

(20444)

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

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 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 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 preventative measures (e.g., sun block) 	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 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.

Summary of Evidence

For individuals who have cutaneous malignant melanoma and a family history of this disease who receive 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 do 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 individuals who are asymptomatic and in a family at high risk of developing cutaneous malignant melanoma who receive 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 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.

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

Human Genome Variation Society (HGVS) 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 evidence review updates starting in 2017 (see Table PG1). HGVS nomenclature is recommended by HGVS, the Human Variome Project, and the HUMAN Genome Organization (HUGO).

The American College of Medical Genetics and Genomics (ACMG) and Association for Molecular Pathology (AMP) standards and guidelines for interpretation of sequence variants represent expert opinion from ACMG, AMP, and 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

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 alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

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 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 kindreds with three or more affected first-degree relatives.² Variant detection rates of 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* disease-associated variant are available.^{3,4}

Familial CMM has been described as a family 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 No widely accepted guidelines for the management of families with hereditary risk of melanoma exist.⁷

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, 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.

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 is a commercially available genetic test of the *CDKN2A* gene.

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.

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

References

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

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