The following Protocol contains medical necessity criteria that apply for this service. It is applicable to Medicare Advantage products unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Preauthorization is not required if, despite this Protocol position, you feel this service is medically necessary; supporting documentation must be submitted to Utilization Management. 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.

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. Although some of the familial risk may be related to shared environmental factors, three 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. 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 six 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 three 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.

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. (3) 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. (4) Other malignancies associated with familial 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.

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 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 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 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 mutations. (5)

Melaris® is a commercially available genetic test of the CDKN2A gene.

**Policy (Formerly Corporate Medical Guideline)**

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

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.


