Familial Malignant Melanoma Testing

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.

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What is familial malignant melanoma

Definition

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

- 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 usually is 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.\(^1,4\)
- About 4-8% of people with melanoma have a family history of at least one first-degree relative (parent, child, sibling) with melanoma.\(^3,5\) Less than 1% to 2% have multiple affected relatives, which suggests a stronger genetic susceptibility.\(^2,5\)
- 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:\(^2,4,5\)
  - 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.

- 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.\(^6\)

- FMM is an autosomal dominant condition, meaning that only one gene mutation is needed to increase susceptibility to melanoma. A person with FMM has a 50% chance to pass the mutation to each child.

- People who inherit an FMM mutation do not always develop melanoma. Data for CDNK2A mutations suggest that in the United States the melanoma risk is 50% by age 50 and 76% by age 80.\(^4\) The likelihood may vary with geographic location and sun exposure.\(^5\)

- Carriers of the CDKN2A p16-Leiden mutation have been found to have between 17% to 25% risk for pancreatic cancer. Estimates from studies using population based identification of subjects have shown a 7.4 relative-risk (95% CI 2.3 to 18.7) for pancreatic cancers in families with other CDKN2A/p16 mutations.\(^7\)

- Familial melanoma is also associated with some other inherited cancer syndromes, like Li Fraumeni syndrome, inherited retinoblastoma, and xeroderma pigmentosum.\(^2\) Additionally, germline mutations in the BAP1 gene have been identified in families with cutaneous and ocular melanoma.\(^8\)

### Test information

- **CDKN2A Sequencing:** Identifies the majority of FMM-causing mutations, and 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\(^9\)
  - 74% of families with FMM and pancreatic cancer\(^6\)

- **CDKN2A Deletion/Duplication Analysis:** Tests for large deletions that cannot be identified by sequencing.
• CDK4 Sequencing: Sequencing, sometimes of only exon 2, is also available, but mutations are uncommon, accounting for only 2-3% of FMM cases.\textsuperscript{6}

• CDKN2A Known Familial Mutation Analysis: When the family mutation is known, testing for only the family mutation can be performed in at-risk relatives. Test accuracy approaches 100%.\textsuperscript{2}

• CDK4 Known Familial Mutation Analysis: When the family mutation is known, testing for only the family mutation can be performed in at-risk relatives. Test accuracy approaches 100%.\textsuperscript{2}

Guidelines and evidence

• No evidence-based U.S. guidelines were identified.

• FMM genetic testing outside of the research setting is not currently recommended for several reasons, including:
  
  o 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.\textsuperscript{2}
  
  o 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).\textsuperscript{2} Therefore, identifying an FMM-causing mutation is also not expected to change screening or treatment.\textsuperscript{5}
  
  o 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.\textsuperscript{2}
  
  o A significant percentage of people with recognized FMM mutations do not develop melanoma, which is especially true when sun exposure is limited by geography or prevention.\textsuperscript{4}

• The Melanoma Genetics Consortium (GenoMEL), an international research collaborative group, published a consensus statement in 1999 stating, “DNA testing for mutations in known melanoma susceptibility genes should only rarely be performed outside of defined research programs. With this general proviso, two distinct clinical situations need further consideration: families in which a CDKN2A mutation has been identified in a proband as part of a research study and families for which no prior testing of affected individuals has been conducted.” \textsuperscript{2}
  
  o “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.” \textsuperscript{2}
  
  o 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.” They do acknowledge potential benefits could include enhanced motivation to adhere to prevention and screening guidelines, earlier melanoma diagnosis if the biopsy threshold is lower, and lower anxiety for those who learn they are negative for a known family mutation.²

- The National Comprehensive Cancer Network (NCCN) Melanoma Guideline (updated 2019) includes family history as a melanoma risk factor and alters management based on this risk. However, these guidelines do not address genetic testing for FMM.¹

**Criteria**

- This test is considered investigational and/or experimental.
  - Investigational and experimental (I&E) molecular and genomic (MolGen) tests refer to assays involving chromosomes, DNA, RNA, or gene products that have insufficient data to determine the net health impact, which typically means there is insufficient data to support that a test accurately assesses the outcome of interest (analytical and clinical validity), significantly improves health outcomes (clinical utility), and/or performs better than an existing standard of care medical management option. Such tests are also not generally accepted as standard of care in the evaluation or management of a particular condition.
  - In the case of MolGen testing, FDA clearance is not a reliable standard given the number of laboratory developed tests that currently fall outside of FDA oversight and FDA clearance often does not assess clinical utility.

**References**


