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

**Coding**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td></td>
</tr>
<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>
</tr>
</tbody>
</table>

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**Related Information**

**Genetics Nomenclature Update**

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics (see Table 1). The Society’s nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These
recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table 2 shows the recommended standard terminology—“pathogenic,” “likely pathogenic,” “uncertain significance,” “likely benign,” and “benign”—to describe variants identified that cause Mendelian disorders.

**Table 1. Nomenclature to Report on Variants Found in DNA**

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated variant</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
<tr>
<td>Variant</td>
<td>Change in the DNA sequence</td>
<td></td>
</tr>
<tr>
<td>Familial variant</td>
<td>Disease-associated variant found</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
</tr>
</tbody>
</table>

**Table 2. ACMG-AMP Standards and Guidelines for Variant Classification**

<table>
<thead>
<tr>
<th>Previous</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Likely pathogenic</td>
<td>Likely disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Variant of uncertain significance</td>
<td>Change in DNA sequence with uncertain effects on disease</td>
</tr>
<tr>
<td>Likely benign</td>
<td>Likely benign change in the DNA sequence</td>
</tr>
<tr>
<td>Benign</td>
<td>Benign change in the DNA sequence</td>
</tr>
</tbody>
</table>

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

**Genetic Counseling**

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.
Benefit Application

Genetic testing for genes associated with cutaneous 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

**Cutaneous Malignant Melanoma**

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 in families in which either 2 first-degree relatives are diagnosed with melanoma or a family with 3 melanoma patients, irrespective of the degree of relationship. 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 one was diagnosed before age 50 years, or pancreatic cancer occurred in a first- or second-degree relative or 1 member had multiple primary melanomas. 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.  

Management

No widely accepted guidelines for the management of families with hereditary risk of melanoma exist. Melaris is a commercially available genetic test of the CDKN2A gene.

Summary of Evidence

For individuals who have CMM and a family history of this disease who receive genetic testing for genes associated with familial CMM, the evidence includes genetic association studies correlating variants in certain genes and the risk of developing cutaneous melanoma. Relevant outcomes are overall survival, disease-specific survival, test accuracy, and test validity. 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 CMM, therefore, clinical utility is lacking. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are asymptomatic and in a family at high-risk of developing CMM who receive genetic testing for genes associated with familial CMM, the evidence includes genetic association studies correlating variants in certain genes and the risk of developing CMM. Relevant outcomes are overall survival, disease-specific survival, test accuracy, and test validity. 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 CMM focuses on the 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 CMM 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 in Table 3.

Table 3. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT00339222</td>
<td>Family Study of Melanoma in Italy</td>
<td>1600</td>
<td>NR</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>
<td>3000</td>
<td>NR</td>
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<tr>
<td>NCT00591500</td>
<td>A Model for Genetic Susceptibility: Melanoma</td>
<td>4082</td>
<td>Jul 2018</td>
</tr>
<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>
</tr>
</tbody>
</table>

NCT: national clinical trial.

Practice Guidelines and Position Statements

American Society of Clinical Oncology

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

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

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

**American Academy of Dermatology**

In 2011, the American Academy of Dermatology published guidelines on the management of primary cutaneous melanoma. The use of genetic testing in patients diagnosed with cutaneous malignant melanoma or asymptomatic patients with family history of the disease was not addressed.

**National Comprehensive Cancer Network**

Current National Comprehensive Cancer Network guidelines for melanoma (v.1.2018) have added under Common Follow-Up Recommendations for All Patients: “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. Testing for other genes that can harbor melanoma-predisposing mutations (eg, CDK4, TERT, MITF, and BAP1) may be warranted.”

**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


## History

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>05/24/12</td>
<td>Policy renumbered to 12.04.44 (previously 2.04.44) and reassigned to new Genetic Testing category.</td>
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<tr>
<td>01/14/13</td>
<td>Coding update. CPT codes 83890 – 83913 deleted as of 12/31/12; CPT codes 81200 – 81479 and 81599, effective 1/1/13, are added to the policy.</td>
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<tr>
<td>05/14/13</td>
<td>Update Related Policies. Add 12.04.91.</td>
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<tr>
<td>12/09/13</td>
<td>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.</td>
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<tr>
<td>09/18/15</td>
<td>Coding update. Remove ICD-10-CM codes; informational only.</td>
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<tr>
<td>12/08/15</td>
<td>Annual Review. Policy updated with literature search. NCCN Guidelines info in Rationale updated to current version. No change to the policy statement.</td>
</tr>
<tr>
<td>02/09/16</td>
<td>Annual Review. Policy updated with literature search through October 6, 2015; no references added; reference 34 updated. Policy statement unchanged.</td>
</tr>
<tr>
<td>05/01/18</td>
<td>Annual Review, approved April 18, 2018. Policy updated with literature search through January 2018; references 28 and 34 added. Policy statement unchanged.</td>
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</table>

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200 Independence Avenue SW, Room S09F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

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Hmoob (Hmong):

Ilokano (Ilocano):
Daytoy a Pakdaar ket naglaon iti Napateg nga Impomarson. Daytoy a pakdaar mabaliban nga adda ket naglaon iti napateg nga impomarson maianggpegg iti aplikasyonwo yowo覆盖 babaen iti Premera Blue Cross. Daytoy ket mabaliban dagiti importante a pelsa iti daytoy a pakdaar. Mabalibin nga adda rumbeng a aramideny nga adda sabbay dagiti partikular a naalting naga adda taglom tapno mapataganlaidayo te coverage ti salun-atyo wenno tulong kadagiti gastos. Adda karbenganyo a mangala iti daytoy nga impomarson ken tulong ti bukodyo a pagasasao nga awan ti bayadanyo. Tumawag ti numero nga 800-722-1471 (TTY: 800-842-5357).

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