Multiple Endocrine Neoplasia Type 2 (MEN2)

Introduction

Multiple Endocrine Neoplasia Type 2 (MEN2) 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.

<table>
<thead>
<tr>
<th>Procedures addressed by this guideline</th>
<th>Procedure codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>RET Known Familial Mutation Analysis</td>
<td>81403</td>
</tr>
<tr>
<td>RET Targeted Mutation Analysis</td>
<td>81404</td>
</tr>
<tr>
<td>RET Targeted Sequencing</td>
<td>81405</td>
</tr>
<tr>
<td>RET Full Gene Sequencing</td>
<td>81406</td>
</tr>
</tbody>
</table>

What is Multiple Endocrine Neoplasia Type 2

Definition

Multiple Endocrine Neoplasia Type 2 (MEN2) is a group of autosomal dominant hereditary cancer predisposition syndromes caused by mutations in the RET proto-oncogene. There are two different clinical subtypes of MEN2: MEN2A, which includes the familial medullary thyroid cancer subtype (91%; 35% with isolated FMTC), and MEN2B (9%)\(^1\).

Incidence or Prevalence

The prevalence of all subtypes of MEN2 worldwide is estimated to be 1/35,000 to 1/40,000.\(^1,2\)

Symptoms

MEN 2A

MEN2A is further subclassified:
o Classic MEN2A
  o MEN2A with cutaneous lichen amyloidosis (CLA)
  o MEN2A with Hirschsprung's disease (HD)
  o Familial medullary thyroid cancer (FMTC) was once considered to be a separate subtype from MEN2A, and is now widely considered to be a variant of MEN2A with decreased penetrance of pheochromocytoma and primary hyperparathyroidism (PHPT).  

MEN 2A should be suspected in individuals with one or more specific endocrine tumors- medullary thyroid cancer (and/or its precursor, C-cell hyperplasia), pheochromocytoma, or parathyroid adenoma/hyperplasia.

  o Approximately 95% of individuals will have medullary thyroid cancer (MTC), typically at a younger age of onset than sporadic MTC, as a presenting symptom. The MTC is more often associated with C-cell hyperplasia and tends to be multifocal or bilateral.
  o Approximately 50% of individuals with MEN2A will develop pheochromocytoma (PCC). PCC has the tendency to be adrenal and bilateral.  
  o Approximately 20-30% of individuals with MEN2A will develop primary hyperparathyroidism.  

MEN2B

MEN2B should be suspected in individuals with distinctive facies (including lip mucosal neuromas resulting in thick vermillion of the upper and lower lip), mucosal neuromas of the lips and tongue, medullated corneal nerve fibers, marfanoid habitus, and MTC.

  o MEN2B is characterized by early development of an aggressive form of MTC in all affected individuals.  
  o PCCs occur in 50% of individuals with MEN2B, where approximately half are multiple and often bilateral.
  o Clinically significant parathyroid disease is absent in MEN2B.
  o MEN2B may be identified in infancy or early childhood by the presence of mucosal neuromas on the anterior dorsal surface of the tongue, palate, or pharynx, and a distinct facial appearance. Approximately 40% of affected individuals have diffuse ganglioneuromatosis of the gastrointestinal tract. Approximately 75% of affected individuals have a marfanoid habitus, often with kyphoscoliosis or lordosis, joint laxity, and decreased subcutaneous fat.
Cause

Over 95% cases of MEN 2 are due to mutations in RET, a proto-oncogene and tyrosine kinase. Gain of function mutations allow activation without dimerization of the protein or dimerization of the protein in the absence of ligand (constitutive activation). Pathogenic variants have been reported in exons 5, 8, 10, 11, 13, 14, 15, and 16 (with mutations in exons 10 and 11 comprising 95% of individuals with MEN2A). Genotype-phenotype correlations are known for RET mutations.

Inheritance

MEN2 is inherited in an autosomal dominant pattern, meaning that an affected individual has inherited one RET mutation from an affected parent. MEN2 can also result from a new (de novo) RET mutation in the affected individual.

Individuals with MEN2 have a 50% chance of passing the mutation to their children. Additionally, parents and siblings of known carriers have a 50% chance of being carriers of the same mutation.

Approximately 5-9% of MEN2A and 50% of MEN2B are caused by de novo RET mutations not inherited from an affected parent. Siblings would still need to be tested to rule out germline mutations.

MEN2 is associated with high penetrance and variable expressivity.

Diagnosis

The diagnosis of MEN2 is established based on clinical presentation, family history, and genetic testing. Identification of a pathogenic RET variant establishes the diagnosis if clinical features are inconclusive. Genetic testing to identify germline RET mutations is indicated in all individuals with primary C-cell hyperplasia or medullary thyroid cancer or a clinical diagnosis of MEN2, regardless of whether there is a family history.

MEN2A

- The occurrence of two or more specific endocrine tumors (medullary thyroid cancer, pheochromocytoma, and/or parathyroid adenoma/hyperplasia) in the patient or in close relatives

- Familial medullary thyroid carcinoma (FMTC) is suspected in families with four or more cases of MTC in the absence of pheochromocytoma or parathyroid adenoma/hyperplasia. However, distinguishing this subtype from classical MEN2A can be challenging for some small families.
MEN2B

- The presence of early-onset medullary thyroid cancer, mucosal neuromas of the lips and tongue, medullated corneal nerve fibers, distinctive facies with enlarged lips, and a marfanoid body habitus.²

Treatment

Management and prevention strategies for those with or at-risk for MEN2 include prophylactic thyroidectomy, biochemical screening for functioning pheochromocytoma, and ongoing monitoring for residual MTC, hypoparathyroidism, and pheochromocytoma.

Survival

Survival in MEN2 can be reduced and is largely dependent on clinical presentation and stage of cancer at the time of diagnosis.¹

Test information

Introduction

Testing for MEN2 may include targeted mutation analysis, sequence analysis, or known familial mutation testing.

Targeted mutation analysis

Targeted mutation analysis use hybridization, single nucleotide extension, select exon sequencing, or similar methodologies to assess a set of disease-causing mutations.

This analysis identifies common and/or recurring mutations.

Targeted mutation panels or select exon sequencing may have differing clinical sensitivities dependent upon patient ethnicity, phenotypic presentation, or other case-specific characteristics.

RET targeted sequencing may evaluate exons 5, 8, 10, 11, and 13-16, where most disease-causing mutations have been reported. Such testing will detect 98% of mutations associated with MEN2A and 95% of mutations associated with FMTC.⁸⁻¹¹

Targeting 2 RET mutations (p.Met918Thr and p.Ala883Phe) will detect 98% of RET mutations associated with MEN2B.¹²,¹³ As the phenotype is distinct from MEN2A, targeting these two mutations may be more efficient than select exon sequencing for MEN2B.

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.

**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.

Deletion/duplication analysis for MEN2 is typically not a consideration as the mutational mechanism is gain of function caused by missense variants and small in frame deletions and duplications.

**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 MEN2 testing.
National Comprehensive Cancer Network

Evidence-based guidelines from the National Comprehensive Cancer Network (NCCN, 2019) support genetic counseling and RET genetic testing for the following: 14

- An individual with a diagnosis of medullary thyroid cancer, a clinical diagnosis of MEN2, or primary C-cell hyperplasia
- An at-risk relative of an individual with a known germline RET mutation

American Thyroid Association

Revised Guidelines from the American Thyroid Association for the Management of Medullary Thyroid Carcinoma (2015) recommend the following as Grade B Recommendations (based on fair evidence of health outcomes improvement): 8

- MEN2A (Recommendations 3 and 4): initial testing of “either a single or multi-tiered analysis to detect RET mutations in exon 10 (codons 609, 611, 618, and 620), exon 11 (codons 630 and 634), and exons 8, 13, 14, 15, and 16. Sequencing of the entire coding region should be reserved for situations in which no RET mutation is identified or there is a discrepancy between the MEN2 phenotype and the expected phenotype.”
- MEN2B (Recommendation 5): “Patients with the MEN2B phenotype should be tested for the RET codon M918T mutation (exon 16), and if negative, the RET codon A883F mutation (exon 15). If there are no mutations identified in these two exons, the entire RET coding region should be sequenced.”
- MTC (Recommendation 6): “Patients with presumed sporadic MTC should have genetic testing to detect a RET germline mutation.”
- Other groups who should be tested (Recommendation 7): “Genetic counseling and genetic testing for RET germline mutations should be offered to:
  - First-degree relatives of patients with proven hereditary MTC,
  - Parents whose infants or young children have the classic phenotype of MEN2B,
  - Patients with CLA
  - Infants or young children with Hirschsprung’s Disease 2,15 and exon 10 RET germline mutations and adults with MEN2A and exon 10 mutations who have symptoms suggestive of Hirschsprung’s Disease”

Criteria

Introduction

Requests for MEN2 testing are reviewed using the following criteria.
RET 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 RET, AND

- Diagnostic and Predisposition Testing:
  - Known deleterious family mutation in RET identified in 1st, 2nd, or 3rd degree biological relative(s), AND

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

RET Targeted 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 RET, AND

- Diagnostic Testing for Symptomatic Individuals:
  - Personal history of medullary thyroid cancer, or
  - Personal history of primary C-cell hyperplasia, or
  - Personal history of other MEN2-related tumor diagnosed before age 35 years, or
  - Personal history of a clinical diagnosis of MEN2A: occurrence of two or more specific endocrine tumors (medullary thyroid cancer, pheochromocytoma, and/or parathyroid adenoma/hyperplasia), or
  - Personal history of a clinical diagnosis of FMTC: families with four or more cases of medullary thyroid cancer in the absence of pheochromocytoma or parathyroid adenoma/hyperplasia, or
  - Personal history of a clinical diagnosis of MEN2B: the presence of early-onset medullary thyroid cancer, mucosal neuromas of the lips and tongue, medullated corneal nerve fibers, distinctive facies with enlarged lips, and a marfanoid body habitus, OR

- Predisposition Testing for Presymptomatic/Asymptomatic Individuals:
First-degree relative of an individual with a clinical diagnosis of MEN2A, MEN2B, or FMTC (Note: whenever possible, an affected family member should be tested first), AND

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

**RET 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 RET full gene sequencing, and
  - Previous RET targeted analysis performed and no mutations found, and
  - No known familial mutation, AND

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

**References**

**Introduction**

This guideline cites the following references.


