Genetic Testing for Familial Cutaneous Malignant Melanoma

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.

OBJECTIVE

The objective of this evidence review is to evaluate the clinical validity and clinical utility of genetic testing of individuals with or at high-risk for familial cutaneous malignant melanoma and to determine if its use improves the net health outcome.

POLICY STATEMENT

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

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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 evidence review updates starting in 2017 (see Table PG1). The Society’s nomenclature is recommended by the Human Variome Project, the HUman Genome Organization, 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

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated variant</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
<tr>
<td>Variant</td>
<td>Change in the DNA sequence</td>
<td></td>
</tr>
<tr>
<td>Familial variant</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
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Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Likely pathogenic</td>
<td>Likely disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Variant of uncertain significance</td>
<td>Change in DNA sequence with uncertain effects on disease</td>
</tr>
<tr>
<td>Likely benign</td>
<td>Likely benign change in the DNA sequence</td>
</tr>
<tr>
<td>Benign</td>
<td>Benign change in the DNA sequence</td>
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</table>

American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

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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 difficult 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.

BENEFIT APPLICATION

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient’s existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

FDA 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.

RATIONALE

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. The relevant outcomes are OS, DSS, 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. The relevant outcomes are OS, DSS, 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.
SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

American Society of Clinical Oncology

In an ASCO publication, Kefford et al (2002) noted that the sensitivity and specificity of tests for CDKN2A variants are not fully known. Because interpreting genetic tests is difficult and because test results do not alter patient management, ASCO recommended that CDKN2A genetic testing should be performed only in clinical trials, for several reasons, including a low likelihood of finding disease-associated variants in known melanoma susceptibility genes, uncertainty about the functionality and phenotypic expression of the trait among disease-associated variant carriers, and lack of proven melanoma prevention and surveillance strategies. Additionally, it was noted that all individuals with risk factors for cutaneous melanoma should follow programs of sun protection and skin surveillance, not just those considered high-risk due to family history.

In 2003 and 2010, the American Society of Clinical Oncology issued policy statements on genetic and genomic testing for cancer susceptibility. Both statements recommended that, outside of a research setting, genetic testing for cancer susceptibility should only be offered when the following three criteria are met: (1) the individual being tested has a personal or family history suggestive of an underlying hereditary component; (2) the genetic test can be adequately interpreted; and (3) test results will guide diagnosis and management.

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

American Academy of Dermatology

In 2019, the American Academy of Dermatology published guidelines for the care and management of primary cutaneous melanoma. There was a single recommendation related to genetic testing, which was directed to pregnant women: "Referral for genetic counseling and possible germline genetic testing for select patients with cutaneous melanoma" - strength of recommendation: C; level of evidence: III. The Work Group explained that "there is no strong evidence that genetic evaluation is either harmful or helpful."

National Comprehensive Cancer Network

Current National Comprehensive Cancer Network guidelines for cutaneous melanoma (v.1.2019) have added under Common Follow-Up Recommendations for All Patients: "consider referral to a genetics counselor for p16/CDKN2A mutation [variant] testing in the presence of 3 or more invasive melanomas or a mix of invasive melanoma and pancreatic cancer diagnoses in an individual or family. Testing for other genes that can harbor melanoma-predisposing mutations (e.g., CDK4, TERT, MITF, and BAP1) may be warranted."

U.S. Preventive Services Task Force Recommendations

Not applicable.
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

REFERENCES

15. Potrony, MM, Puig-Butill, JJ, Aguiler, PP, Badenas, CC, Carrera, CC, Malvhey, JJ, Puig, SS. Increased prevalence of lung, breast, and pancreatic cancers in addition to melanoma risk in families bearing the cyclin-dependent kinase inhibitor 2A mutation.

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34. Aspinwall LG, Stump TT, Taber JJ, Drummond DD, Kohlmann WW, Champine MM, Leachman SS. Genetic test reporting of CDKN2A provides informational and motivational benefits for managing melanoma risk. Transl Behav Med, 2018 Feb; 1,8(1). PMID 29385581.


POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

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<tr>
<td>December 2011</td>
<td>New policy</td>
<td>Policy statement changed to not medically necessary.</td>
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<td>June 2012</td>
<td>Replace policy</td>
<td></td>
</tr>
<tr>
<td>December 2013</td>
<td>Replace policy</td>
<td>Policy updated with literature review, References added and updated.</td>
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<td>December 2014</td>
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<td>Policy updated with literature review. References 3, 4, 7, 20, 27, 28, and 30 added. Policy statement changed from not medically necessary to investigational. Title revised to Genetic Testing for Familial Cutaneous Malignant Melanoma.</td>
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<tr>
<td>June 2017</td>
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<td>Policy updated with literature search through January 25, 2017; reference 18 added; reference 34 and 35 updated. The policy is revised with updated genetics nomenclature. &quot;Mutations&quot; changed to &quot;variants&quot; in policy statement. Policy statement otherwise unchanged.</td>
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<tr>
<td>June 2018</td>
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<td>Policy updated with literature search through January 8, 2018; references 28 and 34 added. Policy statement unchanged.</td>
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<tr>
<td>June 2019</td>
<td>Replace</td>
<td>Policy updated with literature search through February 14, 2019; references added. Policy statement unchanged.</td>
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