Genetic Testing for Familial Cutaneous Malignant Melanoma

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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Gene Expression Profiling for Cutaneous Melanoma is addressed separately in medical policy 00622.

Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers genetic testing for genes associated with familial cutaneous malignant melanoma (CMM) or associated with susceptibility to cutaneous malignant melanoma (CMM) to be **investigational.***

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 Organisation, 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

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

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

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.

Background/Overview

Genetics of Cutaneous Malignant Melanoma

A genetic predisposition to cutaneous malignant melanoma cutaneous malignant melanoma 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, 3 principal 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% to 40% in patients with 3 or more affected first-degree relatives. Variant detection rates of the *CDKN2A* gene are generally estimated to be 20% to 25% in hereditary cutaneous malignant melanoma 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 has been described in families 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 cutaneous malignant melanoma 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. Other malignancies associated with familial cutaneous malignant melanoma, 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.

Some common allele(s) are associated with increased susceptibility to cutaneous malignant melanoma 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 cutaneous malignant melanoma. This gene is associated with fair complexion, freckles, and red hair, all risk factors for cutaneous malignant melanoma. Variants in *MC1R* also modify the cutaneous malignant melanoma risk in families with *CDKN2*A variants.

Cutaneous malignant melanoma can occur either with or without a family history of multiple dysplastic nevi. Families with both cutaneous malignant melanoma and multiple dysplastic nevi have been referred to as having familial atypical multiple mole and melanoma syndrome. 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 cutaneous malignant melanoma. Initially, the phenotypes of atypical nevi and cutaneous malignant melanoma were thought to co-segregate in familial atypical multiple mole and melanoma syndrome 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 cutaneous malignant melanoma susceptibility in these families.

In 2012, Ward et al reviewed the literature on germline melanoma susceptibility and concluded that in addition to the 2 rare, high-penetrance variants (*CDKN2A* and *CDK4*), there are potentially many single nucleotide polymorphisms which have small effects and low penetrance.

Management
No widely accepted guidelines for the management of families with hereditary risk of melanoma exist. In 2012, Badenas et al suggested several parameters to guide genetic testing for melanoma: in countries with a low to medium incidence of melanoma, genetic testing should be offered to families with 2 cases of melanoma or to an individual with 2 primary melanomas (the rule of 2); in countries with a high incidence of melanoma, genetic testing should be offered to families with 3 cases of melanoma, or to an individual with 3 primary melanomas (the rule of 3). In 2017, Delaunay et al suggested a modification to the recommendations by Badenas et al (2012). In countries with a low to medium incidence of melanoma, Delaunay et al (2017) proposed that the rule of 2 should guide genetic testing only if there is an individual with melanoma before the age of 40, otherwise the rule of 3 should apply.

In general, individuals with increased risk of melanoma are educated on prevention strategies such as reducing sun exposure and on skin examination procedures.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
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 (CLIA). Melaris®‡ (Myriad Genetics) and other *CDKN2A* tests are available under the auspices of the CLIA. Laboratories that offer laboratory-developed tests must be licensed by the CLIA for high-complexity testing. To date, the U.S. FDA has chosen not to require any regulatory review of this test.

Rationale/Source

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 the disease and in unaffected individuals in a high-risk family.

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 measuring prevalence of variants in certain genes

among those with cutaneous malignant 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, which involves surveillance and education on sun avoidance behaviors, does 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 correlating 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. 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 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 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.

Supplemental Information

Practice Guidelines and Position Statements

American Society of Clinical Oncology

In an American Society of Clinical Oncology (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 ASCO 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 3 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.

In 2010, the ASCO 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."

In 2014, the ASCO commissioned another update to its policy statement on genetic and genomic testing for cancer susceptibility. The ASCO "affirms that it is sufficient for cancer risk assessment to evaluate genes of established clinical utility that are suggested by the patient's personal and/or family history."

American Academy of Dermatology
In 2019, the American Academy of Dermatology published guidelines for the care and management of primary cutaneous melanoma. Referral for genetic counseling and possible germline genetic testing for select patients with cutaneous melanoma was recommended for consideration with a level IIIC grade of evidence. The Work Group explained that "there is no strong evidence that genetic evaluation is either harmful or helpful." Criteria for cancer risk genetic counseling with possible multigene testing for patients with cutaneous melanoma include:

- A family history of invasive cutaneous melanoma or pancreatic cancer (≥3 affected members on 1 side of the family)
- Multiple primary invasive cutaneous melanomas (≥3), including 1 early-onset tumor (at age <45 years)
- A family history of mesothelioma, meningioma, and/or uveal melanoma and ≥1 melanocytic BAP1-mutated atypical intradermal tumor (MBAIT)
- ≥2 MBAITs

These 2019 guidelines are similar to standards previously established by the International Melanoma Genetics Consortium in 2009.

National Comprehensive Cancer Network
Current (v.1.2020) National Comprehensive Cancer Network (NCCN) guidelines for cutaneous melanoma 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, and/or astrocytoma diagnoses in an individual or family. Testing for other genes that can harbor melanoma-predisposing mutations (e.g., *MC1R*, *CDK4*, *TERT*, *MITF*, *BRCA2*, and *BAP1*) may be warranted."[i,ii]

[i] Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)‡ for Cutaneous Melanoma V.1.2020.©‡ National Comprehensive Cancer Network, Inc. 2020. All rights reserved. Accessed January 27, 2020. To view the most recent and complete version of the guideline, go online to NCCN.org.
[ii] NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
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.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			

NCT00339222	Family Study of Melanoma in Italy	2000	NR
NCT00040352	Clinical, Laboratory, and Epidemiologic Characterization of Individuals and Families at High Risk of Melanoma	3000	NR
NCT00849407	Genetic Risk Factors and Acquired Oncogenic Mutations of Melanoma	2000	Dec 2020
NCT00450593	Studies of Familial Melanoma	5000	Dec 2020
NCT00445783	Melanoma Family Case-Control Study Protocol	3700	Dec 2020
NCT00591500	A Model for Genetic Susceptibility: Melanoma	4082	Jul 2021
NCT03174574	Two Cancers, One Gene	500	Jul 2021
Unpublished			
NCT03177941a	Teaching Skin Self-Examination to First-degree Relatives of Melanoma Patients Using Mobile App Technology	0	Withdrawn

NCT: national clinical trial; NR: not reported.
[a] Denotes industry-sponsored or cosponsored trial

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09/06/2006	Medical Director review
09/20/2006	Medical Policy Committee approval
10/01/2008	Medical Director review
10/22/2008	Medical Policy Committee approval. No change to coverage eligibility.
10/01/2009	Medical Policy Committee review
10/14/2009	Medical Policy Implementation Committee approval. No change to coverage eligibility.
10/14/2010	Medical Policy Committee review

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10/20/2010	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
10/06/2011	Medical Policy Committee review
10/19/2011	Medical Policy Implementation Committee approval. Added "familial" to the policy title. Replaced "hereditary" with "familial" in the investigational statement and throughout the policy.
10/11/2012	Medical Policy Committee review
10/31/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
10/03/2013	Medical Policy Committee review
10/16/2013	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/06/2014	Medical Policy Committee review
11/21/2014	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
10/29/2015	Medical Policy Committee review
11/16/2015	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/03/2016	Medical Policy Committee review
11/16/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
11/02/2017	Medical Policy Committee review
11/15/2017	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/08/2018	Medical Policy Committee review
11/21/2018	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/07/2019	Medical Policy Committee review
11/13/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/05/2020	Medical Policy Committee review
11/11/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/11/2020	Coding update

Next Scheduled Review Date: 11/2021

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2019 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of

descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	81404 Code added eff 1/1/2021: 81529
HCPCS	No codes
ICD-10 Diagnosis	C43.0-C43.9, C44.00-C44.99, D03.0-D03.9, D04.111-D04.122, D22.111-D22.122, D23.111-D23.122

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and

whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.