Genetic Testing for Familial Cutaneous Malignant Melanoma

Description

Because some cases of cutaneous malignant melanoma (CMM) are familial, potential genetic markers for this disease are being evaluated. Some of these markers are being evaluated in those with a family history of disease; other markers are being evaluated to estimate risk of CMM in those who may not have a family history.

Background

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

The incidence of CDKN2A mutations in the general population is very low. For example, it is estimated that in Queensland, Australia, an area with a high incidence of melanoma, only 0.2% of all patients with melanoma will harbor a CDKN2A mutation. Mutations are also infrequent in those with an early age of onset or those with multiple primary melanomas. (1) However, the incidence of CDKN2A mutations increases with a positive family history; CDKN2A mutations will be found in 5% of families with first-degree relatives, rising to 20–40% in kindreds with 3 or more affected first-degree relatives. (2) Mutation detection rates in the CDKN2A gene are generally estimated as 20–25% in hereditary CMM but can vary between 2% and 50%, depending on the family history and population studied. Validated clinical risk prediction tools to assess the probability that an affected individual carries a germline CDKN2A mutation are available.(3,4)

Hereditary 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. (5) Others have defined hereditary 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. (6) No widely accepted guidelines for the management of families with hereditary risk of melanoma exist.(7)

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

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

Some common allele(s) are associated with increased susceptibility to CMM but have low penetrance. One such gene 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. (8)

Melaris® (Myriad Genetic; alt Lake City, Utah) is a commercially available genetic test of the CDKN2A gene.

**Regulatory Status**

No U.S. Food and Drug Administration (FDA)-approved CDKN2A mutation tests were identified. Melaris® and other CDKN2A tests are laboratory-developed tests (LDTs). 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® is 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.

**Related policies**

None
Policy

This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Genetic testing for mutations associated with cutaneous malignant melanoma or associated with susceptibility to cutaneous malignant melanoma is considered investigative.

Rationale

Validation of the clinical use of any diagnostic test focuses on 3 main principles: 1) the analytic validity of the test; i.e., the technical performance of the test; 2) the clinical validity, i.e., the diagnostic performance of the test, such as sensitivity, specificity, and positive and negative predictive values in different populations of patients and compared to the gold standard; and 3) the clinical utility of the test, i.e., how the results of the diagnostic test will be used to improve patient management.

Analytic Validity

Genetic testing typically consists of sequence analysis of the coding regions and intron/exon splice sites or analysis of a specific mutation. Studies report identifying deleterious mutations in the 5’ untranslated region and deep intronic mutations in the CDKN2A gene.

Clinical Validity

The clinical validity is related to the interpretation of the results of the genetic analysis for the individual patient. One issue common to genetic testing for any type of cancer susceptibility is determining the clinical significance of individual mutations. For example, mutations in the CDKN2A gene can occur along its entire length, and some of these mutations represent harmless polymorphisms or noncoding mutations. Interpretation will improve as more data accumulate regarding the clinical significance of individual mutations in families with a known hereditary pattern of melanoma. However, the penetrance of a given mutation will also affect its clinical significance, particularly since the penetrance of CDKN2A mutations may vary with ethnicity and geographic location. (1, 2) For example, exposure to sun and other environmental factors, as well as behavior and ethnicity may contribute to the penetrance. Bishop and colleagues have estimated that the calculated risk of developing melanoma before age 80 years in carriers of CDKN2A mutations ranges from 58% in Europe to 91% in Australia. (9)

Interpretation of a negative test is another issue. CDKN2A mutations are found in less than half of those with strong family history of melanoma. Therefore, additional melanoma predisposition genes are likely to exist, and patients with a strong family history with normal test results must not be falsely reassured that they are not at increased risk. (1) For example, in a 2011 meta-analysis of 145 genome-wide association studies, 8 independent, genetic loci were identified as being associated with a statistically significant risk of cutaneous melanoma, including 6 with strong epidemiological credibility (MC1R, TYR, TYRP1, SLC45A2, ASIP/PIGU/MYH7B, and CDKN2A/MTAP). (10) Also, in a 2011 meta-analysis 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. (8) In a 2012 review, Ward and colleagues noted the genetics of melanoma are far from being understood, and "it is likely a large number of SNPs (single nucleotide polymorphisms), each with a small effect and low penetrance, in addition to the small number of large effect, high-penetrance SNPs, are responsible for CMM (cutaneous malignant melanoma) risk.” (12)

In 2009, Yang and colleagues conducted a study to identify modifier genes for CMM in CMM-prone families with or without CDKN2A mutations. (13) The investigators genotyped 537 individuals (107 CMM) from 28 families (19 CDKN2A-positive, 9 CDKN2A-negative) for genes involved in DNA repair, apoptosis, and immune response. Their analyses identified some candidate genes, such as FAS, BCL7A, CASP14, TRAF6, WRN, IL9, IL10RB, TNFSF8, TNFRSF9, and JAK3, that were associated with CMM risk; after correction for multiple comparisons, IL9 remained significant. The effects of some genes were stronger in CDKN2A-positive families (BCL7A and IL9), and some were stronger in CDKN2A-negative families (BCL2L1). The authors concluded that these findings support 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 mutations.

In 2010, Kanetsky and colleagues conducted a study to describe associations of MC1R (melanocortin 1 receptor gene) variants and melanoma in a U.S. population and to investigate whether genetic risk is modified by pigmentation characteristics and sun exposure. (14) The study population included melanoma patients (n=960) and controls (n=396), with self-reported phenotypic characteristics and sun exposure information. Logistic regression was used to estimate associations of high- and low-risk MC1R variants and melanoma, overall and within phenotypic and sun exposure groups. Carriage of 2 low-risk, or any high-risk MC1R variants, was associated with increased risk of melanoma (odds ratio [OR]: 1.7; 95% confidence interval [CI]: 1.0–2.8; and OR: 2.2; 95% CI: 1.5–3.0, respectively). However, risk was noted to be stronger in or limited to individuals with protective phenotypes and limited sun exposure, such as those who tanned well after repeated sun exposure (OR: 2.4), had dark hair (OR: 2.4), or had dark eyes (OR: 3.2). The authors concluded that 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.

Two subsequent studies in southern European populations examined further the association of MC1R variants and melanoma. Ibarrola-Villava et al. (2012) conducted a case control study in 3 sample populations from France, Italy, and Spain. (15) Susceptibility genotypes in 3 genes involved in pigmentation processes were examined in 1,639 melanoma patients (15% familial) and 1,342 controls. MC1R variants associated with red hair color were successfully genotyped in 85% of cases and 93% of controls. (Two other genes not associated with familial cutaneous melanoma – TYR, which encodes a tyrosinase, and SLC45 A2, which encodes a melanosome enzyme – also were studied.) In univariate logistic regression analysis, MC1R red hair color variants were significantly associated with the odds of developing melanoma in a dose-dependent fashion: OR for one allele: 2.2 (95% CI: 1.9–2.6); OR for two alleles: 5.0 (95% CI: 2.8–8.9). In analysis stratified by self-reported phenotype, these variants were statistically associated with increased odds of melanoma not only in individuals with fair phenotype (eye, hair and skin color) but also in those with dark/olive phenotype. The authors suggested that MC1R genotyping to identify elevated risk in Southern European patients considered not at risk based on phenotype alone warranted further investigation. Effects on health outcomes are unknown.
Ghiorzo et al. (2012) studied 49 CDKN2A-mutation positive and 390 CDKN2A-mutation negative Italian patients with cutaneous melanoma. (16) MC1R variants were associated with increased odds of melanoma only in CDKN2A-mutation-negative patients in a dose-dependent fashion: OR for one high-risk allele: 1.5 (95% CI: 1.1–2.0); OR for two high-risk alleles: 2.5 (95% CI: 1.7–3.7). In multivariate logistic regression, effects of MC1R variants were statistically significant in most CDKN2A mutation-negative subgroups and few mutation-positive subgroups defined by phenotype (eye and hair color, skin complexion and phototype, presence or absence of freckles or atypical nevi, and total nevus count), sun exposure, and history of severe sunburn. In contrast, first-degree family history of cutaneous melanoma increased the odds of developing melanoma in both mutation-positive (OR: 71.2, 95% CI: 23.0–221.0) and mutation-negative (OR: 5.3, 95% CI: 2.0–14.3) patients, although uncertainty in the estimates of association was considerable. Family history of cutaneous nevi (at least 1 first-degree relative with >10 nevi and/or atypical nevi) increased the odds of melanoma in mutation-positive cases only (OR: 2.44, 95% CI: 1.3–4.5). This finding underscores the significance of nongenetic factors (eg, sun exposure, and history of severe sunburn) for development of melanoma and the complexity of interpreting a positive family history.

Cust and colleagues (2012) classified 565 patients with invasive cutaneous melanoma diagnosed between 18-39 years of age, 518 sibling controls, and 409 unrelated controls into MC1R categories defined by presence of high risk or other alleles. (17) Compared to sibling controls, two MC1R high-risk alleles (R151C and R160W) were associated with increased odds of developing melanoma (OR: 1.7 [95% CI: 1.1–2.6] and OR: 2.0 [95% CI: 1.2–3.2], respectively), but these associations were no longer statistically significant in analyses adjusted for pigmentation, nevus count, and sun exposure. Compared to unrelated controls, only the R151C high-risk allele was associated with increased odds of developing melanoma in adjusted analysis. There was no association between other MC1R alleles (not considered high risk) and odds of developing melanoma in unadjusted or adjusted analyses. In 2010, Psaty and colleagues published an article on identifying individuals at high risk for melanoma and emphasized the use of family history. (18)

In 2013, Puntervoll et al. published a description of the phenotype of individuals with CDK4 mutations in 17 melanoma families (209 individuals; 62 cases, 106 related controls, and 41 unrelated controls). (19) The incidence of atypical nevi was higher in those with CDK4 mutations (70% in melanoma patients; 75% in unaffected individuals) than in those without CDK4 mutations (27%; p<0.001). The distribution of eye color or hair color was not statistically different between CDK4 mutation-positive individuals (with or without melanoma) and mutation-negative family members. The authors conclude that “it is not possible to distinguish CDK4 melanoma families from those with CDKN2A mutation based on phenotype.” As noted previously, the clinical significance of this genetic distinction is currently unclear.

Clinical Implications

In 2003(20) and 2010,(21) the American Society of Clinical Oncology (ASCO) issued policy statements on genetic and genomic testing for cancer susceptibility. Both statements recommended that, outside of a research setting, genetic testing for cancer susceptibility should be offered only when the following 3 criteria are met: (1) the individual being tested has a personal or family history suggestive of an underlying
hereditary component; (2) the genetic test can be adequately interpreted; and (3) test results will guide diagnosis and management.

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

1. Affected individual with a positive family history

If an affected individual tests positive for a CDKN2A mutation, he/she may be at increased risk for a second primary melanoma compared to 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 mutation. However, a positive result will establish a mutation, thus permitting targeted testing for the rest of the family. In addition, a positive mutation in an affected family member increases the likelihood of its clinical significance if detected in another family member. As described, a negative test is not interpretable.

2. 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 mutation), it is very difficult to interpret the clinical significance of a mutation, as described. The likelihood of clinical significance is increased if the identified mutation is the same as one reported in other families, although the issue of penetrance is a confounding factor. If the unaffected individual has the same mutation as an affected relative, then the patient is at high risk for melanoma. However, again 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.

The published data on genetic testing of the CDKN2A and CDK4 genes focus on the underlying genetics of hereditary melanoma, identification of mutations in families at high risk of melanoma, and risk of melanoma in those harboring these mutations. Other studies have also focused on the association between CDKN2A and pancreatic cancer. (22-24) 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. (25)

In a 2008 study, Aspinwall et al. found short term change in behavior among a small group of patients without melanoma who were positive for the CDKN2A mutation. (26) In this prospective study of 59 members of a CDKN2A mutation-positive pedigree, behavioral assessments were made at baseline, immediately after CDKN2A test reporting and counseling, and at 1-month follow-up (42 participants). Across multiple measures, test reporting caused CDKN2A mutation carriers without a melanoma history to improve to the level of adherence reported by participants with a melanoma history. CDKN2A-positive participants without a melanoma history reported greater intention to obtain total body skin examinations, increased intentions and adherence to skin self-examination recommendations, and increased number of body sites examined at 1 month. In 2013, Aspinwall et al reported outcomes for 37 patients (62%) of this cohort who were available for 2-year follow-up.(27,28) Anxiety, depression, and cancer-specific worry
declined over 2 years, although baseline values were low and the declines are of uncertain clinical significance. Adherence to annual total body skin examinations and monthly skin self-examinations varied by carrier status; however, without a comparison group, it is not possible to attribute any change in adherence to knowledge of test results.

In a 2011 retrospective case-control study, van der Rhee and colleagues sought to determine whether a surveillance program of families with CDKN2A mutations allowed for earlier identification of melanomas. (29) Characteristics of 40 melanomas identified in 35 unscreened patients (before heredity was diagnosed) were compared to 226 melanomas identified in 92 relatives of those 35 unscreened melanoma patients that were found to have the CDKN2A mutation and participated in a surveillance program over a 25-year period. Surveillance consisted of a minimum of an annual total skin evaluation which became more frequent if melanoma was diagnosed. Melanomas diagnosed during surveillance were found to have a significantly lower Breslow thickness (median thickness 0.50 mm) than the melanomas identified in the 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 less than 24 months) and melanoma tumor thickness at time of diagnosis. The authors also noted that despite understanding the importance of surveillance, patient noncompliance was still observed in the surveillance program and almost half of patients were noncompliant when first diagnosed with melanoma.

In 2013, van der Rhee et al reported on a retrospective case-control study of 21 families with the p16-Leiden founder mutation. (30) The purpose of the study was to investigate the yield of surveillance of first- and second-degree relatives of patients with melanoma (n=14 families) or with melanoma and pancreatic cancer (n=7 families). Overall, melanoma incidence rate was 9.9 per 1000 person-years (95% CI, 7.4 to 13.3) in first-degree relatives and 2.1 per 1000 person-years (95% CI, 1.2 to 3.8) in second-degree relatives. In comparison with the general population in the Netherlands, overall standardized morbidity ratio for melanoma was 101.0 (95% CI, 55.9 to 182.3) in first-degree relatives and 12.9 (95% CI, 7.2 to 23.4) in second-degree relatives (observed: 45, expected: 0.76) and 12.9 (95% CI, 7.2 to 23.4) in second-degree relatives (observed: 11, expected: 0.31). Although the authors conclude that surveillance of second- (as well as first-) degree relatives from very high-risk melanoma families is justified based on these findings, it is unclear whether these findings apply to families without or with other CDKN2A mutations. Further, because increased sun protection and surveillance are recommended for any member of a high-risk family, clinical relevance of the finding is uncertain.

Branstrom and colleagues examined a survey of self-reported genetic testing perceptions and preventive behaviors in 312 family members with increased risk of melanoma. Fifty-three percent had been diagnosed with melanoma, and 12% had a positive susceptibility genetic test. (31) The study indicated that a negative test might be associated with an erroneous perception of lower risk and fewer preventive measures.

**Ongoing and Unpublished Clinical Trials**

A search of online site ClinicalTrials.gov using the search terms “melanoma”, “pancreatic cancer”, “genetic,” and “families” identified 35 observational studies, 4 sponsored by the National Cancer Institute...
and 1 sponsored by the Medical University of Vienna. Four seek to identify genetic and environmental factors related to melanoma risk in individuals and families at high risk for melanoma (NCT00040352, NCT00450593, NCT00339222, NCT00849407). Another study to develop a model for genetic susceptibility for melanoma is active but no longer recruiting patients (NCT00591500).

Practice Guidelines and Position Statements

In 2002, The Melanoma Genetics Consortium, comprising familial melanoma researchers from North America, Europe, and Australia indicated that genetic testing for melanoma susceptibility should not be offered outside of a research setting. (32)

In 2002, in an American Society of Clinical Oncology (ASCO) publication, Kefford noted the sensitivity and specificity of tests for CDKN2A mutations are not fully known. (33) Because interpreting genetic tests is difficult and because test results do not alter patient management, the Kefford publication indicated CDKN2A genetic testing should be performed only in clinical trials for several reasons including: a low likelihood of finding mutations in known melanoma susceptibility genes, uncertainty about the functionality and phenotypic expression of the trait among mutation carriers and the lack of proven melanoma prevention and surveillance strategies. Additionally, it was noted all patients with risk factors for cutaneous melanoma should follow programs of sun protection and skin surveillance, not just those patients considered to be high risk due to family history.

In 2010, ASCO updated its policy statement on genetic and genomic testing for cancer susceptibility.(21) ASCO recommends that “genetic tests with uncertain clinical utility, including genomic risk assessment, be administered in the context of clinical trials.”

National Comprehensive Cancer Network
Current NCCN clinical practice guidelines for melanoma (version 4.2014) include no specific recommendation for genetic testing for melanoma.(34)

U.S. Preventive Services Task Force Recommendations

No U.S. Preventive Services Task Force recommendations for genetic testing for malignant melanoma have been identified.

Summary

Because some cases of cutaneous malignant melanoma (CMM) are familial, potential genetic markers for this disease are being evaluated. Some of these markers are being evaluated in those with a family history of disease; other markers are being evaluated to estimate the risk of CMM in those who may not have a family history.

The evidence to date is insufficient to permit conclusions concerning the effect of genetic testing for melanoma on health outcomes. Although research continues in this area, none of the articles identified demonstrate how the presence or absence of these genetic mutations would impact clinical care—either
for those with melanoma or for those at risk due to a family history. Changes in patient management that result from finding a mutation in a patient at risk are unknown. The conclusion concerning unknown impact on outcomes applies both to mutations with high penetrance (CDKN2A) and to those with low penetrance (MC1R) that may increase susceptibility. Therefore, genetic testing for mutations associated with cutaneous malignant melanoma or associated with susceptibility to cutaneous malignant melanoma is considered investigational.

Medicare National Coverage

There is no national coverage determination.

References


12. Ward KA, Lazovich D, Hordinsky MK. Germline melanoma susceptibility and prognostic genes: A
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<th>Section: Medicine</th>
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<tr>
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- Aspinwall LG, Taber JM, Leaf SL, et al. Genetic testing for hereditary melanoma and pancreatic...


### Policy History

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<td>December 2011</td>
<td>New Policy</td>
<td>Policy statement changed to not medically necessary</td>
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<tr>
<td>June 2012</td>
<td>Update Policy</td>
<td>Policy updated with literature review, References added and updated,</td>
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<tr>
<td>December 2013</td>
<td>Update Policy</td>
<td>Policy updated with literature review. References 3, 4, 7, 20, 27, 28, and 30 added. Policy statement changed from not medically necessary to investigational. Title revised to Genetic Testing for <em>Familial</em> Cutaneous Malignant Melanoma.</td>
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### Keywords

Genetic Testing, Melanoma
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This policy was approved by the FEP® Pharmacy and Medical Policy Committee on December 5, 2014 and is effective January 15, 2015.

**Signature on File**

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