

*Familial Cancer Syndromes*

Multiple Endocrine  
Neoplasia Type 1 (MEN1)

Multiple Endocrine  
Neoplasia Type 2 (MEN2)

von Hippel-Lindau  
Syndrome (VHL)



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## *Molecular testing for MEN1 may help identify individuals with a high risk for endocrine neoplasia.*

### *What is Multiple Endocrine Neoplasia Type 1 (MEN1)?*

- Multiple endocrine neoplasia type 1 (MEN1) is a hereditary cancer syndrome often characterized by the occurrence of multifocal tumors in at least two of three endocrine target tissues:<sup>1</sup>
  - **Parathyroid glands** - Over 90% of MEN1 patients develop primary hyperparathyroidism (HPT). Primary HPT is often the initial manifestation of MEN1 and, in a minority of cases, may remain the only manifestation (familial idiopathic hyperparathyroidism).<sup>1</sup>
  - **Anterior pituitary** – Between 10% and 60% of MEN1 patients develop a tumor of the anterior pituitary, most often prolactinoma. Pituitary disease is the initial manifestation in about 20% or less of patients.<sup>1</sup>
  - **Entero-pancreatic tumors** – Between 30% and 75% of MEN1 carriers develop entero-pancreatic tumors.<sup>1</sup> Gastrinomas leading to Zollinger-Ellison Syndrome (ZES) are the most common type of functional entero-pancreatic neoplasm and have a high malignancy potential. ZES is the initial manifestation in about half of all MEN1 patients with gastrinomas.<sup>2</sup>
- MEN1 is associated with germline autosomal dominant loss-of-function mutations in the tumor suppressor gene *MEN1*.<sup>3,4</sup>

### *Why genetic testing?*

#### **Genetic testing for MEN1-associated mutations in *MEN1* can:**

- Confirm a diagnosis of MEN1 in about 80% of patients.
- Allow a definitive diagnosis after only one of the characteristic manifestations has become apparent.<sup>1</sup> Early diagnosis is important because:
  - tumor screening through biochemical tests and imaging techniques can detect further neoplasms years before they become clinically apparent.<sup>1,5</sup>
  - treatment of MEN1-associated entero-pancreatic tumors may differ from that of sporadic tumors.<sup>1,2</sup>
- Identify family members of MEN1 patients who harbor the pathogenic *MEN1* mutation identified in the index patient and therefore have a predisposition for MEN1. These family members should undergo regular biochemical screening for neoplasms associated with MEN1.<sup>1</sup>
- Identify family members of MEN1 patients who do not harbor the pathogenic *MEN1* mutation identified in the index patient and therefore do not need to undergo surveillance for manifestations of MEN1.<sup>5</sup>

### *Indications for testing:*

- Tumors in at least two of three target tissues (parathyroid glands, anterior pituitary, duodenum/pancreas)
- Multiple parathyroid tumors before age 30
- Zollinger-Ellison Syndrome
- Familial idiopathic hyperparathyroidism (FIHPT)
- Family history of MEN1

# Sequence analysis of the RET gene can help make a diagnosis of MEN2A, MEN2B, or FMTC and guide therapy.

## What is Multiple Endocrine Neoplasia Type 2 (MEN2)?

- MEN2 is a hereditary cancer syndrome often associated with multifocal medullary thyroid cancer (MTC), pheochromocytoma, and hyperparathyroidism.<sup>1,6</sup>
- MEN2-associated MTC accounts for about 25-30% of all MTC.<sup>6</sup>
- Subtypes of MEN2 include MEN2A, MEN2B, and FMTC (familial medullary thyroid cancer).<sup>1,6</sup>
  - All types of MEN2 show high penetrance for MTC. Approximately 90% of MEN2 carriers will develop characteristics of MTC.<sup>1</sup>
- MEN2 is associated with germline autosomal dominant gain-of-function mutations in the proto-oncogene *RET*.<sup>7,8</sup>
- Detection of an MEN2-associated mutation in the *RET* DNA sequence can indicate the need for prophylactic thyroidectomy, which has been shown to decrease occurrence of MTC.<sup>9,10</sup>

### MEN2 Subtypes<sup>1,6</sup>

	Age at MTC Onset	MTC	Pheo	HPT	Additional Symptoms
MEN2A	childhood to early adulthood	95%	50%	10-20%	Hirschsprung disease and cutaneous lichen amyloidosis possible
MEN2B	infancy to early childhood	100%	50%	0%	Mucosal neuromas of the lips and tongue; marfanoid attributes; distinctive facies with enlarged lips
FMTC	adulthood	100%	0%	0%	None

## Why genetic testing?

**Genetic testing for MEN2-associated mutations in *RET* is the method of choice for diagnosing MEN2. Genetic testing:**

- Can confirm a clinical diagnosis of MEN2
- Facilitates diagnosis of MEN2 before clinical or biochemical symptoms appear.
  - Carrier detection and early diagnosis of MEN2 are crucial, since prophylactic thyroidectomy has been shown to increase survival.<sup>1,6</sup>
- Can distinguish MEN2 from isolated MTC in patients without a family history.
- Is more sensitive and more specific than biochemical testing.
- May guide the timing of prophylactic thyroidectomy, as the position and type of a mutation within *RET* is often correlated to the age of onset and the aggressiveness of MTC.<sup>1,6,11</sup>
- Permits appropriate genetic counseling.

## Indications for testing:

- Medullary thyroid cancer
- Pheochromocytoma
- Family history of MEN2

# *Molecular testing for von Hippel-Lindau Syndrome may help identify patients at high risk for hemangioblastoma and/or renal cell carcinoma.*

## *What is von Hippel-Lindau Syndrome (VHL)?*

- Von Hippel-Lindau Syndrome (VHL) is a hereditary cancer syndrome often characterized by multifocal occurrence of retinal, cerebellar, and/or spinal hemangioblastomas, pheochromocytomas, and renal cell carcinomas.<sup>12,13</sup>
- Early diagnosis has been shown
  - to improve the survival rate of patients with VHL-associated renal cell carcinoma through early treatment.<sup>14</sup>
  - to help prevent vision loss by promoting timely treatment of retinal hemangioblastomas with laser photocoagulation or cryotherapy.<sup>12</sup>
- VHL is associated with germline autosomal dominant loss-of-function mutations in the tumor suppressor gene *VHL*.<sup>15</sup>

## *Why genetic testing?*

### **Genetic testing for VHL-associated mutations in VHL can:**

- Confirm a diagnosis of VHL in most patients after only one of the characteristic manifestations has become apparent.<sup>16</sup>
- Identify family members of VHL patients who harbor the pathogenic *VHL* mutation identified in the index patient and therefore have a predisposition for VHL. These family members should undergo regular biochemical screening for neoplasms associated with VHL.
- Identify family members of VHL patients who do not harbor the pathogenic *VHL* mutation identified in the index patient and therefore do not need to undergo surveillance for manifestations of VHL.

## *Indications for testing:*

- Cerebellar hemangioblastoma
- Pheochromocytoma
- Retinal hemangioblastoma
- Family history of VHL

## *Athena's Pheochromocytoma Evaluation can help to identify MEN2 or von Hippel-Lindau Syndrome in patients presenting with apparently sporadic pheochromocytoma.*

### **Germline mutations in VHL and RET have been identified as causes of sporadic pheochromocytoma.**

- Taken together, mutations in *VHL* and *RET* account for about 16% of nonsyndromic pheochromocytoma in patients without a family history.<sup>17</sup>
- By identifying VHL or MEN2 as the underlying cause for apparently sporadic pheochromocytoma, genetic testing can alert physician and patient to the risk of specific additional neoplasms.

## *Indications for testing:*

- Sporadic pheochromocytoma

# *Athena Diagnostics Testing for Familial Cancer Syndromes: MEN1, MEN2, VHL*

## *What are familial cancer syndromes?*

- Familial cancer syndromes are a group of monogenic diseases characterized by the autosomal dominant inheritance of a very high lifetime risk for specific tumors.
- Familial cancer syndromes are associated with gain-of-function mutations in a proto-oncogene or loss-of-functions in a tumor suppressor gene.
  - In carriers of a germline mutation associated with a familial cancer syndrome, the risk of cancer is dramatically increased. These carriers commonly develop tumors early in life and at several different places within the target tissue.
- Genetic testing can confirm a clinical diagnosis of a familial cancer syndrome or establish the diagnosis before a characteristic combination of tumors has developed.
  - Early diagnosis of a familial cancer syndrome and identification of at risk family members can facilitate targeted screening to identify neoplasms before they become clinically apparent.
- Genetic testing is widely accepted as an important tool in the diagnosis of familial cancer syndromes.
  - For example, MEN2 has been identified by the American Society of Clinical Oncologists as a well-defined hereditary cancer syndrome for which genetic testing is considered part of the standard management for at-risk family members.<sup>18</sup>

## *Why choose Athena?*

- Athena is your single source for a wide variety of molecular diagnostics for endocrine disorders.
- Athena Diagnostics offers full sequencing analysis of the familial cancer syndrome genes *MEN1*, *MEN2*, and *VHL*.
  - Studies have shown that mutations exist throughout the entire coding regions of the *MEN1*, *MEN2*, and *VHL* genes. Therefore, full sequencing will identify more patients than targeted analysis.
  - Athena offers consultation with lab directors or genetic counselors for assistance in result report interpretation.
- Athena provides phlebotomy services through a home draw service or partner hospital.
- Only Athena offers the Patient Protection Plan to help patients with commercial insurance gain coverage for genetic testing and limit their out-of-pocket expenses. Patients who choose to participate in the Patient Protection Plan are limited to 20% of the amount billed to insurance, regardless of what their insurance company pays.

# Familial Cancer Syndromes: MEN1, MEN2, VHL

## TEST DETAILS

### MEN1 (MEN1) Evaluation, #818:

**Typical Presentation:** Hyperparathyroidism, Zollinger-Ellison Syndrome, or pituitary disease

### MEN2 (RET) Evaluation, #813:

**Typical Presentation:** **MEN2A and FMTC:** Neck mass or pain; diarrhea  
**MEN2B:** Diarrhea or constipation; neuromas on distal surface of tongue, mucosal surface of upper eyelids, or vermillion border of lips; marfanoid habitus

### Von Hippel-Lindau Syndrome (VHL) Evaluation, #858:

**Typical Presentation:** Vision loss, headache, slurred speech, nystagmus, positional vertigo, dysmetria, hypertension, palpitations, tachycardia, or nausea

### Pheochromocytoma Evaluation, #859:

Includes sequencing of *VHL* and *RET* genes

**Typical Presentation:** Headache, hypertension, palpitations, tachycardia, or nausea

## TECHNICAL INFORMATION AND SHIPPING CONSIDERATIONS

**Methodology:** Polymerase Chain Reaction (PCR), DNA sequencing of entire protein coding region of gene

**Test Turnaround:** 21-28 days

**Specimen Type:** Whole blood

**Volume:** 10 mL (pediatric minimum: 2 mL)

**Collection Tube:** Yellow or lavender top

**Stability:** Hemolysis may compromise DNA recovery and integrity after 48 hrs

**Storage Conditions:** For short periods (until shipped) at 4°C

**Shipping Conditions:** Overnight at room temperature (specimen arrival must be less than 24 hrs after collection); ship Monday through Thursday only

To order testing for Familial Cancer Syndromes  
call Athena Diagnostics Customer  
Service Representatives at:

**800-394-4493 x2**



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