MEDICAL POLICY – 12.04.44

Genetic Testing for Familial Cutaneous Malignant Melanoma

Introduction

Melanoma is one type of skin cancer. It begins in the melanocyte cells of the skin. These cells produce a pigment (melanin) that gives the skin its color, all the way from pink to dark. Damage to the DNA in melanocytes can cause the cells to grow out of control, leading to melanoma. It’s believed the main cause of melanoma is too much exposure to ultraviolet light, such as getting bad sunburns or using tanning lamps. Another risk factor is family history. If one person has melanoma then there’s a greater chance that the parent, child, brother, or sister could also develop melanoma. For those at high risk of getting melanoma, medical experts say the best ways to reduce the risk are to limit sun exposure, use sunscreen, and watch for unusual moles or other unusually colored areas of the skin. Genetic tests have been created to look for genetic changes related to melanoma. But results from these genetic tests wouldn’t change recommendations for high risk people. Medical studies don’t show how genetic testing will lead to better health results. Genetic testing for melanoma is considered unproven.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.
Policy Coverage Criteria

<table>
<thead>
<tr>
<th>Testing</th>
<th>Investigational</th>
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<tbody>
<tr>
<td>Genetic testing</td>
<td>Genetic testing for variants associated with familial cutaneous malignant melanoma (CMM) or associated with susceptibility to cutaneous malignant melanoma is considered investigational.</td>
</tr>
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</table>

Coding

<table>
<thead>
<tr>
<th>CPT</th>
<th>Description</th>
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<tbody>
<tr>
<td>81404</td>
<td>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)</td>
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</tbody>
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Related Information

Melaris® (Myriad Genetics. Salt Lake City, UT) is one commercially available genetic test of the CDKN2A gene. To date FDA does not require regulatory review of this test.

Genetic Counseling

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

counseling should be performed by an individual with experience and expertise in

genetic medicine and genetic testing methods.

**Benefit Application**

Genetic testing for variants associated with malignant melanoma will likely be performed at

specialty laboratories.

**Evidence Review**

**Description**

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

**Background**

A genetic predisposition to Cutaneous Malignant Melanoma (CMM) is suspected in these
specific clinical situations:

- Melanoma has been diagnosed in multiple family members
- Multiple primary melanomas are identified in a single patient
- Melanomas began at an early age

A positive family history of melanoma is the most significant risk factor. It is estimated that
approximately 10% of patients with melanoma have a first- or second-degree relative with
melanoma. Although some of the familial risk may be related to shared environmental factors, 3
main genes involved in CMM susceptibility have been identified. Cyclin-dependent kinase
inhibitor 2A (CDKN2A), located on chromosome 9p21, encodes proteins that act as tumor
suppressors. Variants 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 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 variant. Variants are also infrequent in those with an early age of onset or those with multiple primary melanomas. However, the incidence of CDKN2A variants increases with a positive family history; CDKN2A variants will be found in 5% of families with first-degree relatives, rising to 20% to 40% in kindreds with 3 or more affected first-degree relatives. Variant detection rates in the CDKN2A gene are generally estimated as 20% to 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 being a family in which either 2 first-degree relatives are diagnosed with melanoma, or else there are 3 melanoma patients regardless of how closely they are related. Others have defined familial CMM as being a family that either a) has at least 3 affected members (first-, second-, or third-degree), or b) has 2 affected family members and at least 1 was diagnosed before age 50 years, or c) pancreatic cancer occurred in a first- or second-degree relative, or d) one member had multiple primary melanomas. No widely accepted guidelines for the management of families with hereditary risk of melanoma exist.

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

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 because there is no agreement on a standard phenotype, and dysplastic nevi occur in up to 50% of the general population. Atypical or dysplastic nevi are associated with an increased risk for CMM. Initially, the phenotypes of atypical nevi and CMM were thought to cosegregate 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. 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 variants.8

Melaris® (Myriad Genetics. Salt Lake City, UT) is a commercially available genetic test of the CDKN2A gene.

**Summary of Evidence**

For individuals who have cutaneous malignant melanoma and a family history of this disease who undergo genetic testing for genes associated with familial cutaneous malignant melanoma, the evidence includes genetic association studies between variants in certain genes and the risk of developing cutaneous melanoma. Relevant outcomes are overall survival, disease-specific survival, test accuracy, and test validity. Data on the analytic validity of testing are lacking. 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 does not change based on genetic variants identified in genes associated with familial cutaneous malignant melanoma; therefore, clinical utility is lacking. The evidence is insufficient to determine the effects of the technology on health outcomes.

For asymptomatic individuals in a family at high risk of developing cutaneous malignant melanoma who undergo genetic testing for familial cutaneous malignant melanoma, the evidence includes genetic association studies between variants in certain genes and the risk of developing cutaneous malignant melanoma. Relevant outcomes are overall survival, disease-specific survival, test accuracy, and test validity. Data on the analytic validity of testing are lacking. Limitations with clinical validity include difficulties with variant interpretations, variable penetrance of a given variant, and residual risk with a benign variant. Currently, management of patients considered high risk for cutaneous malignant melanoma focuses on reduction of sun exposure, use of sunscreens, vigilant cutaneous surveillance of pigmented lesions, and prompt biopsy of suspicious lesions. It is unclear how genetic testing for variants associated with increased risk of cutaneous malignant melanoma would alter these management recommendations; therefore, clinical utility is lacking. The evidence is insufficient to determine the effects of the technology on health outcomes.
Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed below.

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<td>Family Study of Melanoma in Italy</td>
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<tr>
<td>NCT00040352</td>
<td>Clinical, Laboratory, and Epidemiologic Characterization of Individuals and Families at High Risk of Melanoma</td>
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<tr>
<td>NCT00591500</td>
<td>A Model for Genetic Susceptibility: Melanoma</td>
<td>4082</td>
<td>Jul 2017</td>
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<tr>
<td>NCT00849407</td>
<td>Genetic Risk Factors and Acquired Oncogenic Variants of Melanoma</td>
<td>2000</td>
<td>Dec 2020</td>
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<tr>
<td>NCT00450593</td>
<td>Studies of Familial Melanoma</td>
<td>5000</td>
<td>Dec 2020</td>
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</table>

NCT: national clinical trial.

Practice Guidelines and Position Statements

*Melanoma Genetics Consortium*

In 2002, 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.33

*American Society of Clinical Oncology*

In a 2002 American Society of Clinical Oncology (ASCO) publication, Kefford et al. noted that the sensitivity and specificity of tests for CDKN2A variants are not fully known.34 Because interpreting genetic tests is difficult and because test results do not alter patient management, the Kefford publication indicated that CDKN2A genetic testing should be performed only in clinical trials for several reasons including: a low likelihood of finding variants in known melanoma susceptibility genes, uncertainty about the functionality and phenotypic expression
of the trait among variant carriers, and lack of proven melanoma prevention and surveillance strategies. Additionally, it was noted that all individuals with risk factors for cutaneous melanoma should follow programs of sun protection and skin surveillance, not just those considered high risk due to family history.

In 2010, ASCO updated its policy statement on genetic and genomic testing for cancer susceptibility. 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 National Comprehensive Cancer Network guidelines for melanoma (v.1.2017) have added a new bullet to “consider referral to a genetics counselor for p16/CDKN2A mutation [variant] testing in the presence of 3 or more invasive melanomas or a mix of invasive melanoma and pancreatic cancer diagnoses in an individual or family.”

**Medicare National Coverage**

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

**Regulatory Status**

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). Melaris® (Myriad Genetics, Salt Lake City, UT) 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, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

**References**


81479 and 81599, effective 1/1/13, are added to the policy.

05/14/13  Update Related Policies. Add 12.04.91.

12/09/13  Replace policy. Policy updated with literature search through August 2013; references 12-14, 16, and 26 added; reference 25 updated. Policy statement unchanged. CPT codes 81200-81479 and 81599 removed; these are not specific to policy; specific CPT code 81404 retained.


09/18/15  Coding update. Remove ICD-10-CM codes; informational only.

12/08/15  Annual Review. Policy updated with literature search. NCCN Guidelines info in Rationale updated to current version. No change to the policy statement.

02/09/16  Annual Review. Policy updated with literature search through October 6, 2015; no references added; reference 34 updated. Policy statement unchanged.


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