BAP1* ($p=0.03$), and *EBF3* ($p<0.001$), a candidate risk locus, all showing evidence of replication. *EBF3* was then evaluated using germline data from a set of 132 familial melanoma cases and 4769 controls of UK origin (joint $p<0.0001$). Somatically, loss of *EBF3* expression correlated with progression, poorer outcome, and high *MITF* tumors.

In 2017, Borroni published an Italian case series of 92 consecutive, unrelated patients with familial atypical mole/multiple melanoma syndrome (FAMMM) that were offered genetic counseling and testing for *CDKN2A* and *CDK4* variants.^[21] FAMMM is characterized by primary cutaneous melanoma in at least two relatives and/or two or more primary cutaneous melanomas in the same patient. Genetic testing was extended to family members of patients with identified variants. *CDKN2A* variants were found in 19 of the 92 unrelated patients (20.6%) and in 14 healthy relatives. Of these relatives with variants, 11 later underwent excision of dysplastic nevi.

In 2016, Di Lorenzo published a study of 400 patients with cutaneous melanoma who were observed in a six-year period at an Italian university.^[22] Forty-eight patients have 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 one patient harbored the rare *CDKN2A* p.R87W variant. The study did not identify a high variant rate of *CDKN2A* in patients affected by familial melanoma or multiple melanomas. This difference could be attributed to different factors, including the genetic heterogeneity of the Sicilian population. It is likely that, as in the Australian 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 (as latitude and sun exposure), could determine the occurrence of melanoma.

Bruno (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).^[23] Rates of the variants were 19.1% and 4.4% in patients with multiple primary versus single primary melanoma. 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.

Mangas (2016) measured the rate of *CDKN2A* variants among individuals considered high risk for melanoma, defined as families with at least two cases of melanoma or individuals with multiple melanomas.^[24] A total of 57 individuals were tested, 41 of which were considered the index cases. Of the 41, a *CDKN2A* variant was identified in four index cases.

Puig (2016) conducted genetic testing for *CDKN2A* variants among patients with melanoma in Latin America and Spain.^[25] The variant rates among patients with familial melanoma were 23.9% and 14.1% in Latin America and Spain, respectively. The *CDKN2A* variant rates were

lower among patients in Latin America and Spain with sporadic MPM, 10.0% and 8.5%, respectively.

A 2016 study by Wendt evaluated *MC1R* variants and melanoma risk in a hospital-based case-control study that included 991 melanoma patients and 800 controls.^[26] *MC1R* variants were associated with a higher risk of melanoma after adjustment for age, sex, and ultraviolet radiation exposure (≥ 2 variants, OR, 2.13 [95% confidence interval [CI], 1.66-2.75], $P < .001$; P for trend $< .001$).

Harland (2014) conducted a case control study on patients with melanoma from Australia, Spain, and United Kingdom.^[27] *CDKN2A* variant rates for each of the populations were similar (2.3%, 2.5%, and 2.0% in patients from Australia, Spain, and United Kingdom, respectively). Case-control analyses showed that the strongest predictor of carrying a variant was having multiple primaries odds ratio [OR] = 5.4, 95% CI = 2.5 to 11.6; and having three 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 two or more relatives, OR = 23.2, 95% CI = 11.3 to 47.6).

Potrony (2014) measured the rate of *CDKN2A* variants among patients in Spain with sporadic multiple primary melanoma (MPM) and familial melanoma.^[28] Variant rates were 14.1% in patients with familial melanoma and 8.5% in patients with sporadic multiple primary melanoma.

In 2013, Puntervoll published a description of the phenotype of individuals with *CDK4* variants in 17 melanoma families (209 individuals; 62 cases, 106 related controls, 41 unrelated controls).^[29] The incidence of atypical nevi was higher in those with *CDK4* variants (70% in melanoma patients; 75% in unaffected individuals) than in those without *CDK4* variants (27%; $p < 0.001$). The distribution of eye color or hair color was not statistically different 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* variant based on phenotype." Therefore, the clinical significance of this genetic distinction is currently unclear.

In 2012, Cust classified 565 patients with invasive cutaneous melanoma diagnosed between 18 to 39 years of age, 518 sibling controls, and 409 unrelated controls into *MC1R* categories defined by presence of high risk or other alleles.^[30] Compared with sibling controls, two *MC1R* high-risk alleles (R151C, R160W) were associated with increased odds of developing melanoma (OR=1.7; 95% CI, 1.1 to 2.6; OR=2.0; 95% CI, 1.2 to 3.2, respectively), but these associations were no longer statistically significant in analyses adjusted for pigmentation, nevus count, and sun exposure. Compared with unrelated controls, only the R151C high-risk allele was associated with increased odds of developing melanoma in adjusted analysis. There was no association between other *MC1R* alleles (not considered high risk) and odds of developing melanoma in unadjusted or adjusted analyses. In 2010, Psaty published an article on identifying individuals at high risk for melanoma and emphasized the use of family history.^[31]

In 2012, two studies further examined the association of *MC1R* variants and melanoma in southern European populations.^[32, 33] Ibarrola-Villava conducted a case-control study in three sample populations from France, Italy, and Spain.^[32] Susceptibility genotypes in three genes involved in pigmentation processes were examined in 1639 melanoma patients (15% familial) and 1342 controls. *MC1R* variants associated with red hair color were successfully genotyped in 85% of cases and 93% of controls. Two other genes not associated with familial cutaneous

melanoma—TYR, which encodes a tyrosinase, and SLC45 A2, which encodes a melanosome enzyme 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: OR for one allele: 2.2 (95% CI, 1.9 to 2.6); OR for two alleles: 5.0 (95% CI, 2.8 to 8.9). In analysis stratified by self-reported phenotype, these variants were statistically associated with increased odds of melanoma not only in individuals with fair phenotype (eye, hair and skin color) but also in those with dark/olive phenotype. The authors suggested that *MC1R* genotyping to identify elevated risk in Southern European patients considered not at risk based on phenotype alone warranted further investigation. Effects on health outcomes are unknown.

Ghiorzo (2012) studied 49 *CDKN2A*-variant positive and 390 *CDKN2A*-variant negative Italian patients with cutaneous melanoma.^[33] *MC1R* variants were associated with increased odds of melanoma only in *CDKN2A*-variant-negative patients in a dose-dependent fashion: OR for one high-risk allele: 1.5 (95% CI, 1.1 to 2.0); OR for two high-risk alleles, 2.5 (95% CI, 1.7 to 3.7). In multivariate logistic regression, effects of *MC1R* variants were statistically significant in most *CDKN2A* variant-negative subgroups and few variant-positive subgroups defined by phenotype (eye and hair color, skin complexion and phototype, presence or absence of freckles or atypical nevi, and total nevus count), sun exposure, and history of severe sunburn. In contrast, first-degree family history of cutaneous melanoma increased the odds of developing melanoma in both 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 uncertainty in the estimates of association was considerable. Family history of cutaneous nevi (at least 1=one 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, and history of severe sunburn) for development of melanoma and the complexity of interpreting a positive family history.

In 2010, Kanetsky conducted a study to describe associations of *MC1R* (melanocortin one receptor gene) variants and melanoma in a U.S. population and to investigate whether genetic risk is modified by pigmentation characteristics and sun exposure.^[34] 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 of high- and low-risk *MC1R* variants and melanoma, overall and within phenotypic and sun exposure groups. Carriage of two 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 to 2.8; OR=2.2; 95% CI, 1.5 to 3.0, respectively). However, risk was noted to be stronger in or limited to people with protective phenotypes and limited sun exposure, such as those who tanned well after repeated sun exposure (OR=2.4), had dark hair (OR=2.4), or had dark eyes (OR=3.2). The authors concluded that these findings indicate *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.

In 2009, Yang conducted a study to identify modifier genes for CMM in CMM-prone families with or without *CDKN2A* variants.^[35] Investigators genotyped 537 individuals (107 CMM) from 28 families (19 *CDKN2A*-positive, nine *CDKN2A*-negative) for genes involved in DNA repair, apoptosis, and immune response. Their analyses identified some candidate genes, such as *FAS*, *BCL7A*, *CASP14*, *TRAF6*, *WRN*, *IL9*, *IL10RB*, *TNFSF8*, *TNFRSF9*, and *JAK3*, that were associated with CMM risk; after correction for multiple comparisons, *IL9* remained significant.

The effects of some genes were stronger in *CDKN2A* variant-positive families (*BCL7A*, *IL9*), and some were stronger in *CDKN2A*-negative families (*BCL2L1*). The authors considered these findings supportive of the hypothesis that common genetic polymorphisms in DNA repair, apoptosis, and immune response pathways may modify the risk of CMM in CMM-prone families, with or without *CDKN2A* variants.

CLINICAL UTILITY

Although genetic testing for *CDKN2A* variants is recognized as an important research tool, its clinical use will depend on how results of genetic analysis can be used to improve patient management. Currently, management of patients considered high risk for malignant melanoma focuses on reduction of sun exposure, use of sunscreens, vigilant cutaneous surveillance of pigmented lesions, and prompt biopsy of suspicious lesions. Presently, it is unclear how genetic testing for *CDKN2A* would alter these management recommendations. The following clinical situations can be considered.

Affected Individual with a Positive Family History

If an affected individual has a *CDKN2A* or other germline gene variant associated with high risk for melanoma, they may be at increased risk for being diagnosed at an advanced stage and for having poorer survival than people without detectable gene variants.

Pissa (2023) compared melanoma survival rates before and after initiation in 1987 into a familial dermatologic surveillance program for Swedish families with *CDKN2A* pathologic variants.^[36] The study included 473 people with melanoma from 261 families who were diagnosed between 1958 and 2009, with follow-up through 2011. Of the melanoma cases, 96 belonged to 31 families that harbored a *CDKN2A* variant; and 377 were from 230 families that did not have a *CDKN2A* variant. Four cohorts were compared:

1. MUT-pre (n=53): *CDKN2A* carriers (MUT), or relative of a carrier, with first invasive melanoma before inclusion in the surveillance program.
2. MUT-post (n=43): *CDKN2A* carriers (or relative of a carrier) with first invasive melanoma after inclusion in the surveillance program.
3. WT-pre (n=255): *CDKN2A*-negative participants, i.e., wild type (WT), or relative of participant with negative *CDKN2A* test, with first invasive melanoma before inclusion in the surveillance program.
4. WT-post (n=122): *CDKN2A*-negative participants (or relative of participant with negative *CDKN2A* test) with first invasive melanoma after inclusion in the surveillance program.

Overall, worse melanoma-specific survival was associated with tumor T-stage 2-4 (hazard ratio [HR] 5.45, 95% CI 3.15-9.43, p=0.023), male sex (HR 1.80, 95% CI 1.15-2.83, p=0.011), and diagnosis at >50 years (HR 1.69, 95% CI 1.08-2.64, p=0.023). Survival was not significantly different in the MUT-pre cohort compared to the MUT-post cases, both when unadjusted for age, sex, and T-stage (HR 2.16, 95% CI 0.79-5.94, p=0.134) and after adjusting for factors associated with worse survival (HR 1.17, 95% CI 0.77-2.15, p=0.344). Survival was also similar in the WT-pre compared to the WT-post cohort, using both unadjusted (p=0.444) and adjusted (p=0.781) models. Survival was worse in the MUT-pre cohort compared to the WT-pre cases using both the unadjusted (HR 2.33, 95% CI 1.33-4.08, p=0.003) and adjusted (HR 2.70, 95% CI 1.46-5.00, p=0.001) models. Survival was not significantly different between the MUT-post and WT-post cases in either the unadjusted (HR 0.81, 95% CI 0.30-2.20, p=0.678) or adjusted (HR 1.57, 95% CI 0.6-4.20, p=0.300) models. A secondary analysis was performed

to assess whether worse survival in the MUT-pre cohort was associated with second invasive melanoma, but the survival difference between the two cohorts persisted (HR 2.83, 95% CI 1.23-6.52, $p=0.015$).

The authors suggest that inclusion in the surveillance program benefited the families with *CDKN2A* variants because the MUT-pre cohort had worse survival than the WT-pre cohort, and the survival rates were similar in the post-surveillance cohorts. However, neither of the post-surveillance cohorts had significantly different survival when compared to the pre-surveillance cohorts. Importantly, the study does not address whether the difference in survival could be due to other factors, such as treatment differences over the study period. Genetic testing for *CDKN2A* was performed for at least one member of each family, but the genetic status was not known for all study participants and there was no randomization of the surveillance intervention or genetic testing. Therefore, conclusions about the benefit of genetic testing for hereditary melanoma in the study population cannot be drawn.

The National Cancer Institute familial melanoma study compared trends in melanoma thickness in high-risk families to trends in the general U.S. population using Surveillance, Epidemiology, and End Results (SEER) data. Sargen (2021) followed 293 melanoma cases from 56 families. Of 274 melanoma cases with genetic test information, 160 had either a *CDKN2A* or *CDK4* variant, and 114 had neither gene variant. The study found smaller thickness ($p<0.001$) and earlier stage diagnosis ($p<0.001$) of invasive melanoma in people from melanoma-prone families in the surveillance program compared to tumors that were diagnosed before study involvement. However, changes in tumor thickness and stage were similar in families with and without *CDKN2A* or *CDK4* variants ($p<0.05$). During the course of the study reductions in tumor thickness and disease stage in the high-risk study participants generally paralleled reductions seen in the general population obtained from SEER data. While a trend was seen for lower thickness in the study population compared to SEER data, the difference was not significant in the high risk cases pre-study ($p=0.922$) or after study enrollment when assessed for mean thickness ($p=0.20$) and changes over time ($p=0.198$).^[8]

People with hereditary melanoma may also be at increased risk for a second primary melanoma compared with the general population. However, limited and protected sun exposure and increased surveillance would be recommended to any patient with a history of malignant melanoma, regardless of the presence of a *CDKN2A* or pathogenic variant. A positive result will establish a familial variant, thus permitting targeted testing for the rest of the family. Additionally, a positive mutation in an affected family member increases the likelihood of its clinical significance if detected in another family member; but, as described earlier, a negative test result is not interpretable.

Unaffected Individual in a High-Risk Family

If the unaffected individual is the first to be tested in the family (i.e., no affected relative has been previously tested to define the target variant), it is very difficult to interpret the clinical significance of a variant, as described. The likelihood of clinical significance is increased if the identified variant is the same as one reported in other families, although the issue of penetrance is a confounding factor. If the unaffected individual has the same variant as an affected relative, then the patient is at high risk for melanoma. However, again it is unclear how this would affect the management of the patient. Even patients who have a genetic test result that rules out a known familial variant associated with melanoma (i.e., “true negatives”) may

still be considered at increased risk for melanoma.^[8] Increased sun protection and surveillance are recommended for any patient in a high-risk family.

Published data on genetic testing of the *CDKN2A* and *CDK4* genes focus on the underlying genetics of hereditary melanoma, identification of variants in families at high risk of melanoma, and risk of melanoma in those harboring these variants. Other studies have focused on the association between *CDKN2A* and pancreatic cancer.^[37-39] One publication added the caution that differences in melanoma risk across geographic regions justify the need for studies in individual countries before counseling should be considered.^[40]

Stump (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 three kindreds and accounted for 32 carriers and 46 noncarriers. No-test control subjects (n=50) were derived from nine *CDKN2A*-negative families. The daily standard erythemal 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 one 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 one 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.

Aspinwall (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).^[42] 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 one month and one year followup, 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.

Dalmaso (2018) conducted a retrospective case-control study to determine if there was an association between *CDKN2A* variants and survival among patients with melanoma.^[43] 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 two groups.

In 2018, Stump reported changes in sun protection and stress levels following genetic counseling and test reporting for the *CDKN2A/p16* variant.^[44] Participants included 18 minors from melanoma-prone families, with a mean age of 12.4. Nine were carriers and nine were noncarriers. Compared to baseline, at one-year post-disclosure, all subjects self-reported significantly fewer sunburns. In addition, a greater proportion reported sun protection adherence. There were no significant differences between genotypes. Depressive symptoms and cancer worry declined and anxiety symptoms, which began low, remained unchanged post-disclosure. In interviews, all mothers of the subjects indicated that genetic testing was beneficial. Reasons included that it promoted risk awareness (90.9%) and sun protection (81.8%) without making their children scared (89.9%). Independent practice of sun protection by their children was reported by 45.4% of mothers.

Two behavioral studies were published in 2016. Levin examined behavior patterns in families in Norway in which a *CDKN2A* variant was identified.^[45] The authors reported that 66 % (95/144) of carriers' first-degree relatives contacted the researchers within the study period, 98% (126/128) of all relatives who came for genetic counseling requested genetic testing, and 93 % (66/71) of those with variants wanted referral for yearly skin examinations. Wu studied the impact of melanoma genetic test reporting and counseling on the frequency of discussion about preventive behaviors between 24 counseled adults and their children and grandchildren.^[46] Conversations about preventive behaviors were assessed before testing and at one and six months after testing, using open-ended questions. The authors reported that these discussions declined after test reporting, with a faster decline in variant non-carriers, and that there was a large gap between the number of participants who intended to have preventive behavior discussions and the number that reported having had such discussions at follow-up.

In 2013, Aspinwall reported outcomes for 37 patients (62%) of this cohort who were available for two-year follow-up.^[47, 48] Anxiety, depression, and cancer-specific worry declined over two years, although baseline values were low and the declines are of uncertain clinical significance. Adherence to annual total body skin examinations and monthly skin self-examinations varied by carrier status; however, without a comparison group, it is not possible to attribute any change in adherence to knowledge of test results.

In 2012, Branstrom examined a survey of self-reported genetic testing perceptions and preventive behaviors in 312 family members with increased risk of melanoma.^[49] Fifty-three percent had been diagnosed with melanoma, and 12% had a positive susceptibility genetic test. The study indicated that a negative test might be associated with an erroneous perception of lower risk and fewer preventive measures.

In a 2011 retrospective case-control study, van der Rhee sought to determine whether a surveillance program of families with a Dutch founder variant in *CDKN2A* (the p16-Leiden

variant) allowed for earlier identification of melanomas.^[50] Characteristics of 40 melanomas identified in 35 unscreened patients (before heredity was diagnosed) were compared with 226 melanomas identified in 92 relatives of those 35 unscreened melanoma patients who were found to have the *CDKN2A* variant and participated in a surveillance program over a 25-year period. Surveillance comprised a minimum of an annual total skin evaluation, which became more frequent if melanoma was diagnosed. Melanomas diagnosed during surveillance were found to have a significantly lower Breslow thickness (median thickness, 0.50 mm) than melanomas identified in unscreened patients (median thickness, 0.98 mm), signifying earlier identification with surveillance. However, only 53% of melanomas identified in the surveillance group were detected on regular screening appointments. Additionally, there was no correlation between length of screening intervals (for intervals <24 months) and melanoma tumor thickness at the time of diagnosis. The authors also noted that despite understanding the importance of surveillance, patient noncompliance was still observed in the surveillance program, and almost half of patients were noncompliant when first diagnosed with melanoma.

In a 2008 study, Aspinwall found short-term change in behavior among a small group of patients without melanoma who were positive for the *CDKN2A* variant.^[51] 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 one 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 one month.

PRACTICE GUIDELINE SUMMARY

NATIONAL COMPREHENSIVE CANCER NETWORK

The current (v1.2024) National Comprehensive Cancer Network (NCCN) clinical guidelines on melanoma state:^[52]

- Follow-up recommendations for all patients with cutaneous melanoma:
 - Consider genetic counseling referral for *p16/CDKN2A* testing in the presence of three or more invasive cutaneous 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 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 may be warranted.
- Risk Factors for Development of Single or Multiple Primary Melanomas:
 - Genetic predisposition: Presence of germline mutations or polymorphisms predisposing to melanoma (e.g. *CDKN2a*, *CDK4*, *MC1R*, *BAP1* [especially for uveal melanoma], *TERT*, *MITF*, *PTEN* and potential other genes).
 - Family history of cutaneous melanoma (especially if multiple); pancreatic, renal, and/or breast cancer; astrocytoma; uveal melanoma; and/or mesothelioma.

AMERICAN CANCER SOCIETY

According to the American Cancer Society, genetic testing for *CDKN2A* and other genes associated with melanoma is available, but “doctors aren’t sure how useful they are at this time.”^[53]

AMERICAN SOCIETY OF CLINICAL ONCOLOGY

In 2010, the American Society of Clinical Oncology (ASCO) updated its policy statement on genetic and genomic testing for cancer susceptibility.^[54] ASCO recommends that “genetic tests with uncertain clinical utility, including genomic risk assessment, be administered in the context of clinical trials.”

In 2014, the ASCO commissioned another update to its policy statement on genetic and genomic testing for cancer susceptibility.^[55] 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.^[56] 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.”

SUMMARY

There is not enough research to show that genetic testing for cutaneous melanoma can improve health outcomes, including for people with melanoma or a family history of melanoma. There are no clinical guidelines based on research that specifically recommend this type of testing. Therefore, genetic testing for variants associated with hereditary cutaneous malignant melanoma or associated with susceptibility to cutaneous malignant melanoma is considered investigational.

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CODES

Codes	Number	Description
CPT	81404	Molecular pathology procedure, Level 5
	81479	Unlisted molecular pathology procedure
HCPCS	None	

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