Genetic Testing for Familial Cutaneous Malignant Melanoma

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DESCRIPTION

The American Cancer Society estimates for cutaneous malignant melanoma (CMM) in the United States for 2022 is the following: About 99,780 new cutaneous malignant melanomas will be diagnosed (about 57,180 in men and 42,600 in women) and about 7,650 people are expected to die of cutaneous malignant melanoma (about 5,080 men and 2,750 women). The rates of cutaneous malignant melanoma have been rising rapidly over the past few decades, and this has varied by age. Cutaneous malignant melanoma is not the most prevalent form of skin cancer, but it is the most aggressive. Unlike other more common skin malignancies like basal cell and squamous cell carcinomas, melanoma often spreads widely to other parts of the body. While it represents just 4% of skin cancers, cutaneous malignant melanoma accounts for about 80% of skin cancer-related deaths. Some cases of cutaneous malignant melanoma (CMM) are familial. Potential genetic markers for this disease are being evaluated in affected individuals with a family history of disease and in unaffected individuals in a high-risk family.

A genetic predisposition to cutaneous malignant melanoma (CMM) is suspected in specific clinical situations: 1) melanoma has been diagnosed in multiple family members; 2) multiple primary melanomas are identified in a single patient; and 3) 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. Some of the familial risk may be related to shared environmental factors, 3 principal genes involved in CMM susceptibility have been identified. Cyclin-dependent kinase inhibitor 2A (CDKN2A*)*, located on chromosome 9p21 encodes proteins that act as tumor suppressors. Variants in this gene can alter the tumor suppressor function. The second gene, cyclin-dependent kinase 4 (CDK4*)*, is an oncogene located on chromosome 12q13 and has been identified in about 6 families worldwide. A third gene, not fully characterized, maps to chromosome 1p22.

The incidence of CDKN2*A* disease associated variants in the general population is very low. For example, it is estimated that in Queensland, Australia, an area with a high incidence of melanoma, only 0.2% of all patients with melanoma will harbor a CDKN2A disease-associated variant. Variants are also infrequent in those with an early age of onset or those with multiple primary melanomas. However, the incidence of CDKN2A disease-associated variants increases with a positive family history; CDKN2A disease-associated variants will be found in 5% of families with first-degree relatives, rising to 20–40% in patients with 3 or more affected first-degree relatives. 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. Validated clinical risk prediction tools to assess the probability that an affected individual carries a germline CDKN2A variant are available.

Familial CMM has been described as a family in which either 2 first-degree relatives are diagnosed with melanoma or a family with 3 melanoma patients, irrespective of the degree of relationship. Others have defined familial CMM as having at least 3 (first-, second-, or third-degree) affected members or 2 affected family members in which at least 1 was diagnosed before age 50 years or pancreatic cancer occurred in a first- or second-degree relative, or 1 member had multiple primary melanomas. No widely accepted guidelines for the management of families with hereditary risk of melanoma exist. In general, individuals with increased risk of melanoma are educated on prevention strategies such as reducing sun exposure and on skin examination procedures.

Other malignancies associated with familial CMM, specifically those associated with CDKN2A variants, have been described. The most pronounced associated malignancy is pancreatic cancer, followed by other gastrointestinal malignancies, breast cancer, brain cancer, lymphoproliferative malignancies, and lung cancer. It is also important to recognize that other cancer susceptibility genes may be involved in these families. In particular, germline BRCA2 gene mutations have been described in families with melanoma and breast cancer, gastrointestinal cancer, pancreatic cancer, or prostate cancer.

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, some family members with multiple atypical nevi who were non-carriers of the CDKN2A familial variant. Thus, the nevus phenotype cannot be used to distinguish carriers from non-carriers of CMM susceptibility in these families.

Some common allele(s) are associated with increased susceptibility to CMM but have low to moderate penetrance. One gene of moderate penetrance is the melanocortin 1 receptor gene (MC1R). Variants in this gene are relatively common and have low penetrance for CMM. This gene is associated with fair complexion, freckles, and red hair; all risk factors for CMM. Variants in *MC1R* also modify the CMM risk in families with CDKN2A mutations.

Commercially Available Testing

Melaris® (Myriad Genetics. Salt Lake City, UT) is commercially available genetic test of the CDKN2A gene. Melaris® testing assesses a person's risk of developing hereditary melanoma by detecting inherited mutations in the p16 gene (also called CDKN2A or INK4A). The proposed benefits for this testing include: personalized patient care and increase clinical efficacy by targeting screening and surveillance specifically to individuals with p16 gene mutation; improve patient compliance with tailored screening recommendations and preventative measures; improve outcomes through earlier diagnosis and treatment of cancer; counsel patients and their family members on the underlying cause of the pattern of melanoma; and avoid unnecessary interventions for family members who do not test positive for the mutation known to be in the family.

MelanomaNext (Ambry Genetics) is genetic testing for hereditary melanoma and analyzes 9 genes (BAP1, BRCA2, CDK4, CDKN2A, MITF, POT1, PTEN, RB1 and TP53) that are linked to an increased lifetime risk of melanoma. All genes are evaluated by next generation sequencing (NGS) or Sanger sequencing. The proposed benefits to this genetic testing include the healthcare provider adjusting an individual's cancer screening plan (such as age of initial screening, type and frequency) which may include a dermatology exam; healthcare provider may discuss possible cancer prevention options to reduce the risk of melanoma; and the healthcare provider may discuss the possibility of other personalized treatment options based on the genetic test result.

Testing in Individuals with Cutaneous Malignant Melanoma and Family History of the Disease

Clinical Context and Test Purpose
The purpose of genetic testing of individuals with cutaneous malignant melanoma (CMM) and family history of the disease is to identify variants in genes association with familial CMM to inform management decisions and potentially inform the decision to test asymptomatic family members for variants associated with familial CMM.

Populations
The relevant population of interest is individuals with cutaneous malignant melanoma (CMM) and a family history of the disease.

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

Comparators
The following practice currently being used; standard clinical management without getting testing.

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

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

The primary outcomes of interest are the initiation and frequency of monitoring and short-term and long-term survival.

Clinically Valid
A test must detect the presence of absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

One issue common to genetic testing for any type of cancer susceptibility is determining the clinical significance of the 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 known hereditary pattern of melanoma. However, the penetrance of a given variant will also affect its clinical significance, particularly because the penetrance of CDKN2A variants may vary with ethnicity and geographic location. For example, exposure to sun and other environmental factors, as well as behavior and ethnicity, may contribute to penetrance.

Interpretation of a negative test is another issue. CDKN2A variants are found in less than half of those with strong family history of melanoma. Therefore, additional melanoma predisposition genes are likely to exist, and patients with a strong family history with normal test results must not be falsely reassured that they are not at increased risk.

Systematic Reviews

For example, in a 2011 meta-analysis of 145 genome-wide association studies, 8 independent genetic loci were identified as associated with statistically significant risk of cutaneous melanoma, including 6 with strong epidemiologic credibility (MCR1, TYR, TYRP1, SLC45A, ASIP/PIGU/MUH7B, CDKN2A/MTAP). Also, in 2011 meta-analyses of 20 studies with data from 25 populations, red hair color variants on the MC1R gene were associated with the highest risk of melanoma, but non-red hair color variants also were associated with an increased risk of melanoma. In a 2012 review, Ward et. al. noted the genetics of melanoma are far from being understood, and "it is likely a large number of single nucleotide polymorphisms (SNPs), each with a small effect and low penetrance, in addition to the small number of large effects, high penetrance SNPs, are responsible for cutaneous malignant melanoma (CMM) risk."

In 2010, Kanetsky et. al. conducted a study to describe associations between MC1R (melancortin 1 receptor gene) variants and melanoma in a U.S. population and to investigate whether genetic risk is modified by pigmentation characteristics and sun exposure. The study population included melanoma patients (n=960) and controls (n=396) who self-reported phenotypic characteristics and sun exposure information. Logistic regression was used to estimate associations between high and low risk MC1R variants and melanoma, overall and within phenotypic and sun exposure groups. Carriage of 2 low risk or any high risk MC1R variants was associated with increased risk of melanoma (low risk odds ratio [OR], 1.7; 95% confidence interval [CI], 1.0 to 2.8; high risk OR = 2.2; 95% CI, 15. To 3.0). 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 indicated MC1R genotype provided information about melanoma risk in those individuals who would not be identified as high risk based on their phenotypes or exposure alone. However, how this information impacts patient care and clinical outcomes is unknown.

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

Observational Studies

In 2020, De Simone et. al. conducted a single center retrospective review of melanoma predisposition variants (e.g., *CDKN2A*, *CDK4*) in 888 patients with multiple primary melanomas and/or familial melanoma from Central Italy. Recent studies have led to the identification of new genes involved in CMM susceptibility: beyond CDKN2A and CDK4, BAP1, POT1, and MITF were recently identified as potential high-risk melanoma susceptibility genes. 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. Genetic analyses included the sequencing CDKN2A, CDK4, BAP1, POT1, and MITF in 202 cases, and of only CDKN2A and CDK4 codon 24 in 686 patients. By the evaluation of the personal and familial history, patients were divided in two clinical categories: "low significance" and "high significance" cases. 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. It is important to verify the genetic predisposition in CMM patients for an early diagnosis of further melanomas and/or other tumors associated with the characterized genotype. The ultimate objective is to be able to create a personalized follow-up program that takes into account the patient's clinical and biological risk factors and exposure to environmental factors. To achieve this target, it is essential to develop a multidisciplinary approach enabling early diagnosis and improvement in prognosis with a consequent reduction in health expenditure. The instrumental follow-up must be personalized and aimed at the possible early recognition of other associated neoplasms.

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. 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) p 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=-0.759), number of total common melanocytic nevi (p=0.131). However, a personal history of previously excised dysplastic nevi was more frequent among *CDKN2A* variant-positive patients compared to wildtype (62.5% vs. 26%; p=<0.001). 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<0.001). This significance was maintained for cutaneous melanoma 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 cutaneous melanoma. 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 multiple primary melanomas compared to the wildtype 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% 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=0.006). There was no significant difference in CDKN2A status with respect to meeting inclusion criteria for sentinel node biopsy (15.6% *CDKN2A*, 22% wildtype; p=0.302). Additionally, 0/5 (0%) patients who underwent the procedure with a *CDKN2A* variant showed metastases compared to 4/22 (18.2%) of wildtype patients.

In 2017, Artomev et. al. assessed the rate of rare genetic variants including *CDKN2A* among patients with familial cutaneous melanoma (n=273) in the United States and Greece. A validation set utilizing case-matched European controls against data obtained from The Cancer Genome Atlas melanoma cohort (n=379) confirmed statistically significant association for the *CDKN2A* variant (p=0.009). Despite limitations, the analyses in this report represent a major first step toward understanding the landscape of rare mutations in hereditary melanoma.

In 2016, Di Lorenzo et. al. published a study on 400 patients with CMM who were observed for a 6-year period at an Italian university. Forty-eight patients met the criteria of the Italian Society of Human Genetics (SIGU) for the diagnosis of familial melanoma and were screened for CDKN2A and CDK4 variants. Genetic testing revealed that none of the families carried variants in the CDK4 gene and only 1 patient harbored the rare CDKN2A p.R87W variant. 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 the different factors, including the genetic heterogeneity of the Sicilian population. It is likely that 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.

Bruno et. al. (2016) reported on the multiMEL study, in which genetic testing for CDKN2A and CDK4 variants were performed on 587 consecutive patients with MPM and 587 consecutive patients with single primary melanoma. CDKN2A germline mutations were found in 19% of patients with MPM versus 4.4% of patients with single primary melanoma. In familial MPM cases the mutation rate varied from 36.6% to

58.8%, whereas in sporadic MPM cases it varied from 8.2% to 17.6% in patients with 2 and 3 or more melanomas, respectively.

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. From July 2010 to July 2012, 57 patients (41 pedigrees) were included. Twenty-six were melanoma-prone families (with at least two cases) and 15 had multiple cutaneous melanomas (CMs). Pancreatic cancer was found in six families. The CDKN2A mutation p.V126D was identified in seven patients (four families) with a founder effect, whereas CDKN2A A148T was detected in seven cases (five families) and seven healthy donors (odds ratio 2·76, 95% confidence interval 0·83-9·20). At least one MC1R melanoma-associated polymorphism was detected in 32 patients (78%) and 97 healthy donors (66%), with more than one polymorphism in 12 patients (29%) and 25 healthy donors (17%). The MITF variant p.E318K was identified in four patients from three additional pedigrees (7%) and one healthy control (0·7%). The authors concluded, inclusion criteria for the Ticino population for genetic assessment should follow the rule of two (two affected individuals in a family or a patient with multiple CMs), as we detected a CDKN2A mutation in almost 10% of our pedigrees (four of 41), MITF p.E318K in 7% (three of 41) and a higher number of MC1R variants than in the control population.

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

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. 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 (increased by 2.3% for the Australia population and 2.8% for the United Kingdom population. TheMC1R gene variants, which are related to pigmentation, were responsible for most of the incremental improvement in the risk prediction models.

Section Summary

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 (CMM) is difficult to ascertain due to differences in gene penetrance, variant interpretation, study populations,

sun exposure, and preventive measures. These studies have not provided evidence that there is a clinically valid association between genetic variants and familial CMM.

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

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Preferred evidence comes 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 genetic analysis can be used to improve patient management and health outcomes. 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.

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 a malignant melanoma, regardless of the presence of a CDKN2A variant. A positive result will 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.

Section Summary
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 family history of the disease.

Direct evidence of clinical utility of genetic testing in individuals with melanoma and a family history of disease is lacking. While genetic variants associated with increased risk for developing melanoma have been identified, changes in clinical management and

improved health outcomes because of genetic testing for individuals with melanoma is uncertain. Patients with melanoma, regardless of variant status, will receive instructions on recurrence preventative measures regarding sun avoidance techniques.

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

Clinical Context and Test Purpose
The purpose of genetic testing of asymptomatic individuals cutaneous malignant melanoma (CMM) is to identify variants in genes associated with melanoma for increased surveillance to potentially detect disease at an earlier, more treatable stage.

Populations
The relevant population of interest is asymptomatic individuals in a family at high risk of developing cutaneous malignant melanoma (CMM).

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

Comparators
The following practice currently being used: standard clinical management without genetic testing.

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

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

The primary outcomes of interest are clinician-directed changed in patient

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

In 2013, Puntervoll et. al. described the phenotype of individuals with CDK4 variants in 17 melanoma families (209 individuals; 62 cases, 160 related controls, 41 unrelated controls). Incidence of atypical nevi was higher in those with CDK4 variants (70% in melanoma patients vs 75% in unaffected individuals) than in those without CDK4 variants (27%; $p<0.001$). The distribution of eye color 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 a phenotype. The clinical implication is that, although CDK4 mutation carriers are rarely seen, exon 2 of this gene should be examined in melanoma families seeking gene testing whenever tests are negative for CDKN2A.

In 2009, Yang et. al. conducted a study to identify modifier genes for cutaneous malignant melanoma (CMM) in CMM prone families with or without CDKN2A mutations. Investigators genotyped 537 individuals (107 CMM) from 28 families (19 CDKN2A+, 9 CDKN2A-) 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), while some were stronger in CDKN2A variant negative families (BCL2L1). The authors concluded that the analysis was limited by the small number of CMM cases particularly in analyses stratified by CDKN2A status. The stronger effects of most genes in CDKN2A positive families may be due to the smaller number of CDKN2A negative families examined in the study. The study should be viewed as an exploratory study and replication in larger samples is warranted. Also, they noted they could not adequately assess the interaction of genetic factors and host factors and sun exposure related variable. Because of small numbers, they used MC1R variants as surrogate for skin type, eye/hair color, and sun burn/tanning abilities. They included nevi as a covariate in all models with CMM as the outcome variable. Adjustments for MC1R and nevi did not change results significantly, suggesting that these SNPs might be risk factors of CMM independently from host factors and sun exposure. The study was also limited by the selection of genes and pathways included as the panel did not include all genes or SNPs that were found to be important in CMM by previous studies. Despite these limitations 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 CMM in CMM prone families with and without CDK2NA variants.

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

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

Direct evidence 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).

If the asymptomatic individual is the first to be tested in the family (i.e. no affected relative has been previously tested to define a familial 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 that reported in other families, although the issue of penetrance is a confounding factor. If the asymptomatic individual has the same variant as an affected relative, then the patient is at high risk for melanoma. However, it is unclear how this would affect the management of the patient. Increased sun protection and surveillance are recommended for any patient in a high-risk family, regardless of whether the patient has undergone genetic testing.

Prospective Studies

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

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. Patients aged 10-15 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.

Aspinwall et. al. (2018), the aim of this study was to test whether melanoma genetic counseling and test disclosure conferred unique informational, motivational, or emotional benefits compared to family history-based counseling. Participants included were 114 unaffected members of melanoma-prone families, ages 16-69, 51.8% men, 65.8% with minor children or grandchildren. Carriers (n = 28) and noncarriers (n = 41) from families with a CDKN2A mutation were compared to no-test controls (n = 45) from melanoma-prone families without an identifiable CDKN2A mutation. All participants received equivalent counseling about melanoma risk and management; only CDKN2A participants received genetic test results. Using newly developed inventories, participants rated perceived costs and benefits for managing their own and their children's or grandchildren's melanoma risk 1 month and 1 year after counseling. Propensity scores controlled for baseline family differences. Compared to no-test controls, participants who received test results (carriers and noncarriers) reported feeling significantly more informed and prepared to manage their risk, and carriers reported greater motivation to reduce sun exposure. All groups reported low negative emotions about melanoma risk. Parents reported high levels of preparedness to manage children's risk regardless of group. Carrier parents reported greater (but moderate) worry about their children's risk than no-test control parents. Women, older, and more educated respondents reported greater informational and motivational benefits regardless of group. Genetic test results were perceived as more informative and motivating for personal sun protection efforts than equivalent counseling based on family history alone. The authors concluded, the present findings suggest that adding a high-penetrance melanoma genetic test result to individualized melanoma genetic counseling provides both informational and motivational benefits to members of high-risk families. Parents reported high levels of preparedness to manage children’s risk regardless of group. Understanding how information about genetic vulnerability to cancer informs and motivates prevention behaviors, both for oneself and one’s children, is an important future direction for research and intervention. Future studies might examine the ways family discussions and action plans may unfold differently when there is an identifiable contributor to risk (here a genetic mutation) rather than a more abstract sense of family risk. As this work

proceeds, it will also be important to test whether similar benefits may be observed for reporting of lower-penetrance genetic risks and in less intensive intervention contexts.

Borroni et. al. (2017) identified asymptomatic individuals at high genetic risk of PCM (primary cutaneous melanoma), from January 2012 to December 2015, and offered genetic counseling and molecular analysis of the two high-penetrance FAMMM (familial atypical mole/multiple melanoma syndrome) susceptibility genes, cyclin-dependent kinase inhibitor 2A (CDKN2A) and cyclin-dependent kinase 4 (CDK4), to 92 consecutive, unrelated patients with FAMMM. Age at diagnosis and number of PCMs were obtained from medical records; the number of PCMs and affected relatives were recorded for each family. The diagnostic work-up consisted of genetic counselling and cascade genetic testing in patients and further extension to relatives of those identified as mutation carriers. All exons and exon/intron boundaries of CDKN2A and CDK4 genes were screened by direct bidirectional sequencing. They identified CDKN2A mutations in 19 of the 92 unrelated patients (20.6%) and in 14 additional, clinically healthy relatives. Eleven of these latter subsequently underwent excision of dysplastic nevi, but none developed PCM during a median follow-up of 37.3 months.

In 2013, Aspinwall et. al. conducted a study evaluating the long-term impact of melanoma genetic test reporting and counseling on screening adherence. This study assessed adherence to recommendations for annual total body skin examinations (TBSEs) and monthly skin self-examinations (SSEs) among 37 members of Utah CDKN2A/p16 patients (10 unaffected carriers, 11 affected carriers, 16 unaffected carriers; response rate = 64.9% of eligible participants). Two years following test reporting, adherence to annual TBSE among unaffected carriers increased from 40% to 70%. However, unaffected non-carriers' adherence decreased from 56% to 13%. Affected carriers reported TBSEs at both assessments 91% and 82% respectively. Monthly SSE frequency remained highly variable in all patient groups: at 2 years, 29.7% reported monthly SSEs, 27.0% reported more frequent self-examinations, and 43.2% reported under-screening. However, SSE quality improved: participants checked more body sites at 2 years than at baseline, especially feet, shoulders, legs and genitals. Perceived logistic barriers to TBSEs (e.g., expensive, inconvenient) and SSEs (hard to remember, time consuming) predicted lower adherence. The primary limitation to this study is the modest sample size and this limitation was compounded by the high level of variability in reported SSE frequency. The conclusions presented in this study await data from larger studies powered to analyze complex changes in SSE frequency in each patient group. An additional limitation is the high degree of prior research involvement of all patients in the present study, participants had not only received extensive prior counseling, but also demonstrated considerable commitment to melanoma research by participating in two prior studies over a period of several years. With respect to the possibility that participants were especially motivated, investigators obtained very high levels of participation in the initial test reporting phase of the study, along with the 2-year follow-up rate of 64.9%. It is unknown whether members of high-risk families without prior research participation would respond similarly to melanoma genetic counseling and test reporting. The authors concluded unaffected carriers reported increased TBSE adherence and thoroughness of SSEs 2 years

following melanoma genetic test reporting, suggesting clinical benefit in this modest sample. Unaffected non-carriers' reportable gains in SSE thoroughness but decreased TBSEs. Melanoma genetic counseling and test reporting may improve adherence among affected carrier members of CDKN2A/p16 families. Further investigations to distinguish the impact of receiving genetic test results from general genetic education and counseling is needed to determine how these different types of information effect adherence and motivation. Intervention efforts should also target logistic barriers to screening.

Retrospective Studies

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

In 2013, van der Rhee et. al. reported on a retrospective case-control study of 21 families with the p16 Leiden founder variant. The purpose of the study was to investigate the yield of surveillance of first- and second-degree relatives of patients with melanoma (n=14 families) or with melanoma and pancreatic cancer (n=7 families). Overall, melanoma incidence rates were 9.9 per 1000 person-years (95% CI, 7.4 to 13.3) in first degree relatives and 2.1 per 1000 person-years (95% CI, 1.2 to 3.8) in second degree relatives. 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 and 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 high-risk family, the clinical relevance of these findings is uncertain.

Section Summary

Direct evidence of the clinical utility of genetic testing in asymptomatic individuals in a family at high risk for developing cutaneous malignant melanoma (CMM) is lacking. Among the prospective studies, only one had an outcome of melanoma occurrence. None of the carriers developed melanoma, but the sample size was small, and duration of the follow-up may not have been long enough to detect disease development. While familial variants associated with increased risk for developing melanoma have been identified, changes in clinical management and improved health outcomes as a result of genetic testing for asymptomatic individuals is uncertain.

Expanded Multigene Panel Testing (51 or More Genes)
Although single-gene *CDKN2A* testing is used less commonly in the age of multigene panels, the lessons learned from *CDKN2A* testing may be relevant for other melanoma susceptibility genes. The interpretation of such test results is difficult, especially in the context of a negative result. Importantly, unaffected individuals from hereditary melanoma families who test negative for the familial *CDKN2A* mutation are still at increased risk of developing melanoma despite their negative genetic status. This leads to the concern that a negative test result will result in decreased surveillance and vigilance. Many of the melanoma associated genes on multigene panels do not have a precisely defined risk for melanoma. The personal and family history should be used to make surveillance and management decisions. The current NCCN Guideline Cutaneous Melanoma Version 2.2022 includes family history as a melanoma risk factor and alters management based on risk, however, this guideline does not address genetic testing for familial cutaneous malignant melanoma. Genetic testing is based on actual diagnosis and prognostication of cutaneous melanoma using BRAF and KIT to determine targeted therapy, see medical policy 02.04.20 KRAS/NRAS and BRAF. The evidence is insufficient to determine the effects of the technology on net health outcomes.

Summary of Evidence
For individuals who have cutaneous malignant melanoma (CMM) and a family history of this disease who receive genetic testing for genes associated with familial cutaneous malignant melanoma (CMM), the evidence includes genetic association studies measuring prevalence of variants in certain genes among those with cutaneous melanoma (CMM). Limitations with clinical validity include difficulties with variant interpretations, variable penetrance of a given variant, and residual risk with a benign variant. Currently, management of melanoma patients, which involves surveillance and education on sun avoidance behaviors, does not change based on genetic variants identified in genes associated with familial cutaneous malignant melanoma (CMM), therefore, clinical utility is lacking. The evidence is insufficient to determine the effects of the technology on net health outcomes.

For individuals who are asymptomatic and in a family at high risk of developing cutaneous malignant melanoma (CMM) who receive genetic testing for genes associated with familial cutaneous malignant melanoma (CMM), the evidence includes genetic association studies correlating variants in certain genes and the risk of developing cutaneous malignant melanoma (CMM). Limitations with clinical validity include difficulties with variant interpretations, variable penetrance of a given variant, and residual risk with a benign variant. Currently, management of patients considered at high risk for cutaneous malignant melanoma (CMM) focuses on reduction of sun exposure, use of sunscreens, vigilant cutaneous surveillance of pigmented lesions, and prompt biopsy of suspicious lesions. It is unclear how genetic testing for variants associated with increased risk of cutaneous malignant melanoma (CMM) would alter these management recommendations; therefore, clinical utility is lacking. The evidence is insufficient to determine the effects of the technology on net health outcomes.

Practice Guidelines and Position Statements

National Comprehensive Cancer Network (NCCN)

Melanoma: Cutaneous Version 1.2022

Overview
Risk factors for melanoma include skin type, personal history of prior melanoma, multiple clinically atypical moles or dysplastic nevi, a positive family history of melanoma, and rarely, inherited genetic mutations. Genetic counseling could be considered for individuals with strong family history of invasive melanoma with or without pancreatic cancer. In addition to genetic factors, environmental factors including excess sun exposure and UV-based artificial tanning contribute to the development of melanoma. The interaction between genetic susceptibility and environmental exposure is illustrated in individuals with an inability to tan and fair skin that sunburns easily who have a greater risk of developing melanoma. However, melanoma can occur in any ethnic group and in areas of the body without substantial sun exposure.

As with nearly all malignancies, the outcome melanoma depends on the state at presentation. In the United States, it is estimated that 84% of patients with melanoma initially present with localized disease, 9% with regional disease, and 4% with distant metastatic disease.

Principles of Molecular Testing
The current NCCN guideline does not include or indicate genetic testing for genes associated with familial cutaneous malignant melanoma (CMM). The current guideline includes biomarker testing for individuals for patients diagnosed with stage III at high-risk for recurrence for whom BRAF-directed therapy may be an option.

American Academy of Dermatology
In 2019, the American Academy of Dermatology published a guideline for the care and management of primary cutaneous melanoma. This guideline states the following regarding genetic testing for prediction of germline risk for patients or families at high of cutaneous melanoma: “The ultimate decision to pursue genetic testing for germline mutations is a complex decision based on pedigree structure, cancer patterns, patient wishes, and perceived risk versus benefits. The working group suggests a referral for genetic counseling and optional genetic testing for select patients because not all individuals need to undergo formal genetic evaluation as there is no strong evidence that genetic evaluation is either harmful or helpful.”

Cancer risk counseling by a qualified genetic counselor is recommended for patients with CM who have:

- A family history of invasive CM or pancreatic cancer (≥ 3 affected members on 1 side of the family)

- Multiple primary invasive CM (≥ 3) including 1 early onset tumor (at age < 45 years)
    - ≥ 1 MBAIT and a family history of mesothelioma, meningioma and/or uveal melanoma
    - ≥ 2 MBAITs

CM= cutaneous melanoma; MBAIT= melanocytic, BAP1-mutated atypical intradermal tumor

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

Commercially available tests include but are not limited to:

Test	Manufacturer
Melaris: assesses a person's risk of developing hereditary melanoma by detecting inherited mutations in the p16 gene (also called CDKN2A or INK4A), associated with hereditary melanoma and pancreatic cancer. It is a simple blood test that determines whether a patient has a mutation in the p16 gene (CDKN2A or INK4A) which is inherited in an autosomal dominant pattern.	Myriad Genetics
MelanomaNext: is a next generation sequencing panel that simultaneously analyzes 9 genes associated with increased risk for melanoma (BAP1, BRCA2, CDK4, CDKN2A, MITF, POT1, PTEN, RB1 and TP53). Test results are reported as Positive (a mutation was found in at least one of the genes tested); Negative (no genetic changes were found in any of the genes tested); or Variant of Unknown Significance (VUS) (at least one genetic change was found, but it is unclear if this change will cause an increased risk for cancer or not).	Ambry Genetics

PRIOR APPROVAL

Not applicable.

POLICY

See Related Medical Policies

- 02.04.20 KRAS/NRAS and BRAF Mutational Analysis
- 02.04.53 Gene Expression Profiling of Melanomas

Genetic testing for genes associated with familial cutaneous malignant melanoma (CMM) or associated with susceptibility to cutaneous malignant melanoma is considered **investigational,** including but not limited to the following:

- CDKN2A and/or CDKN2A deletion/duplication analysis
- Expanded genetic panels 51 or more genes
- Melaris
- MelanomaNext

The evidence to date is insufficient to permit conclusions concerning the effect of genetic testing for familial cutaneous malignant melanoma (CMM) on net health outcomes. Currently available testing does not detect genetic mutation(s) in melanoma in a significant number of people who appear to have familial cutaneous malignant melanoma (CMM), therefore, a negative result cannot rule out familial cutaneous malignant melanoma (CMM). Although research continues in this area, the literature identified does not demonstrate how the presence or absence of the genetic mutations would impact clinical care/alter management recommendations (reduction of sun exposure, use of sunscreens, vigilant cutaneous surveillance of pigmented lesions and prompt biopsy of suspicious lesions). The evidence is insufficient to determine the effects of the technology on net health outcomes.

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 81404 Molecular pathology procedure, Level 5 (e.g., analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis) - Component within this panel CDKN2A (cyclin dependent kinase inhibitor 2A) (e.g., CDKN2A related cutaneous malignant melanoma familial atypical mole malignant melanoma syndrome), full gene sequence
- 81455 Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes (e.g., ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MET,

MLL, NOTCH1, NPM1, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; DNA analysis or combined DNA and RNA analysis

- 81456 Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes (e.g., ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MET, MLL, NOTCH1, NPM1, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; RNA analysis
- 81479 Unlisted molecular pathology procedure (code may be utilized for MelanomaNext or Melaris or CDKN2A deletion/duplication analysis)

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POLICY HISTORY		
Date	**Reason**	**Action**
February 2022	Annual Review	Policy Revised
February 2021	Annual Review	Policy Revised
February 2020	Annual Review	Policy Revised
February 2019	Annual Review	Policy Renewed
February 2018	Annual Review	Policy Revised
February 2017	Annual Review	Policy Renewed
February 2016	Annual Review	Policy Revised
March 2015	Annual Review	Policy Renewed
April 2014	Annual Review	Policy Revised
June 2013	Annual Review	Policy Revised
April 2013	Interim Review	Policy Revised
February 2013	Interim Review	Policy Revised
July 2012	Interim Review	Policy Revised

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
PO Box 9232
Des Moines, IA 50306-9232

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