Multiple Endocrine Neoplasia Type 1: MEN1 Gene Sequencing

Test Code: VQ
Turnaround time: 4 weeks
CPT Codes: 81405 x1

Condition Description

Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant condition that includes a varying combination of more than 20 endocrine and non-endocrine tumors. Endocrine tumors associated with MEN1 include parathyroid tumors, pituitary tumors, well-differentiated endocrine tumors of the gastro-entero-pancreatic (GEP) tract, carcinoid tumors, and adrenocortical tumors. These tumors can become evident by overproduction of hormones by the tumor or by growth of the tumor itself. Non-endocrine tumors associated with MEN1 syndrome include facial angiofibromas, collagenomas, lipomas, meningiomas, epedymomas, and leiomyomas.

Parathyroid tumors are the main MEN1-associated endocrinopathy with onset in 90% of individuals at 20-25 years of age and manifest as hypercalcemia by age 50 years. Prolactinoma is the most common pituitary tumor. GEP tract endocrine tumors include gastrinoma, insulinoma, glucagonoma, and VIPoma. Carcinoid tumors are non-hormone-secreting and manifest as a large mass after age 50 years. Adrenocortical tumors are associated with primary hypercortisolism or hyperaldosteronism.

Approximately 88% of affected individuals will have facial angiofibromas, which are benign tumors comprising blood vessels and connective tissue. These consist of acneiform papules that do not regress and that may extend across the vermilion border of the lips. Collagenomas are seen in about 72% of affected individuals and are multiple, skin-colored, sometimes hypopigmented, cutaneous nodules symmetrically arranged on the trunk, neck, and upper limbs. They are typically asymptomatic, roundish, and firm-elastic, from a few millimeters to several centimeters in size.

Clinical diagnostic criteria for MEN1 include the presence of two endocrine tumors that are parathyroid, pituitary, or GEP tract tumors. Familial MEN1 is defined as MEN1 in an individual who has either at least one first-degree relative with at least one of these endocrine tumors or only one organ involvement and an MEN1 disease-causing germline mutation. Molecular genetic testing of MEN1(11q13), the only gene known to be associated with MEN1, detects MEN1 mutations in about 80-90% of probands with familial MEN1 and in about 65% of individuals with a single occurrence of MEN1 in the family. Approximately 10% of cases are caused by de novo mutations.

For patients with suspected MEN1, 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.

Genes

MEN1

Indications

This test is indicated for:

- Confirmation of a clinical/biochemical diagnosis of MEN1
- Individuals at-risk for MEN1 due to family history

Methodology

PCR amplification of 10 exons contained in the MEN1 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: 80-90% in individuals with familial MEN1 and 65% in individuals with no family history. 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 MEN1 gene by CGH array is available for those individuals in whom sequence analysis is negative (VS).
- 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.