Genetic Testing for Cutaneous Malignant Melanoma

Description of Procedure or Service

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) 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. While some of the familial risk may be related to shared environmental factors, 3 principle genes involved in cutaneous malignant melanoma 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 6 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. 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%–40% in kindreds with 3 or more affected first-degree relatives. Variant detection rates in the CDK2NA 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. Validated clinical risk prediction tools to assess the probability that an affected individual carries a germline CDKN2A disease-associated variant are available.

Familial cutaneous malignant melanoma (CMM) has been described as a family 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 member was diagnosed before age 50 years, or pancreatic cancer occurred in a first- or second-degree relative, or 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, followed by other associated malignancies, such as 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
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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 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 variants, some 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.

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

Related Policies
Gene Expression Profiling for Cutaneous Melanoma

This policy, “Genetic Testing for Cutaneous Malignant Melanoma” is distinguished from the policy titled “Gene Expression Profiling for Cutaneous Melanoma”. Gene expression profiling for cutaneous melanoma requires actual tissue samples for diagnosis as an adjunct to histopathology, and is addressed in the Medical Policy entitled “Gene Expression Profiling for Cutaneous Melanoma”. A blood or plasma sample is used for gene mutation testing for melanoma susceptibility and is within the scope of this policy.

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy

Genetic testing for cutaneous malignant melanoma is considered investigational for all applications. BCBSNC does not provide coverage for investigational services or procedures.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Genetic Testing for Cutaneous Malignant Melanoma is covered

Not applicable

When Genetic Testing for Cutaneous Malignant Melanoma is not covered

Genetic testing for genes associated with familial cutaneous malignant melanoma or associated with susceptibility to cutaneous malignant melanoma is considered investigational.
Genetic Testing for Cutaneous Malignant Melanoma

Policy Guidelines

The evidence for genetic testing for genes associated with familial cutaneous malignant melanoma in individuals who have cutaneous malignant melanoma and a family history of this disease, 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. 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.

The evidence for genetic testing for genes associated with familial cutaneous malignant melanoma for asymptomatic individuals and in a family at high risk for developing cutaneous malignant melanoma includes, genetic associated 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. Limitation 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.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 81404, 81455, 81445, 81479

Specialty Matched Consultant Advisory Panel review 1/2012

Scientific Background and Reference Sources


Specialty Matched Consultant Advisory Panel review 1/2012

Genetic Testing for Cutaneous Malignant Melanoma


Specialty Matched Consultant Advisory Panel review 1/2013


Specialty Matched Consultant Advisory Panel review 1/2014


Specialty Matched Consultant Advisory Panel review 4/2015

Medical Director review 4/2015


Specialty Matched Consultant Advisory Panel review 3/2017

Medical Director review 3/2017


Specialty Matched Consultant Advisory Panel review 3/2018

Medical Director review 3/2018

Policy Implementation/Update Information

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<thead>
<tr>
<th>Date</th>
<th>Description</th>
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<tr>
<td>8/16/11</td>
<td>New policy implemented. Genetic testing for mutations associated with hereditary cutaneous malignant melanoma or associated with susceptibility to cutaneous malignant melanoma is considered investigational. Medical Director review 8/2011. Notice given 8/16/11 for effective date 11/22/11. (mco)</td>
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<tr>
<td>2/7/12</td>
<td>Specialty Matched Consultant Advisory Panel review 1/2012. No changes to Policy Statements. (mco)</td>
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<td>References updated. No changes to Policy Statements. (mco)</td>
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2/12/13 Specialty Matched Consultant Advisory Panel review 1/2013. No changes to Policy Statements. (mco)


3/31/15 References updated. Description section updated. Policy Statement remains unchanged. (td)


2/29/16 Policy Guidelines revised. References updated. (td)


1/26/18 Coding section revised; added 81455, 81445, 81479 and removed G0452. No change to policy intent. (jd)


6/29/18 Related Policies section added to distinguish between this policy and the policy entitled, “Gene Expression Profiling for Cutaneous Melanoma.” No change to policy intent. (jd)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.