Test Specific Guidelines

Familial Malignant Melanoma Genetic Testing

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Introduction

Familial malignant melanoma genetic testing is addressed by this guideline.

Procedures Addressed

The inclusion of any procedure code in this table is provided for informational purposes and is not a guarantee of coverage nor an indication that prior authorization is required.

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

What Is Familial Malignant Melanoma?

Definition

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]

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]

Symptoms

People who inherit an FMM mutation do not always develop melanoma. Data for CDKN2A 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.[6]

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.[7]

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 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:[2,4,5]

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.

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.[2,7]

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[8]

74% of families with FMM and pancreatic cancer[7]

CDK4 next generation sequencing, sometimes of only exon 2, is also available, but mutations are uncommon, accounting for only 2-3% of FMM cases.[7]

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)".[9] 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 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."[10]

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.[2,11,12]

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.

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

Introduction

This section includes relevant guidelines and evidence pertaining to FMM testing.

American Cancer Society

The American Cancer Society (ACS, 2019) stated:[13]

"Some families with high rates of melanoma have mutations in genes such as CDKN2A (also known as p16). Tests for some of these gene changes are now available, although doctors aren't sure how useful they are at this time. In part, this is because people with any of the factors above are already known to have a

higher risk of melanoma regardless of whether they carry a mutated gene, so it's not always clear how helpful the genetic testing results would be."

Melanoma Genetics Consortium

The Melanoma Genetics Consortium (GenoMEL,1999), an international research collaborative group, published a consensus statement which stated:[2]

"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."

"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."

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.

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN, 2022) 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 family."

"Multigene panel testing that includes CDKN2A is also recommended for patients with invasive cutaneous melanoma who have a first degree relative diagnosed with pancreatic cancer."

"Testing 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]

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]

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.[4]

Criteria

Introduction

Requests for FMM testing are reviewed using these 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 and is therefore not reimbursable.

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 address

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