BlueCross BlueShield Federal Employee Program.

# FEP Medical Policy Manual

## FEP 2.04.44 Germline Genetic Testing for Familial Cutaneous Malignant Melanoma (CDKN2A, CDK4)

### Annual Effective Policy Date: July 1, 2024

### Original Policy Date: December 2011

### Related Policies:

2.04.02 - Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers (BRCA1, BRCA2, PALB2)
2.04.101 - Genetic Testing for Li-Fraumeni Syndrome
2.04.146 - Gene Expression Profiling for Cutaneous Melanoma
2.04.77 - Somatic Genetic Testing to Select Individuals with Melanoma or Glioma for Targeted Therapy (BRAF)
2.04.88 - Genetic Testing for PTEN Hamartoma Tumor Syndrome

## Germline Genetic Testing for Familial Cutaneous Malignant Melanoma (CDKN2A, CDK4)

### Description

### Description

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.

## 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** (see Policy Guidelines).

# 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 (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

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 2.04.02, 2.04.88, and 2.04.101.

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.

# BENEFIT APPLICATION

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

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.

# 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 (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.

# RATIONALE

## Summary of Evidence

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 that the technology results in an improvement in the net health outcome.

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 individuals 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. Some guidelines recommend specific screening intervals and modalities for *CDKN2A* variant carriers; however, these screening strategies have not been demonstrated to improve health outcomes in *CDKN2A* carriers; therefore, clinical utility is lacking. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

# SUPPLEMENTAL INFORMATION

## Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

### American Academy of Dermatology

In 2019, the American Academy of Dermatology published guidelines for the care and management of primary cutaneous melanoma.[45,] 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.[46,]

### 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.[47,] 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. These include 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,[48,] and 2010,[49,] 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, ASCO updated its policy statement on genetic and genomic testing for cancer susceptibility.[49,] ASCO recommended that "genetic tests with uncertain clinical utility, including genomic risk assessment, be administered in the context of clinical trials."

In 2015, ASCO commissioned another update to its policy statement on genetic and genomic testing for cancer susceptibility.[50,] 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."

## National Comprehensive Cancer Network

Current (v.1.2024 ) National Comprehensive Cancer Network (NCCN) guidelines for cutaneous melanoma include the following follow-up recommendations:[51,]

- "Consider genetic counseling referral for *p16/CDKN2A* mutation [variant] testing in the presence of 3 or more invasive melanomas, or a mix of invasive melanoma, pancreatic cancer, and/or astrocytoma diagnoses in an individual or family."
- "Multigene panel testing that includes *CDKN2A* is recommended for patients with invasive cutaneous melanoma who have a first-degree relative diagnosed with pancreatic cancer."

- "Testing for other genes that can harbor melanoma-predisposing mutations [e.g., *MC1R*, *CDK4, TERT, MITF*, *PTEN*, *BRCA2*, and *BAP1*] may be warranted."

Current (v.3.2024 ) NCCN guidelines for genetic/familial high-risk assessment in breast, ovarian, and pancreatic cancer state that for *CDKN2A* mutation carriers, "comprehensive skin examination by a dermatologist, supplemented with total body photography and dermoscopy is recommended biannually."[52,]

## 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.

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

| Date | Action | Description |
|---|---|---|
| December 2011 | New policy | |
| June 2012 | Replace policy | Policy statement changed to not medically necessary. |
| December 2013 | Replace policy | Policy updated with literature review, References added and updated. |
| December 2014 | Replace policy | 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. |
| June 2017 | Replace policy | 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. "Mutations€š changed to "variants€š in policy statement. Policy statement otherwise unchanged. |
| June 2018 | Replace policy | Policy updated with literature search through January 8, 2018;references 28 and 34 added. Policy statement unchanged. |
| June 2019 | Replace policy | Policy updated with literature search through February 14, 2019; references added. Policy statement unchanged. |
| June 2020 | Replace policy | Policy updated with literature search through January 2, 2020; references added. Policy statement unchanged. |
| June 2021 | Replace policy | Policy updated with literature search through December 13, 2020; references added. Policy statement unchanged. |
| June 2022 | Replace policy | Policy updated with literature search through February 2, 2022; references added. Policy statement unchanged. |
| June 2023 | Replace policy | Policy updated with literature search through January 18, 2023; no references added. Title changed to be consistent with germline testing policies. Policy statement unchanged. |
| June 2024 | Replace policy | Policy updated with literature search through February 26, 2024; no references added. Policy statement unchanged. |