

## MEDICAL POLICY

<b>POLICY TITLE</b>	<b>GENETIC TESTING FOR FAMILIAL CUTANEOUS MALIGNANT MELANOMA (CDKN2A, CDK4)</b>
<b>POLICY NUMBER</b>	<b>2.246</b>

<b>CLINICAL BENEFIT</b>	<input type="checkbox"/> MINIMIZE SAFETY RISK OR CONCERN. <input checked="" type="checkbox"/> MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. <input type="checkbox"/> ASSURE APPROPRIATE LEVEL OF CARE. <input type="checkbox"/> ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. <input type="checkbox"/> ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. <input type="checkbox"/> ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
<b>Effective Date:</b>	<b>RETIRED 7/1/2026</b>

### POLICY

Genetic testing for genes associated with familial cutaneous malignant melanoma or associated with susceptibility to cutaneous malignant melanoma is considered **investigational** (see Policy Guidelines). There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.

### Policy Guidelines

#### Genetics Nomenclature Update

Human Genome Variation Society (HGVS) 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). HGVS nomenclature is recommended by HGVS, the Human Variome Project, and the Human Genome Organization (HUGO).

The American College of Medical Genetics and Genomics (ACMG) and Association for Molecular Pathology (AMP) standards and guidelines for interpretation of sequence variants represent expert opinion from ACMG, AMP, and 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
<b>Mutation</b>	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
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<b>Pathogenic</b>	Disease-causing change in the DNA sequence
<b>Likely pathogenic</b>	Likely disease-causing change in the DNA sequence
<b>Variant of uncertain significance</b>	Change in DNA sequence with uncertain effects on disease
<b>Likely benign</b>	Likely benign change in the DNA sequence
<b>Benign</b>	Benign change in the DNA sequence

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

### Genetic Counseling

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

### Hereditary Cancer Syndromes and Screening Recommendations

Genetic susceptibility for melanoma can be a component in other hereditary cancer syndromes and therefore risk assessment and screening guidelines related to other cancers may be relevant to consider. See **MP 2.211**, **MP 2.255**, and **MP 2.274**.

National Comprehensive Cancer Network (NCCN) v3.2024 guidelines for genetic/familial high-risk assessment in breast, ovarian, and pancreatic cancer recommend comprehensive skin examination by a dermatologist supplemented with biannual total body photography and dermoscopy for *CDKN2A* variant carriers. The publication referenced in the guidelines to support the recommendation is a review article that does not provide evidence that biannual total body photography and dermoscopy improves outcomes.

#### ***Cross-References:***

**MP 2.211 Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers (BRCA1, BRCA2, PALB2)**

**MP 2.255 Genetic Testing for PTEN Hamartoma Tumor Syndrome**

**MP 2.259 Expanded Molecular Panel Testing of Cancers to Identify Targeted Therapies**

**MP 2.274 Genetic Testing for Li-Fraumeni Syndrome**

**MP 2.360 Gene Expression Profiling for Melanoma**

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### PRODUCT VARIATIONS

This policy is only applicable to certain programs and products administered by Capital Blue Cross and subject to benefit variations. Please see additional information below.

**FEP PPO** - Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at:

<https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies>

### DESCRIPTION/BACKGROUND

#### Genetics of Cutaneous Malignant Melanoma

A genetic predisposition to 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.

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 *CDKN2A* variants.

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.

#### 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 (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. Food and Drug Administration has chosen not to require any regulatory review of this test.

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### 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 correlating 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 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. 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 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.

### DEFINITIONS

**ALLELE(S)** refers to one of two or more different genes containing specific inheritable characteristics that occupy corresponding positions (loci) on paired chromosomes.

**PREDISPOSITION** is a latent susceptibility to disease which may be activated under certain conditions, as by stress.

### DISCLAIMER

*Capital Blue Cross' medical policies are used to determine coverage for specific medical technologies, procedures, equipment, and services. These medical policies do not constitute medical advice and are subject to change as required by law or applicable clinical evidence from independent treatment guidelines. Treating providers are solely responsible for medical advice and treatment of members. These policies are not a guarantee of coverage or payment. Payment of claims is subject to a determination regarding the member's benefit program and eligibility on the date of service, and a determination that the services are medically necessary and appropriate. Final processing of a claim is based upon the terms of contract that applies to*

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*the members' benefit program, including benefit limitations and exclusions. If a provider or a member has a question concerning this medical policy, please contact Capital Blue Cross' Provider Services or Member Services.*

### CODING INFORMATION

**Note:** This list of codes may not be all-inclusive, and codes are subject to change at any time.

The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

#### Investigational, therefore not covered, when used for testing CDKN2A and CDK4:

Procedure Codes						
81403	81404	81479				

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### POLICY HISTORY

<b>MP 2.246</b>	<b>03/13/2020 Consensus Review.</b> Policy statement unchanged. FEP variation unavailable, policy updated to reflect. References updated.
	<b>06/08/2021 Minor Review.</b> Added that CDKN2A testing is MN for 3 or more invasive cutaneous melanomas or for invasive cutaneous melanoma with first-degree relative diagnosed with pancreatic cancer. Added NCCN language and cross-references. Updated FEP, background, rationale, and references. Updated coding so that 81404 is now MN.
	<b>04/06/2022 Consensus Review.</b> Policy statement unchanged. FEP references updated. No coding changes.
	<b>06/02/2023 Consensus Review.</b> Updated background and references. Updated coding table. No changes to procedure codes.
	<b>05/15/2024 Consensus Review.</b> Updated references. No changes to coding.
	<b>06/24/2025 Major review.</b> Title updated; formerly Germline Genetic Testing for Familial Cutaneous Malignant Melanoma. Policy statement changed to INV. Updated policy guidelines, rationale, and references. Updated coding table and added procedure code 81403.
	<b>03/09/2026 Retirement Review.</b> EviCore Delegation.

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