Melanoma-Pancreatic Cancer: **CDKN2A** Gene Sequencing

**Test Code:** VN  
**Turnaround time:** 4 weeks  
**CPT Codes:** 81404 x1

### Condition Description

Members of families with melanoma-pancreatic cancer syndrome (also known as familial atypical multiple-mole melanoma (FAMMM) syndrome) inherit a predisposition to develop multiple atypical cutaneous nevi (> 50), although not all patients with melanoma in these families display this phenotype. These families also appear to be at increased risk of other malignancies, particularly adenocarcinoma of the pancreas. A melanoma family apparently predisposed to pancreatic cancer was reported first in 1968, and a number of additional families have been identified subsequently. Several studies of melanoma-pancreatic cancer syndrome families have found an excess of nonmelanoma malignancies compared with the expected frequency of these malignancies in the general population. The risk of developing malignant disease in these families appears to be increased 10-fold to 40-fold, and the cumulative risk of pancreatic cancer, the second most common cancer in the syndrome, has been estimated at 17% by age 75 years. In addition, these families may be at increased risk of developing other carcinomas, including breast tumors, lung tumors, sarcoma, and digestive tract tumors.

The most common known mutation in these melanoma-prone families involves the **CDKN2A** gene on chromosome 9p21. **CDKN2A** encodes p16, a low-molecular-weight protein that inhibits the cyclin D1-cyclin dependent kinase complex (CDK4).

If it is not inhibited, the CDK4 complex, in turn, phosphorylates the retinoblastoma protein, allowing a cell to progress through the G1 phase of the cell cycle. Thus, p16 acts as a tumor suppressor protein, and mutations in **CDKN2A** can result in unregulated cell growth and neoplastic progression. Germ line **CDKN2A** mutations have been detected in up to 25% of melanoma-prone families worldwide.

For patients with suspected melanoma-pancreatic cancer syndrome, sequence analysis is recommended as the first step in mutation identification. For patients in whom mutations are not identified by full gene sequencing, deletion/duplication analysis is appropriate.

**Reference**


### Genes

**CDKN2A**

### Indications

This test is indicated for:

- Confirmation of a clinical diagnosis of melanoma-pancreatic cancer syndrome
- Individuals at-risk for melanoma-pancreatic cancer syndrome due to family history

### Methodology

PCR amplification of 3 exons contained in the **CDKN2A** gene is performed on the patient’s genomic DNA. Direct sequencing of amplification products is performed in both forward and reverse directions, using automated fluorescence dideoxy sequencing methods. The patient’s gene sequences are then compared to a normal reference sequence. Sequence variations are classified as mutations, benign variants unrelated to disease, or variations of unknown clinical significance. Variants of unknown clinical significance may require further studies of the patient and/or family members. This assay does not interrogate the promoter region, deep intronic regions, or other regulatory elements, and does not detect large deletions.

### Detection

Clinical Sensitivity: Germ line **CDKN2A** mutations have been detected in up to 25% of melanoma-prone families worldwide. Mutations in the promoter region, some mutations in the introns and other regulatory element mutations cannot be detected by this analysis. Large deletions will not be detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient’s biochemical phenotype.
Analytical Sensitivity: ~99%
Specimen Requirements

Submit only 1 of the following specimen types

* Preferred specimen type: Whole Blood

Type: Whole Blood

Specimen Requirements:

In EDTA (purple top) or ACD (yellow top) tube:
Infants (2 years): 3-5 ml
Older Children & Adults: 5-10 ml

Specimen Collection and Shipping: Refrigerate until time of shipment. Ship sample within 5 days of collection at room temperature with overnight delivery.

Type: Saliva

Specimen Requirements:

Oragene™ Saliva Collection kit (available through EGL) used according to manufacturer instructions.

Specimen Collection and Shipping: Store sample at room temperature. Ship sample within 5 days of collection at room temperature with overnight delivery.

Special Instructions

Submit copies of diagnostic biochemical test results with the sample, if appropriate. Contact the laboratory if further information is needed.

Sequence analysis is required before deletion/duplication analysis by targeted CGH array. If sequencing is performed outside of Emory Genetics Laboratory, please submit a copy of the sequencing report with the test requisition.

Related Tests

- Deletion/duplication analysis of the CDKN2A gene by CGH array is available for those individuals in whom sequence analysis is negative (VO).
- Custom diagnostic mutation analysis (KM) is available to family members if mutations are identified by targeted mutation testing or sequencing analysis.
- Prenatal testing is available to individuals who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.