

Protocol

Genetic Testing for Familial Cutaneous Malignant Melanoma

(20444)

Medical Benefit		Effective Date: 01/01/12	Next Review Date: 11/20
Preauthorization	No	Review Dates: 09/10, 09/11, 01/12, 01/13, 01/14, 11/14, 11/15, 11/16, 11/17, 11/18, 11/19	

This protocol considers this test or procedure investigational. If the physician feels this service is medically necessary, preauthorization is recommended.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: <ul style="list-style-type: none">• With cutaneous malignant melanoma and a family history of this disease	Interventions of interest are: <ul style="list-style-type: none">• Genetic testing for genes associated with familial cutaneous malignant melanoma	Comparators of interest are: <ul style="list-style-type: none">• Standard clinical management without genetic testing	Relevant outcomes include: <ul style="list-style-type: none">• Overall survival• Disease-specific survival• Test accuracy• Test validity
Individuals: <ul style="list-style-type: none">• Who are asymptomatic and in a family at high risk of developing cutaneous malignant melanoma	Interventions of interest are: <ul style="list-style-type: none">• Genetic testing for genes associated with familial cutaneous malignant melanoma	Comparators of interest are: <ul style="list-style-type: none">• Routine surveillance and use of preventive measures (e.g., sunblock)	Relevant outcomes include: <ul style="list-style-type: none">• Overall survival• Disease-specific survival• Test accuracy• Test validity

DESCRIPTION

Cutaneous melanoma is the third most common type of skin cancer, but the most lethal. 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 the disease and in unaffected individuals in a high-risk family.

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 measuring prevalence of variants in certain genes among those with 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 melanoma patients, which involves surveillance and education on sun avoidance behaviors, 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.

POLICY

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

POLICY GUIDELINES

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. It is being implemented for genetic testing medical protocol updates starting in 2017 (see Table PG1). The society's nomenclature is recommended by the Human Variome Project the HUMAN Genome Organization (HUGO) 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 PG2 shows the recommended standard terminology—"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"—to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

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 diffi-

cult 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.

BACKGROUND

GENETICS OF CUTANEOUS MALIGNANT MELANOMA

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 have been 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. Although some of the familial risk may be related to shared environmental factors, three 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 six families worldwide. A third gene, not fully characterized, maps to chromosome 1p22.

The incidence of CDKN2A disease-associated variants in the general population is very low. For example, it is estimated that in Queensland, Australia, an area with a high incidence of melanoma, only 0.2% of all patients with melanoma will harbor a CDKN2A disease-associated variant. Variants are also infrequent in those with an early age of onset or those with multiple primary melanomas.¹ 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% to 40% in patients with three or more affected first-degree relatives.² Variant detection rates of the CDKN2A gene are generally estimated to be 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 disease-associated variant are available.^{3,4}

Familial CMM has been described in families in which either two first-degree relatives are diagnosed with melanoma or a family with three melanoma patients, irrespective of the degree of relationship.⁵ Others have defined familial CMM as having at least three (first-, second-, or third-degree) affected members or two affected family members in which at least one was diagnosed before age 50 years, or pancreatic cancer occurred in a first- or second-degree relative or one member had multiple primary melanomas.⁶ 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.

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.⁷

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. 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 co-segregate in familial atypical multiple mole and melanoma syndrome 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 were noncarriers of the CDKN2A familial variant. Thus, the nevus phenotype cannot be used to distinguish carriers from noncarriers of CMM susceptibility in these families.

Ward et al (2012) reviewed the literature on germline melanoma susceptibility and concluded that in addition to the two rare, high-penetrance variants (CDKN2A and CDK4), there are potentially many single nucleotide polymorphisms which have small effects and low penetrance.⁸

Management

No widely accepted guidelines for the management of families with hereditary risk of melanoma exist.⁹ Badenas et al (2012) suggested several parameters to guide genetic testing for melanoma: in countries with a low to medium incidence of melanoma, genetic testing should be offered to families with two cases of melanoma or to an individual with two primary melanomas (the rule of two); in countries with a high incidence of melanoma, genetic testing should be offered to families with three cases of melanoma, or to an individual with three primary melanomas (the rule of three).¹⁰ Delaunay et al (2017) suggested a modification to the recommendations by Badenas et al (2012). In countries with a low to medium incidence of melanoma, Delaunay et al (2017) proposed that the rule of two should guide genetic testing only if there is an individual with melanoma before the age of 40, otherwise the rule of three should apply.¹¹

In general, individuals with increased risk of melanoma are educated on prevention strategies such as reducing sun exposure and on skin examination procedures.

REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Melaris® (Myriad Genetics) and other CDKN2A tests are available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

Services that are the subject of a clinical trial do not meet our Technology Assessment and Medically Necessary Services Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment and Medically Necessary Services Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

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We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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