Familial Malignant Melanoma Genetic Testing

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Introduction

Familial malignant melanoma (FMM) genetic testing is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
CDKN2A deletion/duplication analysis	81479
CDKN2A known familial mutation analysis	81403
CDKN2A sequencing	81404
CDK4 known familial mutation analysis	81403
CDK4 sequencing	81479

Criteria

Introduction

Requests for familial malignant melanoma (FMM) genetic testing are reviewed using the following criteria.

Single Gene Sequencing and Deletion/Duplication Analysis

Due to the low diagnostic yield of single gene sequencing and deletion/duplication analysis, testing of a single gene is not considered medically necessary.

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Other Considerations

FMM testing may be performed as part of a multigene, multisyndrome panel. For information on multigene, multisyndrome panel testing, please refer to the guideline *Hereditary Cancer Syndrome Multigene Panels*, as this testing is not addressed here.

What is familial malignant melanoma?

Familial malignant melanoma (FMM) is a strongly inherited form of melanoma.

Prevalence

The lifetime risk for a cutaneous melanoma for someone born in the U.S is 1 in 34 women and 1 in 53 men. [1] The incidence continues to rise dramatically.[1] Most melanoma is sporadic. It is usually the result of a combination of genetic susceptibility (probably from several relatively low risk gene variants such as those involved with pigment) and environmental risk factors such as sun exposure.[1-4]

Approximately 3-15% of people with melanoma have a family history of melanoma.[3] "The proportion of all cutaneous melanomas that is attributable to the inheritance of autosomal dominantly inherited mutations in melanoma susceptibility genes is unknown, but it is estimated by the Consortium to be less than 1% to 2%."[2]

Symptoms

People who inherit an FMM mutation do not always develop melanoma. Studies have found a 28%-76% risk for melanoma. The likelihood of developing melanoma can be influenced by other factors such as demographic location, family history, and genetic modifiers.[1,5] The risk for pancreatic cancer is 15% or higher and smoking may increase this risk.[1]

Cause

Several genes have been linked to a higher risk of melanoma in families. CDNK2A gene mutations account for most of the currently identifiable FMM mutations, followed by CDK4 mutations.[6]

Inheritance

FMM is an autosomal dominant disorder.

Autosomal dominant inheritance

In autosomal dominant inheritance, individuals have 2 copies of the gene and only one mutation is required to cause disease. When a parent has a mutation, each

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offspring has a 50% risk of inheriting the mutation. Males and females are equally likely to be affected.

Diagnosis

FMM is most likely in a family when there are three or more close relatives diagnosed with melanoma.[2] Other factors that may also suggest FMM include:[2,4]

- Melanoma diagnosed younger than usual (average diagnosis age 30s versus 50s in people without FMM)
- More than one melanoma primary in the same individual
- Melanoma and pancreatic cancer in the same family
- Multiple, atypical moles, called dysplastic nevi that are often larger than 5mm in diameter with irregular borders. Melanoma with multiple nevi has also been called familial atypical mole-malignant melanoma syndrome. However, the presence or absence of such moles is no longer viewed as a reliable predictor of FMM in a family.

CDKN2A next generation sequencing identifies the majority of FMM-causing mutations and, in the absence of a known familial mutation, is usually the first step in testing. The likelihood that genetic testing will identify an FMM mutation varies with the personal and family history. The chance of finding a CDKN2A mutation is:

- 20-40% of people with melanoma from a family with at least 3 affected first-degree relatives.[2,6]
- Less than 5% of those with only 2 affected first-degree relatives[2]
- 15% in someone with multiple melanoma primaries and no known family history[2]
- 25-40% in people diagnosed with familial atypical mole-malignant melanoma syndrome - a subset of FMM characterized by >50 atypical nevi with characteristic microscopy features[7]
- 74% of families with FMM and pancreatic cancer[6]

CDK4 next generation sequencing, sometimes of only exon 2, is also available, but mutations are uncommon, accounting for only 2-3% of FMM cases.[6]

Management

For all individuals with a pathogenic mutation in CDKN2A, "consider pancreatic cancer screening beginning at age 40 years (or 10 years younger than the earliest exocrine pancreatic cancer diagnosis in the family, whichever is earlier)".[8] NCCN does not comment on pancreatic cancer screening for individuals with CDK4 mutations.

For individuals with a mutation in a hereditary melanoma gene such as CDKN2A or CDK4, "[t]hese individuals should be instructed on photoprotection and monthly self-skin screening examinations and should receive a regular skin screening examination by a medical professional. The frequency of examination by a health care provider should be tailored to account for the melanoma status and the difficulty of the examination, with

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higher-risk individuals receiving more frequent examinations ranging from every 3 to 12 months. If the individual has a personal history of melanoma, examinations should be in accordance with NCCN guidelines."[9]

Survival

The increased risk for malignant tumors is the largest factor impacting survival.

Special Considerations

Familial melanoma is also associated with other inherited cancer syndromes such as Li Fraumeni syndrome, hereditary breast and ovarian cancer syndrome, PTEN hamartoma tumor syndrome, inherited retinoblastoma, BAP1 tumor predisposition syndrome, and xeroderma pigmentosum.[2,9,10]

Test information

Introduction

FMM testing may include known familial mutation analysis, next generation sequencing, and/or deletion/duplication analysis.

Known Familial Mutation (KFM) Testing

Known familial mutations analysis is performed when a causative mutation has been identified in a close biological relative of the individual requesting testing. Analysis for known familial mutations typically includes only the single mutation. However, if available, a targeted mutation panel that includes the familial mutation may be performed.

Next Generation Sequencing Assay

Next generation sequencing (NGS), which is also sometimes called massively parallel sequencing, was developed in 2005 to allow larger scale and more efficient gene sequencing. NGS relies on sequencing many copies of small pieces of DNA simultaneously and using bioinformatics to assemble the sequence. Sequence analysis detects single nucleotide substitutions and small (several nucleotide) deletions and insertions. Regions analyzed typically include the coding sequence and intron/exon boundaries. Promoter regions and intronic sequences may also be sequenced if disease-causing mutations are known to occur in these regions of a gene.

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Deletion and Duplication Analysis

Analysis for deletions and duplications can be performed using a variety of technical platforms including exon array, Multiplex ligation-dependent probe amplification (MLPA), and NGS data analysis. These assays detect gains and losses too large to be identified through standard sequence analysis, often single or multiple exons or whole genes.

Guidelines and evidence

American Cancer Society

The American Cancer Society (ACS, 2023) stated the following:[11]

The likelihood an individual has a melanoma-associated gene mutation is higher when any of these characteristics are present:

- multiple family members (usually at least three) on the same side of the family with melanoma
- an individual has had three or more melanomas
- an individual is diagnosed with melanoma before 45 years of age
- an individual has a personal and/or family history of other cancers that are part of an inherited cancer syndrome

"The most common gene changes in families with high rates of melanoma are mutations in the CDKN2A gene (also known as p16). Genetic tests for changes in this gene have been available for several years, although it hasn't always been clear how useful they are. In part, this is because people with any of the factors above are already known to have a higher risk of melanoma whether they carry a mutated CDKN2A gene or not, so it's not always clear how genetic testing results would change what a person does (or what a doctor would recommend). … With advances in technology in recent years, the costs of genetic testing have come down, and testing can now be done to look for changes in several different genes at the same time. Still, most melanoma experts don't recommend genetic testing for all people with a personal or family history of melanoma. Testing is more likely to be helpful if you have any of the factors in the list above, or if your family history includes some of the cancer types listed above."

Melanoma Genetics Consortium

The Melanoma Genetics Consortium (GenoMEL), an international research collaborative group, published guidances which stated:[2,12]

- "GenoMEL, the International Genetics Consortium, supports a qualitative framework to identify candidate individuals for CDKN2A mutation testing based on population-based melanoma incidence rates, diagnosis of multiple primary melanomas, and a verified family history of melanoma and/or pancreatic cancer."[12]

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- "Individuals who choose to undergo genetic testing [in a research setting] should have a second independent diagnostic (as distinct from research) DNA test performed in an accredited genetic testing laboratory."[2]
- For at-risk relatives with a known familial mutation, test sensitivity is virtually 100%. However, the likelihood of developing melanoma in mutation-positive individuals is largely unknown and there is "lack of proved efficacy of prevention and surveillance strategies based on DNA testing, even for mutation carriers."[2]
- "Rapid identification of familial melanoma patients with low probability of a germline mutation in CDKN2A could aid to direct patients toward risk counseling and away from inappropriate genetic testing."[12]

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN, 2025) evidence and consensus based guidelines stated:[1]

- "Consider genetic counseling referral for p16/CDKN2A mutation testing in the presence of 3 or more invasive cutaneous melanomas, or a mix of invasive melanoma, pancreatic cancer, and/or astrocytoma diagnosis 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 may be warranted."

Special Considerations

- FMM genetic testing outside of the research setting is not currently recommended for several reasons, including:
  - Currently available testing does not detect a mutation in a significant number of people who appear to have FMM. Therefore, a negative result cannot rule out FMM and should not change the prevention and screening plan for at-risk people.[2]
  - Individuals with FMM mutations need essentially the same prevention and screening as anyone at high risk for melanoma (family history, pigmentation, multiple moles, history of blistering sunburn).[2] Therefore, identifying an FMM-causing mutation is also not expected to change screening or treatment for melanoma.[5,13,14]
  - When a family FMM mutation has been found, other relatives who test negative for that mutation at best only return to the background risk for melanoma (which may be as high as 1 in 25) and still need regular skin screening.[2]

Note:

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This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for familial malignant melanoma genetic testing will ensure that members will not receive testing for which there is not a body of evidence demonstrating medical necessity. Use of a test that does not have evidence to support medical necessity can lead to negative consequences. These include but are not limited to physical implications, psychological implications, treatment burden, social implications, and dissatisfaction with healthcare.[15] However, it is possible that there will be a delay in care while providers search for an appropriate test with sufficient evidence (analytical validity, clinical validity, and clinical utility).

References

1. Swetter S, Johnson D, Albertini M, et al. National Comprehensive Cancer Network (NCCN) Guidelines Version 2.2025 – January 28, 2025. Melanoma: Cutaneous, available at: **http://www.nccn.org/professionals/physician_gls/PDF/cutaneous melanoma.pdf** . Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guideline®) for Melanoma: Cutaneous V2.2025 – January 28, 2025. ©2025 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guideline® and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guideline® , go online to NCCN.org.
2. Kefford R, Newton Bishop J, Bergman W, Tucker M. Counseling and DNA testing for individuals perceived to be genetically predisposed to melanoma: A consensus statement of the Melanoma Genetics Consortium. *J Clin Oncol.* 1999;17(10):3245-51. doi:10.1200/JCO.1999.17.10.3245
3. Debniak T. Familial malignant melanoma - overview. *Hered Cancer Clin Pract.* 2004;2(3):123-129. doi:10.1186/1897-4287-2-3-123
4. Melanoma Genetics Consortium (GenoMEL). Patient Information. Available at: **https://genomel.org/info-for-patients/having-a-family-history-of-melanoma/#contentjump**
5. Matthews NH, Li WQ, Qureshi AA, et al. Epidemiology of Melanoma. In: Ward WH, Farma JM, editors. Cutaneous Melanoma: Etiology and Therapy [Internet]. Brisbane (AU): Codon Publications; 2017 Dec 21. Chapter 1. Available at: **https://www.ncbi.nlm.nih.gov/books/NBK481862/**
6. Goldstein AM, Chan M, Harland M, et al.; Melanoma Genetics Consortium (GenoMEL). High-risk melanoma susceptibility genes and pancreatic cancer, neural system tumors, and uveal melanoma across GenoMEL. *Cancer Res.* 2006;66(20):9818-28. doi:10.1158/0008-5472.CAN-06-0494
7. Mize DE, Bishop M, Resse E, Sluzevich J. Familial Atypical Multiple Mole Melanoma Syndrome. In Riegert-Johnson D, Boardman L, Hefferon T, Spurck L, eds. *Familial Cancer Syndromes*. National Library of Medicine (US), NCBI; 2009. Available at: **http://www.ncbi.nlm.nih.gov/books/NBK7030/** .
8. Daly M, Pal T, AlHilli Z, et al. National Comprehensive Cancer Network (NCCN) Guidelines Version 3.2025 – March 6, 2025. Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic and Prostate, available at: **https://www.nccn.org/professionals/physician_gls/pdf/genetics_bopp.pdf** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guideline®) for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic V3.2025 – March 6, 2025. ©2025 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guideline® and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guideline® , go online to NCCN.org.
9. Leachman SA, Lucero OM, Sampson JE, et al. Identification, genetic testing, and management of hereditary melanoma. *Cancer Metastasis Rev*. 2017;36(1):77-90. doi:10.1007/s10555-017-9661-5.
10. Nijauw CN, Kim I, Piris A, et al. Germline BAP1 inactivation is preferentially associated with metastatic ocular melanoma and cutaneous-ocular melanoma families. *PLoS One.* 2012;7(4);e35295. doi:10.1371/journal.pone.0035295

11. American Cancer Society. Genetic Counseling and Testing for People at High Risk of Melanoma. Last revised: October 27, 2023. Available at: **https://www.cancer.org/cancer/types/melanoma-skin-cancer/causes-risks-prevention/genetic-counseling-and-testing-for-people-at-high-risk-of-melanoma.html**
12. Taylor NJ, Mitra N, Qian L, et al. GenoMEL Study Group. Estimating CDKN2A mutation carrier probability among global familial melanoma cases using GenoMELPREDICT. *J Am Acad Dermatol*. 2019;81(2):386-394. doi:10.1016/j.jaad.2019.01.079
13. Stump TK, Aspinwall LG, Drummond DM, et al. CDKN2A testing and genetic counseling promote reductions in objectively measured sun exposure one year later. *Genet Med*. 2020;22(1):26-34. doi:10.1038/s41436-019-0608-9.
14. Pauley K, Khan A, Kohlmann W, Jeter J. Considerations for germline testing in melanoma: Updates in behavioral change and pancreatic surveillance for carriers of CDKN2A pathogenic variants. *Front Oncol*. 2022;12:837057. doi:10.3389/fonc.2022.837057.
15. Korenstein D, Chimonas S, Barrow B, et al. Development of a conceptual map of negative consequences for patients of overuse of medical tests and treatments. *JAMA Inter Med*. 2018;178(10):1401-1407. doi:10.1001/jamainternmed.2018.3573

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