Multiple Endocrine Neoplasia Type 1 (MEN1)

Introduction

Multiple Endocrine Neoplasia Type 1 (MEN1) is addressed by this guideline.

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 Multiple Endocrine Neoplasia Type 1

Definition

Multiple Endocrine Neoplasia Type 1 (MEN1) is an inherited form of tumor predisposition characterized by multiple tumors of the endocrine system.

Incidence or Prevalence

MEN1 has a prevalence of 1/10,000 to 1/100,000 individuals.¹

Symptoms

The presenting symptom in 90% of individuals with MEN1 is primary hyperparathyroidism (PHPT). Parathyroid tumors cause overproduction of parathyroid hormone which leads to hypercalcemia. The average age of onset is 20-25 years. Parathyroid carcinomas are rare in individuals with MEN1.²,³,⁴

Pituitary tumors are seen in 30-40% of individuals and are the first clinical manifestation in 10% of familial cases and 25% of simplex cases. Tumors are typically solitary and there is no increased prevalence of pituitary carcinoma in individuals with MEN1.²,⁵
• Prolactinomas are the most commonly seen pituitary subtype and account for 60% of pituitary adenomas. They manifest as amenorrhea, oligomenorrhea, and/or galactorrhea in females and sexual dysfunction and gynecomastia in males.

• Growth hormone (GH)-secreting adenomas account for 25% of pituitary adenomas, with acromegaly as a common manifestation.

• Growth hormone/prolactin (GH/PRL)-secreting adenomas are seen in approximately 5% of individuals with MEN1. Manifestations can include acromegaly, as well as amenorrhea, oligomenorrhea, and/or galactorrhea in females and sexual dysfunction and gynecomastia in males.

• Adrenocorticotropic hormone (ACTH)-secreting adenomas occur in less than 5% of individuals with MEN1 and are associated with Cushing’s syndrome.

• Thyroid-stimulating hormone (TSH)-secreting adenomas are rare and manifest as symptoms of hyperthyroidism.

• Non-secreting tumors occur in less than 5% of individuals with MEN1 and manifest as enlarging pituitary tumors which can compress adjacent structures.

Well-differentiated endocrine tumors of the gastro-entero-pancreatic (GEP) tract include tumors of the stomach, duodenum, pancreas, and intestinal tract.\textsuperscript{2,6,7}

• Gastrinoma resulting in Zollinger-Ellison syndrome (ZES). More than 80% of MEN1-associated gastrinomas are found in the first and second portion of the duodenum. They are frequently multiple and usually malignant.

• Insulinoma resulting in hypoglycemia, which is observed in 10% of individuals with MEN1.

• Glucagonoma resulting in hyperglycemia, gastrointestinal problems, venous thrombosis, and skin rash. They are seen in less than 1% of individuals with MEN1.

• VIPoma (Vasoactive intestinal peptide-secreting tumor). These growths are typically malignant with high metastatic potential.

Other tumor types may include:

• Carcinoid tumors with bronchopulmonary, thymic, and gastric subtypes\textsuperscript{2}

• Adrenocortical tumors including cortisol-secreting, aldosterone-secreting, and rarely, pheochromocytoma\textsuperscript{2}

• Non-endocrine tumors (facial angiofibromas, collagenomas, lipomas, meningiomas, ependymomas, and leiomyomas)

**Cause**

Almost all cases of MEN1 are due to mutations in the MEN1 gene. The MEN1 gene codes for a tumor suppressor called menin. An inherited inactivating mutation plus an acquired (somatic) change in the other gene copy causes clonal growth that leads to tumors.\textsuperscript{1}
Inheritance

MEN1 mutations are inherited in an autosomal dominant manner, meaning that a person only needs a mutation in one copy of the gene to be affected. A child of an affected person has a 50% chance to inherit the mutation. The de novo mutation rate is 10%. The age-related penetrance for all clinical features surpasses 50% by age 20 years and 95% by age 40 years.²,⁸,⁹

Diagnosis

Clinical diagnosis of MEN1 is made when two neuroendocrine tumors of the parathyroid, pituitary, or GEP tract are identified.¹ Diagnostic tests may include biochemical testing for hormone and calcium levels, imaging, and molecular testing of the MEN1 gene, depending on clinical presentation and family history.

Treatment

Management and prevention strategies for those with or at-risk for MEN1 include treatment of specific tumor symptoms. This may include surgeries to remove the affected glands and specific medical therapies. Regular monitoring of at-risk hormone levels, as well as abdominal, chest, and head CTs and/or MRIs may be recommended.

Survival

Survival in MEN1 can be reduced and is largely dependent on clinical presentation and stage of cancer at the time of diagnosis. Thymic tumors in individuals with MEN1 are aggressive and median survival after diagnosis is less than 10 years.¹

Test information

Introduction

Testing for MEN1 may include sequence analysis, deletion/duplication analysis, or known familial mutation testing.

Full Gene Sequence analysis

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.

Results may be obtained that cannot be adequately interpreted based on the current knowledgebase. When a sequence variation is identified that has not been previously characterized or shown to cause the disorder in question, it is called a variant of
uncertain significance (VUS). VUSs are relatively common findings when sequencing large amounts of DNA with NGS.

Additionally, tests should be chosen to

- maximize the likelihood of identifying mutations in the genes of interest
- contribute to alterations in patient management
- minimize the chance of finding variants of uncertain clinical significance.

MEN1 sequencing evaluates each DNA nucleotide to identify mutations throughout the gene and should detect a mutation in 80-90% of familial cases of MEN1 and 65% of simplex cases of MEN1.\(^{10-12}\)

- The likelihood of detecting an MEN1 pathogenic variant is highest when an individual has more main tumors (parathyroid, pancreatic, and pituitary), especially those families with hyperparathyroidism and pancreatic islet tumors.\(^{14,15}\)
- The likelihood of detecting an MEN1 pathogenic variant increases in simplex cases with the presence of pancreatic lesions or with the presence of two main manifestations of MEN1.\(^{16}\)
- Individuals who have a single MEN1-related tumor and no family history of MEN1 syndrome rarely have germline MEN1 pathogenic variants.\(^{14}\)

**Deletion/duplication analysis**

Analysis for deletions and duplications can be performed using a variety of technical platforms including exon array, MLPA, and NGS data analysis.

Deletion/duplication panels may be billed separately from sequencing panels.

These assays detect gains and losses too large to be identified through sequencing technology, often single or multiple exons or whole genes.

The likelihood of identifying a deletion or duplication in an individual with MEN1 and no mutation identified by gene sequencing is 1-4%.\(^{14,15,17-21}\)

**Known familial mutation analysis**

Analysis for known familial mutations is typically performed by Sanger sequencing, but if available, a targeted mutation panel that includes the familial mutation may be performed.

Known familial mutations analysis is performed when a causative mutation has been identified in a close relative of the individual requesting testing.
Guidelines and evidence

Introduction

The following section includes relevant guidelines and evidence pertaining to MEN1 testing.

National Comprehensive Cancer Network

Evidence-based guidelines from the National Comprehensive Cancer Network (NCCN, 2018) support the use of MEN1 genetic testing in those with a clinical diagnosis of MEN1 or an at-risk relative of an individual with a known MEN1 germline mutation. A clinical diagnosis for MEN1 includes two or more MEN1-associated tumors:  

- multi-gland parathyroid hyperplasia;
- pancreatic NET; or
- pituitary tumors

Expert authored review

An expert-authored review (2012)² of MEN1 states MEN1 germline mutation testing should be offered to probands with MEN1 and their first-degree relatives, including relatives who are either asymptomatic or have clinical manifestations of MEN1. MEN1 germline mutation testing should be offered at the earliest opportunity as MEN1 manifestations may occur by the age of 5 years. A diagnosis of MEN1 may be established by one of the three criteria:

- The occurrence of two or more primary MEN1-associated endocrine tumors (such as parathyroid adenoma, enteropancreatic tumor, and pituitary adenoma);
- The occurrence of one of the MEN1-associated tumors in a first-degree relative of a patient with a clinical diagnosis of MEN1;
- The identification of a germline MEN1 mutation in an individual who may be asymptomatic and has not yet developed serum biochemical or radiological abnormalities indicative of tumor development

Criteria

Introduction

Requests for MEN1 testing are reviewed using the following criteria.

MEN1 Known Familial Mutation Analysis

- Genetic Counseling:
- Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND

**Previous Testing:**
- No previous genetic testing of MEN1, AND

**Diagnostic Testing for Symptomatic Individuals:**
- Known disease-causing family mutation in MEN1 identified in 1st, 2nd, or 3rd degree biological relative(s), AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy

**MEN1 Full Gene Sequencing**

- **Genetic Counseling:**
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- **Previous Testing:**
  - No previous genetic testing of MEN1, AND
- **Diagnostic Testing for Symptomatic Individuals**
  - Personal history of two or more of the following:
    - Parathyroid tumor, and/or
    - Pituitary tumor, including prolactinoma, GH-secreting adenoma, GH/PRL-secreting adenoma, TSH-secreting adenoma, ACTH-secreting adenoma, non-secreting pituitary adenoma, and/or
    - Well-differentiated endocrine tumors of the gastro-entero-pancreatic (GEP) tract, including gastrinoma, insulinoma, glucagonoma, VIPoma, non-secreting adenoma, pancreatic polypeptide-secreting adenoma, and/or
    - Carcinoid tumor, and/or
    - Adrenocortical tumor, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy

**MEN1 Duplication/Deletion Analysis**

- **Genetic Counseling:**
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- **Previous Testing:**
- No previous duplication/deletion testing, and
- Previous MEN1 sequencing performed and no mutations found, and
- No known familial mutation, AND

• Rendering laboratory is a qualified provider of service per the Health Plan policy

**Benefit exclusion**

**Exclusions and other considerations**

Testing unaffected individuals (e.g. carrier testing, predictive testing, presymptomatic testing, etc) is a BCBSAZ benefit exclusion and, therefore, not eligible for reimbursement.

**References**

**Introduction**

This guideline cites the following references.


