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Medical Policy Manual

Topic: Genetic Testing for Cutaneous Malignant Melanoma

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Section: Genetic Testing

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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

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 is suspected in specific clinical situations:

- Melanoma has been diagnosed in multiple family members;
- Multiple primary melanomas are identified in a single patient; and
- 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. While some of the familial risk may be related to shared environmental factors, 4 main genes involved in CMM susceptibility have now been identified:

- CDKN2A, located on chromosome 9p21 encodes proteins that act as tumor suppressors. Mutations

at this site can alter the tumor suppressor function.
- 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.
- BAP1, which is located on 3p21, encodes a protein that acts as a tumor suppressor.[1-3]

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.[4] 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 3 or more affected first-degree relatives.[5] 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.

Hereditary 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.[6] Others have defined hereditary CMM as having at least 3 (first-, second-, or third-degree) affected members or 2 affected family members in which at least 1 was diagnosed before age 50 years or pancreatic cancer occurred in a first- or second-degree relative, or 1 member had multiple primary melanomas.[7]

Other malignancies associated with hereditary 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.

Hereditary forms of 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.

Both germline and somatic mutations of BAP1, BRCA1-associated protein, is a tumor suppressor reported to have varying degrees of penetrance and has been described in an autosomal-dominant pattern within 3 families of European descent.[3,8] BAP1 is both a germline and somatic mutation. BAP1 as a germline mutation increases CMM susceptibility, however the complete tumor spectrum associated with germline BAP1 mutations is not known.[1] The information provided by the presence of a germline BAP1 mutation is not clinically actionable at this time.

Some common allele(s) are associated with increased susceptibility to CMM but have low penetrance. One such gene 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 of which are risk factors for CMM. Variants in MC1R also modify the CMM risk in families with CDKN2A mutations.[9]

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

MEDICAL POLICY CRITERIA

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

SCIENTIFIC EVIDENCE

The focus of this review is on evidence from well-designed, randomized controlled trials related to the ability of test results to:

- Guide decisions in the clinical setting related to either treatment, management, or prevention when mutations associated with cutaneous malignant melanoma are identified, and
- Improve health outcomes as a result of those decisions.

The following must be considered:

- Interpretation of test results for cutaneous malignant melanoma is complex. If the unaffected individual is the first to be tested in the family (i.e., no affected relative has been previously tested to define the target mutation), it is very difficult to interpret the clinical significance of a mutation. The likelihood of clinical significance is increased if the identified mutation is the same as one reported in other families, although the issue of penetrance is a confounding factor. Although a positive mutation in an affected family member increases the likelihood of its clinical significance if detected in another family member, there is insufficient information to know what the risk of developing melanoma is with a positive test. In addition, not finding a mutation does not exclude the presence of hereditary cutaneous malignant melanoma. There may be other high risk genes for melanoma that have not yet been identified.[10]

- Regardless of mutation status, the clinical management of patients considered at high risk for malignant melanoma focuses on reduction of sun exposure, use of sun screens, vigilant cutaneous surveillance of pigmented lesions, and prompt biopsy of suspicious lesions. Although an affected individual with a positive CDKN2A mutation may be at increased risk for a second primary melanoma compared to the general population,[11] it is unclear how genetic testing results alter current screening and prevention recommendations. This applies to mutations with high penetrance (CDK2NA) as well as those with low penetrance (MC1R).

Literature Appraisal

- The published data on genetic testing of the CDKN2A and CDK4 genes focus on the underlying genetics of hereditary melanoma, identification of mutations in families at high risk of melanoma, and risk of melanoma in those harboring these mutations. In a recent report, of 437 families, CDKN2A mutations differed by the extent of CMM family clustering. The frequency of CDKN2A mutations were higher in families with 3 or more affected first-degree relatives and early age at initial diagnosis.[12] These patients are at risk due to a family history; screening for CDKN2A would not change the clinical care for this group of patients. A 2010 article on identifying individuals at high risk for melanoma emphasizes the use of the family history upon which to base treatment decisions[13].
- Additional studies address questions of patient compliance with screening or surveillance results associated with genetic testing.[14,15] However, small study samples and lack of study of primary health outcomes (overall, progression, and disease-free survival) limit the ability of these studies to isolate the impact of testing on clinical care — either for those with melanoma or for those at risk due to a family history.
- In a recent study, Branstrom et al used a self-reported survey to investigate genetic testing perceptions and preventive behaviors in 312 family members with increased risk of melanoma[16]. Fifty-three percent had been diagnosed with melanoma, and 12% had a positive susceptibility genetic test. The study indicated that a negative test might be associated with an erroneous perception of lower risk and fewer preventive measures.

Clinical Practice Guidelines

National Comprehensive Cancer Network (NCCN)

After diagnosis of melanoma, NCCN guidelines do not specifically recommend genetic testing for mutations associated with familial risk of melanoma at any stage of diagnosis – neither for the affected patient nor any family members.[17] However, on the basis that risk factors for melanoma include, "rarely inherited genetic mutations," the guidelines do suggest that genetic counseling "could be considered for individuals with a strong family history." There are no further recommendations regarding this type of counseling, nor how the information from genetic mutations could be used to alter clinical management.

Melanoma Genetics Consortium (GenoMEL)[5]

Genetic testing for *CDKN2A* mutations is currently available but the GenoMEL recommends offering such testing to patients only in the context of research protocols because clinical utility is uncertain.

American Society of Clinical Oncology (ASCO)[18]

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

Summary

The evidence to date is insufficient to permit conclusions concerning the effect of genetic testing for melanoma on health outcomes. The changes in patient management that result from finding a mutation in a patient at risk are not known. Therefore, genetic testing for mutations associated with hereditary

cutaneous malignant melanoma or associated with susceptibility to cutaneous malignant melanoma is considered investigational.

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CROSS REFERENCES

Genetic and Molecular Diagnostic Testing, Laboratory, Policy No. 20

CODES	NUMBER	DESCRIPTION
CPT	81404	Molecular pathology procedure, Tier 2 Level 5
HCPCS	None	