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NLM Citation: Giusti F, Marini F, Brandi ML. Multiple Endocrine Neoplasia Type 1. 2005 Aug 31 [Updated 2022 Mar 10]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Multiple Endocrine Neoplasia Type 1

Synonyms: MEN1, MEN1 Syndrome, Multiple Endocrine Adenomatosis, Wermer Syndrome

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Created: August 31, 2005; Updated: March 10, 2022.

Summary

Clinical characteristics

Multiple endocrine neoplasia type 1 (MEN1) includes varying combinations of more than 20 endocrine and non-endocrine tumors.

Endocrine tumors become evident either by overproduction of hormones by the tumor or by growth of the tumor itself.

- **Parathyroid tumors** are the most common MEN1-associated endocrinopathy; onset in 90% of individuals is between ages 20 and 25 years with hypercalcemia evident by age 50 years; hypercalcemia causes lethargy, depression, confusion, anorexia, constipation, nausea, vomiting, diuresis, dehydration, hypercalciuria, kidney stones, increased bone resorption/fracture risk, hypertension, and shortened QT interval.
- **Pituitary tumors** include prolactinoma (the most common), which manifests as oligomenorrhea/amenorrhea and galactorrhea in females and sexual dysfunction in males.
- **Well-differentiated endocrine tumors of the gastroenteropancreatic (GEP) tract** can manifest as Zollinger-Ellison syndrome (gastrinoma); hypoglycemia (insulinoma); hyperglycemia, anorexia, glossitis, anemia, diarrhea, venous thrombosis, and skin rash (glucagonoma); and watery diarrhea, hypokalemia, and achlorhydria syndrome (vasoactive intestinal peptide [VIP]-secreting tumor).
- **Carcinoid tumors** are non-hormone-secreting and can manifest as a large mass after age 50 years.
- **Adrenocortical tumors** can be associated with primary hypercortisolism or hyperaldosteronism.

Non-endocrine tumors include facial angiofibromas, collagenomas, lipomas, meningiomas, ependymomas, and leiomyomas.

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Diagnosis/testing

The clinical diagnosis of MEN1 can be established in a proband with:

- Two or more endocrine tumors including parathyroid, anterior pituitary, and/or GEP tract tumors or one endocrine tumor (parathyroid, anterior pituitary, or GEP tract tumor); and
- A first-degree relative with MEN1.

The molecular diagnosis can be established by identification of a heterozygous pathogenic variant in *MEN1* on molecular genetic testing.

Management

Treatment of manifestations: Hyperparathyroidism is treated with subtotal parathyroidectomy and cryopreservation of parathyroid tissue or total parathyroidectomy and autotransplantation of parathyroid tissue; measure parathyroid hormone (PTH) and/or serum calcium to assess for hypoparathyroidism following subtotal or total parathyroidectomy; calcimimetics are used to treat primary hyperparathyroidism in those for whom surgery is contraindicated or has failed; prior to surgery, bone antiresorptive agents are used to reduce hypercalcemia and limit bone resorption. Prolactinomas are treated with dopamine agonists (cabergoline being the drug of choice). Growth hormone-secreting tumors causing acromegaly are treated by transsphenoidal surgery; medical therapy for growth hormone-secreting tumors includes somatostatin analogs, octreotide, and lanreotide. Adrenocorticotrophic hormone-secreting pituitary tumors associated with Cushing disease are surgically removed; nonsecreting pituitary adenomas are treated by transsphenoidal surgery. Proton pump inhibitors or H_2-receptor blockers reduce gastric acid output caused by gastrinomas. Surgery is indicated for insulinoma and most other pancreatic tumors. Long-acting somatostatin analogs can control the secretory hyperfunction associated with carcinoid syndrome. Surgery is suggested for adrenal tumors greater than 4 cm in diameter, for tumors 1-4 cm in diameter with atypical or suspicious radiologic features, or for tumors that show significant measurable growth over a six-month interval. Measure urinary catecholamines prior to surgery to diagnose and treat a pheochromocytoma to avoid blood pressure peaks during surgery. Skin lesions in individuals with MEN1 are treated the same way as for the general population.

Prevention of primary manifestations: Thymectomy may prevent thymic carcinoid in males, particularly in smokers.

Surveillance: Annual fasting serum calcium, and consider fasting serum intact PTH from age five years; annual serum prolactin, IGF-1, fasting glucose, and insulin from age five years; head MRI every three to five years from age five years; annual chromogranin-A, pancreatic polypeptide, glucagon, and vasoactive intestinal peptide for other pancreatic neuroendocrine tumors from age eight years; annual fasting serum gastrin from age 20 years; consider abdominal CT, MRI, or endoscopic ultrasound every three to five years from age 20 years; consider chest CT, MRI, or somatostatin receptor scintigraphy octreotide scan annually from age 15 years; consider annual skin exam.

Agents/circumstances to avoid: Smoking increases the risk of carcinoid tumors.

Evaluation of relatives at risk: Because early detection affects management, molecular genetic testing is offered to at-risk members of a family in which a germline *MEN1* pathogenic variant has been identified.

Pregnancy management: Women with primary hyperparathyroidism from any cause are at increased risk of developing preeclampsia; infants born to women with primary hyperparathyroidism should be monitored for postnatal hypocalcemia.

Genetic counseling

MEN1 is inherited in an autosomal dominant manner. Approximately 90% of individuals diagnosed with MEN1 have an affected parent; approximately 10% of individuals diagnosed with MEN1 have the disorder as the result of a *de novo MEN1* pathogenic variant that occurred in early embryogenesis. Each child (regardless of sex) of an individual with MEN1 has a 50% chance of inheriting the pathogenic variant. Once the *MEN1* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for MEN1 are possible.

Diagnosis

Suggestive Findings

Multiple endocrine neoplasia type 1 (MEN1) **should be suspected** in individuals with endocrine tumors, although non-endocrine tumors may appear before the manifestations of hormone-secreting endocrine tumors (see Clinical Description). Note: A varying combination of more than 20 endocrine and non-endocrine tumors have been reported in individuals with MEN1; no clinical criteria or definition can capture all affected individuals.

Parathyroid tumors manifest as hypercalcemia (primary hyperparathyroidism [PHPT]) as the result of the overproduction of parathyroid hormone. Imaging is not usually required for diagnosis of parathyroid disease, as the underlying cause of PHPT in MEN1 is usually multiglandular disease with enlargement of all the parathyroid glands rather than a single adenoma.

Anterior pituitary tumors

- Prolactinomas (prolactin-secreting anterior pituitary adenomas) manifest as oligomenorrhea/amenorrhea and galactorrhea in females, and sexual dysfunction and (more rarely) gynecomastia in males.
- Growth hormone-secreting anterior pituitary adenomas cause gigantism in children and signs and symptoms of acromegaly in adults.
- Growth hormone/prolactin (GH/PRL)-secreting anterior pituitary adenomas manifest as signs and symptoms of acromegaly, oligomenorrhea/amenorrhea, and galactorrhea in females, and sexual dysfunction and (more rarely) gynecomastia in males.
- Thyroid-stimulating hormone (TSH)-secreting anterior pituitary adenomas cause signs and symptoms of hyperthyroidism.
- Adrenocorticotrophic hormone (ACTH)-secreting anterior pituitary adenomas are mostly associated with Cushing disease.
- Nonfunctioning (nonsecreting) anterior pituitary adenomas manifest as enlarging tumors, compressing adjacent structures such as the optic chiasm with visual disturbances, and/or hypopituitarism.

Note: The imaging test of choice for all types of pituitary tumors is MRI.

Well-differentiated endocrine tumors of the gastroenteropancreatic (GEP) tract (including tumors of the stomach, duodenum, pancreas, and intestinal tract) manifest as the following clinical presentations (from most to least frequent):

- Zollinger-Ellison syndrome (ZES) (i.e., peptic ulcer with or without chronic diarrhea) resulting from a gastrin-secreting duodenal mucosal tumor (gastrinoma)
- Hypoglycemia resulting from an insulin-secreting pancreatic tumor (insulinoma)
- Hyperglycemia, anorexia, glossitis, anemia, diarrhea, venous thrombosis, and skin rash (necrolytic migratory erythema) resulting from a glucagon-secreting pancreatic tumor (glucagonoma)

- Watery diarrhea, hypokalemia, and achlorhydria (WDHA syndrome) resulting from a vasoactive intestinal peptide (VIP)-secreting tumor (VIPoma)

Note: (1) Nonfunctioning pancreatic endocrine tumors that are difficult to diagnose by biochemical and imaging tests are the most frequently seen tumors in MEN1 [Jensen 1999]. (2) Type II gastric enterochromaffin-like (ECL) cell carcinoids are included in the well-differentiated endocrine tumors of the GEP tract. They are common in MEN1 and are usually recognized incidentally during gastric endoscopy for ZES [Bordi et al 1998, Gibril et al 2000]. (3) Endoscopic ultrasound (EUS) examination is the most sensitive imaging procedure for the detection of small (≤10 mm) pancreatic endocrine tumors in asymptomatic individuals with MEN1 [Gauger et al 2003, Langer et al 2004, Kann et al 2006, Tonelli et al 2006]. Pancreatic gastrinomas are usually evaluated by CT, MRI, and/or EUS [Yates et al 2015].

Non-endocrine tumors associated with MEN1 include facial angiofibromas, collagenomas, lipomas, meningiomas, ependymomas, and leiomyomas.

Cutaneous manifestations may be helpful in the diagnosis of individuals with MEN1 even before manifestations of hormone-secreting tumors appear.

Establishing the Diagnosis

The clinical diagnosis of MEN1 can be **established** in a proband with:

- Two or more endocrine tumors including parathyroid, anterior pituitary, and well-differentiated neuroendocrine tumors of the GEP tract; OR
- One of three endocrine tumors (parathyroid, anterior pituitary, or well-differentiated neuroendocrine tumors of the GEP tract) and a first-degree relative with MEN1.

The molecular diagnosis can be established in a proband with a germline heterozygous *MEN1* pathogenic (or likely pathogenic) variant identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include likely pathogenic variants. (2) Identification of a heterozygous *MEN1* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from many other tumor predisposition disorders may be more likely to be diagnosed using genomic testing (see Option 2).

Option 1

Single-gene testing. Sequence analysis of *MEN1* is usually performed first, which allows detection of small intragenic deletions/insertions, and missense, nonsense, and splice site variants. Note: Sequence analysis may not detect single-exon, multiexon, or whole-gene deletions/duplications. Therefore, if no variant is detected by sequence analysis, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications (e.g., multiplex ligation-dependent probe amplification [MPLA]).

A multigene panel that includes *MEN1* and other genes of interest (see Differential Diagnosis) may also be used. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the phenotype is indistinguishable from many other tumor predisposition disorders, **comprehensive genomic testing,** which does not require the clinician to determine which gene is likely involved, is the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Multiple Endocrine Neoplasia Type 1

Gene [1]	Method	Proportion of Probands with a Germline Pathogenic Variant [2] Detectable by Method
MEN1	Sequence analysis [3]	Familial: 80%-90% [4] Simplex: 65% [4]
	Gene-targeted deletion/duplication analysis [5]	1%-4% [4]

familial = a proband meeting the diagnostic criteria of MEN1 plus a minimum of one first-degree relative with at least one of these tumors; simplex = a single occurrence of MEN1 in a family

1. See Table A. Genes and Databases for chromosome locus and protein.

2. See Molecular Genetics for information on variants detected in this gene.

3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.

4. Brandi et al [2021]

5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

Clinical Characteristics

Clinical Description

Multiple endocrine neoplasia type 1 (MEN1) is characterized by varying combinations of more than 20 endocrine and non-endocrine tumors. Endocrine tumors occurring in individuals with MEN1 are shown in Table 2.

Table 2. Endocrine Tumor Types in Multiple Endocrine Neoplasia Type 1

Tumor Type	Tumor Subtypes	Hormone Secreting	Prevalence in MEN1
Parathyroid	NA	Yes	PHPT in 100% by age 50 yrs

Table 2. continued from previous page.

Tumor Type	Tumor Subtypes	Hormone Secreting	Prevalence in MEN1	
Anterior pituitary	Prolactinoma	Yes	Anterior pituitary tumors in ~30%-40%	60%
	GH-secreting	Yes		25%
	GH/PRL-secreting	Yes		10% [1]
	TSH-secreting	Yes		Rare [2]
	ACTH-secreting	Yes		<5% [1]
	Nonfunctioning	No		<10% [1]
Well-differentiated endocrine of the GEP tract	Gastrinoma	Yes	40%	
	Insulinoma	Yes	10% [1]	
	Glucagonoma	Yes	<3% [1]	
	VIPoma	Yes	3%	
	Somatostatinomas	Yes	<1%	
	Nonfunctioning	No	55% [1]	
Carcinoid	Thymic	No	3%-8% [1]	
	Bronchial	No	4.7%-6.6% [1]	
	Type II gastric ECL carcinoids	No	10% [1]	
Adrenocortical	Cortisol-secreting	Rarely, hypersecreting	40% [1]	
	Aldosterone-secreting	Rarely, hypersecreting		
	Pheochromocytoma	Rarely	<1% [1]	

ACTH = adrenocorticotrophic hormone; ECL = enterochromaffin-like; GEP = gastroenteropancreatic; GH = growth hormone; NA = not applicable; PHPT = primary hyperparathyroidism; PRL = prolactin; TSH = thyroid-stimulating hormone; VIPoma = vasoactive intestinal peptide-secreting tumor

1. Thakker et al [2012], Giusti et al [2019]

2. Socin et al [2003]

Of note, MEN1-associated tumors are often clinically distinct from sporadically occurring tumors of the same tissue type (i.e., as single tumors in the absence of other findings of MEN1) (see Differential Diagnosis).

Primary Hyperparathyroidism (PHPT)

PHPT is often mild, with hypercalcemia often detected in asymptomatic individuals known to have or be at risk for MEN1. PHPT is the most common MEN1-associated endocrinopathy, and the first clinical feature in 90% of individuals. Onset is typically between ages 20 and 25 years. All individuals with MEN1 can be expected to have hypercalcemia by age 50 years [Thakker 2010]. Although most individuals with PHPT are asymptomatic for a long period of time, it may manifest as rickets and osteomalacia in the pediatric population [Wang et al 2017].

Common clinical manifestations of hypercalcemia:

- **Central nervous system.** Altered mental status including lethargy, depression, decreased alertness, confusion (rarely, obtundation and coma)
- **Gastrointestinal.** Anorexia, constipation, nausea, and vomiting
- **Renal.** Diuresis, impaired concentrating ability, dehydration, hypercalciuria, and increased risk for kidney stones
- **Skeletal.** Increased bone resorption and increased fracture risk
- **Cardiovascular.** Cause of and/or exacerbation of hypertension, shortened QT interval

Hypercalcemia may increase the secretion of gastrin from a gastrinoma, precipitating and/or exacerbating symptoms of Zollinger-Ellison syndrome [Norton et al 2008].

Pathology. Multiglandular parathyroid disease with enlargement of all the parathyroid glands, rather than a single adenoma, is typical.

Cancer risk. Parathyroid carcinoma is rare in individuals with MEN1. To date, only 21 cases have been reported in the literature [Song et al 2020].

Anterior Pituitary Adenomas

Pituitary adenomas are the first clinical manifestation of MEN1 in 25% of simplex cases (i.e., a single occurrence of MEN1 in a family) and in 10% of familial cases. The incidence of pituitary adenomas in MEN1 varies from 15% to 55% in different series [Thakker et al 2012]. Pituitary adenomas occurred with significantly greater frequency in women than in men (50% vs 31%) Vergès et al [2002].

Pituitary adenomas are usually solitary, although adenomas that produce more than one hormone have been reported (e.g., growth hormone [GH] and prolactin [PRL] with follicle-stimulating hormone [FSH], luteinizing hormone, or adrenocorticotropic hormone [ACTH]) [Trouillas et al 2008]. Rarely, more than one pituitary adenoma occurs in an individual – for example, Al Brahim et al [2007] reported an individual with one gonadotrope macroadenoma and one corticotrope microadenoma.

Symptoms depend on the pituitary hormone produced:

- **PRL-secreting adenomas.** Amenorrhea and galactorrhea in females; reduction of libido or impotence in males
- **ACTH-secreting adenomas.** Hypercortisolism, as described in four children ages 11 to 13 years with Cushing disease as the first manifestation of MEN1 [Matsuzaki et al 2004, Rix et al 2004]
- **GH-secreting adenomas.** Gigantism in children and acromegaly in adults [Stratakis et al 2000]
- **FSH-secreting adenomas.** Reduced libido and erectile dysfunction described in a male [Sztal-Mazer et al 2008]

Clinically significant symptoms such as nerve compression, headache, and hypopituitarism may also result from pituitary mass effects [Thakker et al 2012].

Pathology. Between 65% and 85% of pituitary adenomas in MEN1 are macroadenomas [Brandi et al 2001, Vergès et al 2002]. MEN1-associated tumors are significantly larger and more often invasive than sporadic pituitary tumors. Multifocal pituitary adenomas are rare in MEN1 (1.5%-4%) [Trouillas et al 2008, Le Bras et al 2021].

Cancer risk. Although Vergès et al [2002] reported that 32% of pituitary macroadenomas were invasive, malignant degeneration of MEN1-associated pituitary tumors is infrequent [Thakker et al 2012]. There are only rare reports of MEN1-associated metastatic or malignant prolactinoma, gonadotropinoma, thyrotropin secreting adenoma, and/or nonfunctioning pituitary adenoma [Benito et al 2005, Scheithauer et al 2009, Morokuma et al 2012, Philippon et al 2012, Incandela et al 2020].

Well-Differentiated Endocrine Tumors of the Gastroenteropancreatic (GEP) Tract

Gastrinoma. Approximately 40% of individuals with MEN1 have gastrinomas, which manifest as Zollinger-Ellison syndrome (ZES). Fewer than than 10% of MEN1-related gastrinomas occur in the pancreas, more than 90% occur in the duodenum. ZES usually occurs before age 40 years [Gibril et al 2004]; 25% of individuals with MEN1-related ZES have no family history of MEN1 [Gibril et al 2004]. Findings can include upper-abdominal pain, diarrhea, esophageal reflux, and ulcers; if not properly diagnosed or treated, ulcer perforation can occur, even without prior symptoms. Weight loss is less commonly reported. ZES-associated hypergastrinemia may

result in multiple duodenal ulcers; epigastric pain generally occurs two or more hours after meals or at night and may be relieved by eating. However, the pain may also be in the right upper quadrant, chest, or back. Vomiting may be related to partial or complete gastric outlet obstruction; hematemesis or melena may result from GI bleeding.

- **Pathology.** Typically, multiple small (diameter <1 cm) gastrinomas are observed in the duodenal submucosa; more than 80% are found within the first and second portions of the duodenum [Hoffmann et al 2005]. MEN1 duodenal gastrinomas are associated with diffuse hyperplastic changes of gastrin cells and multifocal microgastrinomas (<1 mm) [Anlauf et al 2005]. About 50% of duodenal microgastrinomas have loss of heterozygosity at the *MEN1* locus and appear to be precursor lesions. Although pancreatic gastrinomas are rare in MEN1; endocrine pancreatic microadenomatosis is characteristic of MEN1 [Anlauf et al 2006]. Microgastrinomas are not reported in sporadic gastrinomas [Anlauf et al 2007].
- **Cancer risk.** Seventy percent to 80% of MEN1-related duodenal gastrinomas are metastatic to regional lymph nodes at the time of diagnosis; this does not appear to negatively affect overall survival [Albers et al 2019]. However, 25% of individuals with MEN1-related duodenal gastrinomas develop liver metastases and approximately 15% show aggressive tumor growth [Thakker et al 2012].

  Pancreatic gastrinomas are more aggressive than duodenal gastrinomas, as suggested by their larger size and greater risk for hepatic metastasis. Among individuals with multiple pancreatic endocrine tumors, eight asymptomatic individuals operated on at a mean age of 33 years did not have metastases [Tonelli et al 2005], whereas four of 12 symptomatic individuals operated on at a mean age of 51 years had malignant tumors, from which two of the individuals subsequently died.

Insulinoma. The age of onset of insulinoma associated with MEN1 is generally one decade earlier than sporadic insulinoma [Marx et al 1999]. Tumors responsible for hyperinsulinism are usually 1-4 cm in diameter.

- **Pathology.** Generally, a single tumor occurs in the setting of multiple islet macroadenomas [Brandi et al 2001].
- **Cancer risk.** Insulinomas are almost always benign. One individual with cervical metastasis of a glucagonoma and hypoglycemia due to insulinoma recovered well from pancreatoduodenectomy and subsequently remained asymptomatic [Butte et al 2008].

Glucagonoma. Glucagonomas can be associated with other tumors in MEN1, but they are very rare. MEN1-associated glucagonomas are estimated to account for only about 3% of all diagnosed glucagonoma [Castro et al 2011]. Tumor size is often >3 cm.

- **Cancer risk.** About 80% of MEN1-associated glucagonomas are malignant and frequently spread to the liver [Castro et al 2011].

VIPoma. It has been estimated that 3% of individuals with MEN1 develop VIPomas at some stage of their disease. MEN1-associated VIPomas represent about 5% of all diagnosed VIPomas [Yeung & Tung 2014]. Tumor size is often greater than 3 cm.

- **Cancer risk.** VIPomas are malignant and have usually metastasized at the time of diagnosis. Metastases occur most frequently in the liver.

Nonfunctioning GEP tract tumors are frequent in MEN1. A prospective endoscopic ultrasonographic evaluation of the frequency of nonfunctioning pancreatic tumors in MEN1 suggested that their frequency of 54.9% is higher than previously thought [Thomas-Marques et al 2006]. Moreover, the penetrance of 34% for these tumors at age 50 years in persons with MEN1 from the French Endocrine Tumor Study Group indicates that they are the most frequent pancreaticoduodenal tumor in MEN1. Average life expectancy of individuals

with MEN1 with nonfunctioning tumors was shorter than life expectancy of individuals who did not have pancreaticoduodenal tumors [Triponez et al 2006].

Carcinoid Tumors

Thymic, bronchial, and type II gastric enterochromaffin-like (ECL) carcinoids occur in 3%-10% of individuals with MEN1. CT is useful in localizing occult bronchial tumors, while CT and MRI are equally sensitive in detecting thymic carcinoid tumors at initial evaluation [Thakker et al 2012]. Because both plain chest x-ray and somatostatin receptor scintigraphy scan have lower sensitivity than CT and MRI in detecting either primary or recurrent thymic carcinoid, neither is the first imaging study of choice [Gibril et al 2003, Scarsbrook et al 2007, Goudet et al 2009].

Carcinoid tumors are the only MEN1-associated neoplasms currently known to exhibit an unequal male-to-female ratio: thymic carcinoids are more prevalent in males than in females with a male:female ratio of 20:1 and bronchial carcinoids occur predominantly in women (male:female ratio of 1:4) [Thakker et al 2012]. Interestingly, among Japanese individuals with MEN1, thymic carcinoids show a less marked sex difference (male:female ratio of 2:1) [Sakurai et al 2012]. Additionally, individuals with MEN1 who smoke have a higher risk of developing carcinoid tumors than individuals with MEN1 who do not smoke.

The clinical course of carcinoid tumors is often indolent but can also be aggressive and resistant to therapy [Schnirer et al 2003]. Thymic, bronchial, and gastric carcinoids rarely secrete ACTH, calcitonin, or GH-releasing hormone; similarly, they rarely secrete serotonin or histamine and rarely cause the carcinoid syndrome. Thymic carcinoids have been reported to produce GH-related acromegaly [Boix et al 2002] and ACTH-related Cushing disease [Takagi et al 2006, Yano et al 2006].

The retrospective study of Gibril et al [2003] supports the conclusion that thymic carcinoid tumors are generally a late manifestation of MEN1 as no affected individuals had thymic carcinoid as the initial MEN1 manifestation. Thymic carcinoid in MEN1 commonly presents at an advanced stage as a large invasive mass. Less commonly, it is recognized during chest imaging or during thymectomy as part of parathyroidectomy.

The mean age at diagnosis of gastric carcinoids is 50 years [Berna et al 2008].

Pathology. Carcinoids tend to be multifocal and may occur synchronously or over time.

Cancer risk. MEN1-related thymic carcinoids are aggressive and highly lethal, particularly in males who are smokers Goudet et al 2009]. Spinal metastasis of carcinoid tumor [Tanabe et al 2008] and synchronous thymoma and thymic carcinoid have been reported [Miller et al 2008].

Most bronchial carcinoids, in contrast to thymic carcinoids, behave indolently, albeit with the potential for local mass effect, metastasis, and recurrence after resection [Sachithanandan et al 2005].

Therefore, the presence of thymic tumors is reported to be associated with a significantly increased risk of death in individuals with MEN1 (hazard or odds ratio = 4.29) – this is in contrast to the presence of bronchial carcinoids, which have not been associated with increased risk of death [Goudet et al 2010]. The median survival following the diagnosis of a thymic tumor is reported to be approximately 9.5 years, with 70% of affected individuals dying as a direct result of the tumor [Goudet et al 2009].

Adrenocortical Tumors

Adrenocortical tumors, involving one or both adrenal glands, have been described in a variable percentage (20%-73%) of individuals with MEN1, depending on the radiologic screening methods employed. Adrenocortical tumors are most often detected during CT screening.

Most of these tumors are nonfunctioning, and these include cortical adenomas, hyperplasia, multiple adenomas, nodular hyperplasia, cysts, or carcinomas; fewer than 10% of these tumors demonstrate hormonal hypersecretion, and, among these, adrenocortical tumors causing Cushing disease are the most common [Thakker et al 2012].

Rarely, adrenocortical tumors are associated with primary hypercortisolism or hyperaldosteronism [Honda et al 2004]. In a study of 67 individuals, Langer et al [2002] identified ten with nonfunctional benign tumors, eight with bilateral adrenal gland tumors, three with Cushing syndrome, and one with a pheochromocytoma. Four developed adrenocortical carcinomas, three of which were functional.

Pathology. Silent adrenal gland enlargement is a polyclonal or hyperplastic process that rarely results in neoplasm. In the study by Langer et al [2002], the median tumor diameter at diagnosis was 3.0 cm (range 1.2-15.0 cm), with most tumors being ≤3 cm.

Cancer risk. In a study of 715 individuals with MEN1, Gatta-Cherifi et al [2012] estimated the overall incidence of adrenocortical carcinoma at 1%. In individuals with MEN1 who have adrenal tumors larger than 1 cm, the risk of malignancy is about 13%. This risk may be higher in affected individuals whose tumor is >4 cm in diameter [Wang et al 2019].

Non-Endocrine Tumors Associated with MEN1

Skin findings may include the following [Darling et al 1997, Thakker et al 2012]:

- Facial angiofibromas, benign tumors comprising blood vessels and connective tissue, are present in about 85% of affected individuals [Thakker et al 2012]. They consist of acneiform papules that do not regress and may extend across the vermilion border of the lips.
- Collagenomas, present in about 70% of affected individuals, frequently present as multiple skin-colored, sometimes hypopigmented cutaneous nodules, symmetrically arranged on the trunk, neck, and upper limbs [Thakker et al 2012]. They are typically asymptomatic, rounded, and firm-elastic measuring a few millimeters to several centimeters in size. The rapid growth of protuberant multiple collagenomas after excision of multiple pancreatic masses including a pancreatic VIPoma has also been reported in an individual with MEN1 [Xia & Darling 2007].
- Lipomas are benign fatty tissue tumors found anywhere that fat is located and are present in about 30% of affected individuals [Thakker et al 2012]. They can be subcutaneous or, rarely, visceral.
- Other skin findings include café au lait macules in 38% of affected individuals, confetti-like hypopigmented macules in 6%, and multiple gingival papules in 6% [Darling et al 1997].

Central nervous system tumors are rare in individuals with MEN1.

- Meningioma was reported in 8% of 74 individuals [Asgharian et al 2004]; the meningiomas were mainly asymptomatic and 60% showed no growth.
- Ependymoma is present in about 1% of affected individuals.

Leiomyomas are benign neoplasms derived from smooth (nonstriated) muscle [McKeeby et al 2001, Ikota et al 2004]. Sporadic uterine leiomyomas affect 20%-30% of reproductive-age women. No data regarding the frequency of leiomyomas in women with MEN1 versus sporadic incidence are available – nor is any data regarding multiple leiomyomas of the esophagus and lungs in individuals with MEN1.

Thyroid tumors. Adenomas, colloid goiters, and carcinomas have been reported to occur in more than 25% of individuals with MEN1. The presence of thyroid abnormalities may be incidental and not significant, considering the high prevalence of thyroid disorders in the general population [Thakker et al 2012].

Breast cancer. A significantly higher incidence of breast cancer was found in four independent MEN1 cohorts from the Netherlands, France, Tasmania, and the United States. In the Dutch cohort, the relative risk for breast cancer in females with MEN1 was 2.83; the median age of breast cancer diagnosis was 45 years, approximately 15 years younger than in the general Dutch population [Dreijerink et al 2014].

Morbidity and Mortality of MEN1

Improved knowledge of MEN1-associated clinical manifestations, early diagnosis of MEN1-associated tumors, presymptomatic screening of at-risk children, and treatment of metabolic complications of MEN1 have virtually eliminated ZES and/or complicated PHPT as causes of death and decreased morbidity and mortality associated with MEN1-related tumors [van Leeuwaarde et al 2016]. Nonetheless, individuals with MEN1 are at a significantly increased risk for premature death [Geerdink et al 2003]. MEN1-related malignancies account for approximately 30% of deaths in individuals with MEN1.

Quality of life. In a qualitative study of 29 Swedish individuals with MEN1, the participants described physical, psychological, and social limitations in their daily activities and the effect of these limitations on their quality of life. A majority had adjusted to their situation, describing themselves as being healthy despite physical symptoms and treatment. The participants received good care in a clinical follow-up program [Strømsvik et al 2007, Marini et al 2017]. A recent study analyzed the health-related quality of life in 76 Italian individuals with MEN1 using five common targeted questionnaires. Half of affected individuals were moderately optimistic despite their clinical condition because they were managed at a dedicated referral center and received personalized care [Giusti et al 2021].

Genotype-Phenotype Correlations

No direct genotype-phenotype correlations have been identified in MEN1 [Brandi et al 2021].

One study reported a twofold higher risk of death in individuals with a heterozygous *MEN1* pathogenic variant that affects the JunD interacting domain of menin [Thevenon et al 2013] (see Molecular Genetics). Another study by Thevenon et al [2015] showed a minor positive intrafamilial heritability only for pituitary adenomas, adrenal tumors, and thymic tumors that progressively decreases with the degree of the genetic relationship. However, both studies confirmed the absence of any direct genotype-phenotype correlation.

Although a trend (which did not reach statistical significance) suggested that the prevalence of truncating variants in *MEN1*-related thymic carcinoids is higher than in other *MEN1*-related tumors [Lim et al 2006], a review by Lips et al [2012] found no association between single pathogenic variants and specific phenotype.

The only specific clustering of tumors within the MEN1 phenotype was reported in those with the Burin variant c.1378C>T (p.Arg460Ter), identified in four kindreds from Newfoundland and in one from Mauritius, in which the prevalence of prolactinoma is higher than average and the prevalence of gastrinoma is lower than average [Hao et al 2004].

Penetrance

The age-related penetrance for all clinical features surpasses 50% by age 20 years and 95% by age 40 years [Brandi et al 2021].

Prevalence

MEN1 has a prevalence of between 1:10,000 and 1:100,000 individuals. Geographic clustering as a consequence of founder effect has been reported [Carroll 2013].

Genetically Related (Allelic) Disorders

Other phenotypes associated with germline pathogenic variants in *MEN1* are summarized in Table 3.

Table 3. *MEN1* Allelic Disorders

Disorder	MOI	Clinical Characteristics / Comments
MEN1-related familial isolated hyperparathyroidism (FIHP)	AD	FIHP is characterized by parathyroid adenoma or hyperplasia w/o other assoc endocrinopathies. *MEN1* germline pathogenic variants have been reported in 20%-57% of families w/FIHP. [1] In families w/*MEN1*-related FIHP, 38% of pathogenic variants are missense – vs MEN1, in which missense variants account for 20% of cases. [2] *MEN1* nonsense variants are found in only 5% of families w/FIHP – vs 23% in families w/ MEN1. Of note, in 1 family w/FIHP w/an intronic *MEN1* pathogenic variant & no clinical evidence of hyperparathyroidism-jaw tumor syndrome, the mother of the proband (genetic status unknown, but likely w/the same pathogenic variant as the proband) died of parathyroid carcinoma. [3] Thus, in contrast to MEN1 (in which risk for parathyroid carcinoma does not appear to be ↑), FIHP may be assoc w/↑ risk for parathyroid carcinoma (see also Differential Diagnosis).
Familial pituitary tumor	AD	*MEN1* pathogenic variants have been identified in <1% of index cases w/familial pituitary tumor. [4]

AD = autosomal dominant; MEN1 = multiple endocrine neoplasia type 1; MOI = mode of inheritance

1. Miedlich et al [2001], Villablanca et al [2002], Pannett et al [2003]

3. Lemos & Thakker [2008]

3. Carrasco et al [2004]

4. Vierimaa et al [2006]

Sporadic tumors (including parathyroid adenoma, gastrinoma, insulinoma, and bronchial carcinoid) occurring as single tumors in the absence of any other findings of MEN1 frequently contain a somatic pathogenic variant in *MEN1* that is **not** present in the germline. In these circumstances, predisposition to these tumors is not heritable [Carling 2005]. For more details see Molecular Genetics, Cancer and Benign Tumors.

Differential Diagnosis

Table 4. Hereditary Cancer Syndromes in the Differential Diagnosis of MEN1

Gene	Disorder	MOI	Overlapping Feature(s)	Distinguishing Features
AIP	*AIP*-related pituitary adenoma predisposition (PAP) & multiple types of pituitary adenoma (PITA1) (See *AIP* Familial Isolated Pituitary Adenomas.)	AD	Pituitary adenomas	• Earlier-onset pituitary tumors in *AIP*-assoc PAP than in MEN1 • *MEN1*-assoc single pituitary tumors are typically prolactinomas or macroadenomas. • *AIP*-assoc tumors are predominantly GH-secreting adenomas.
GPR101	Pituitary adenoma 2, GH-secreting (PITA2) (OMIM 300943)	XL	GH-secreting pituitary adenoma	Not assoc w/other endocrinopathies typical of MEN1
CDH23	Pituitary adenoma 5, multiple types (PITA5) (OMIM 617540)	AD	GH-secreting & nonfunctional pituitary adenomas in familial pituitary adenoma types; GH-secreting, nonfunctional, PRL-secreting, ACTH-secreting, TSH-secreting, & plurihormonal (GH & TSH) tumors in sporadic pituitary adenoma types	Not assoc w/other endocrinopathies typical of MEN1

Table 4. continued from previous page.

Gene	Disorder	MOI	Overlapping Feature(s)	Distinguishing Features
CASR [1] *CDC73* [2] *GCM2* *MEN1*	Familial isolated primary hyperparathyroidism (FIHP) [3] (OMIM 145980, 145000, 617343)	AD	Parathyroid adenoma or hyperplasia	Not assoc w/other endocrinopathies typical of MEN1. See also Genetically Related Disorders.
CDKN1B	Multiple endocrine neoplasia type 4 (MEN4)	AD	All features	No specific distinguishing clinical features
RET	Multiple endocrine neoplasia type 2A (MEN2A)	AD	PHPT (in ~20%-30% of persons w/MEN2A); hypercalciuria & renal calculi (in some)	• MEN2A is assoc w/medullary thyroid carcinoma & pheochromocytoma. • MEN2A-assoc PHPT is generally milder than MEN1-assoc PHPT. • Most persons w/MEN2A & biochemical PHPT do not have clinical symptoms of PHPT.

ACTH = adrenocorticotropic hormone; AD = autosomal dominant; GH = growth hormone; MEN1 = multiple endocrine neoplasia type 1; MOI = mode of inheritance; PHPT = primary hyperparathyroidism; PRL = prolactin; TSH = thyroid stimulating hormone; XL = X-linked

1. Between 14% and 18% of families with FIHP have identifiable *CASR* pathogenic variants [Simonds et al 2002, Warner et al 2004]. *CASR* pathogenic variants have also been identified in individuals with familial hypocalciuric hypercalcemia (OMIM 601198) and neonatal severe primary hyperparathyroidism (OMIM 239200).

2. Pathogenic variants in *CDC73* are associated with hyperparathyroidism-jaw tumor syndrome (see *CDC73*-Related Disorders). Of note, Warner et al [2004] did not identify any *CDC73* pathogenic variants in 22 individuals with familial isolated primary hyperparathyroidism (FIHP).

3. FIHP is characterized by parathyroid adenoma or hyperplasia without other associated endocrinopathies in two or more individuals in one family.

Sporadic primary hyperparathyroidism (PHPT), generally caused by a single parathyroid adenoma, refers to PHPT that is not inherited. The peak incidence of sporadic PHPT is in the sixth decade, whereas the onset of multiple endocrine neoplasia type 1 (MEN1) is three decades earlier, at ages 20-25 years [Eller-Vainicher et al 2009]. Sporadic PHPT is identified because of symptoms of hypercalcemia in contrast to MEN1, in which affected/at-risk individuals are often asymptomatic when evaluated for MEN1-associated manifestations.

Table 5. Differential Diagnosis of MEN1-Associated Clinical Features

Clinical Feature	Comments
Pituitary tumors	• If single pituitary adenoma: (1) not likely to be assoc w/MEN1 if no other findings of MEN1 [1]; (2) responds better to medical therapy than MEN1-assoc pituitary tumors [1] • If multiple pituitary adenomas: see Table 3, **Familial pituitary tumor**
Zollinger-Ellison syndrome (ZES)	• Sporadically occurring gastrinomas (1) more commonly pancreatic in origin [1]; (2) occur 1 decade later than gastrinomas in MEN1 [1] • 2 persons w/ZES & pathogenic variants in 2 cyclin-dependent kinase inhibitor genes (*RPRD1A* & *CDKN1B*) reported [1] • Gastrinomas may also be present in MEN4, TSC, & NF1.
Nonfunctioning neuroendocrine tumors	• Affect 20%-55% of persons w/MEN1 • May also be present in VHL (10%-17%) & NF1
Insulinoma	• Peak age at onset ~1 decade later in those w/sporadic insulinomas [1] • Insulinomas may also be present in NF1.

Table 5. continued from previous page.

Clinical Feature	Comments
Carcinoid tumors	• When **not** assoc w/MEN1: usually occur in derivatives of the midgut & hindgut; are argentaffin positive; secrete serotonin (5-hydroxytryptamine); & have less severe course than MEN1-assoc thymic carcinoid tumors [1] • Assoc of gastric carcinoids & hyperparathyroidism appears to constitute distinct syndrome in genetically predisposed persons; should not be regarded as "atypical" or "incomplete" expression of MEN1. [1]
Facial angiofibromas	• Also seen in TSC • Age of onset in TSC: 3-4 yrs (vs in MEN1: <40 years)
Leiomyomas	May also be seen in w/Alport syndrome

MEN1 = multiple endocrine neoplasia type 1; MEN4 = multiple endocrine neoplasia type 4; NF1 = neurofibromatosis 1; TSC = tuberous sclerosis complex; VHL = von Hippel-Lindau syndrome
1. Tonelli et al [2018]

Management

Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1) have been developed [Thakker et al 2012] (full text).

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with MEN1, the evaluations summarized in Table 6 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 6. Recommended Evaluations Following Initial Diagnosis in Individuals with MEN1

System/Concern	Evaluation	Comment
Multiglandular parathyroid disease	• Fasting total serum calcium concentration (corrected for albumin) &/or ionized-serum calcium concentration • Consider fasting serum concentration of intact (full-length) PTH.	In those age ≥5 yrs
Anterior pituitary tumors	• Serum concentration of prolactin, IGF-1, fasting glucose, & insulin • Head MRI	In those age ≥5 yrs
Well-differentiated endocrine tumors of the GEP tract	Chromogranin-A, pancreatic polypeptide, glucagon, vasoactive intestinal peptide for other pancreatic NET	In those age ≥8 yrs
	• Fasting serum gastrin concentration • Consider abdominal CT, MRI, or EUS exam.	In those age ≥20 yrs
Carcinoid tumors	Consider: [1] • Chest CT; • Chest MRI; • SRS octreotide scan.	In those age ≥15 yrs
Non-endocrine tumors	Skin exam	

Table 6. continued from previous page.

System/Concern	Evaluation	Comment
Genetic counseling	By genetics professionals [2]	To inform affected persons & their families re nature, MOI, & implications of MEN1 to facilitate early diagnostic, medical, therapeutic & personal decision making

EUS = endoscopic ultrasound; GEP = gastroenteropancreatic; MOI = mode of inheritance; PTH = parathyroid hormone; SRS = somatostatin receptor scintigraphy

1. Chest CT and MRI have better sesitivity than either chest x-ray or somatostatin receptor scintigraphy (SRS) scan in detecting either primary or recurrent thymic carcinoid [Gibril et al 2003, Scarsbrook et al 2007, Goudet et al 2009].

2. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Primary Hyperparathyroidism (PHPT)

Parathyroidectomy is the treatment of choice for individuals with MEN1, but it is controversial whether to perform subtotal (≤3.5 glands) or total parathyroidectomy, and whether surgery should be performed at an early or late stage of the disease. Timing of surgery and type of parathyroid intervention should be tailored to the individual's specific clinical characteristics.

- Subtotal parathyroidectomy (i.e., removal of ≤3.5 glands) has resulted in persistent or recurrent hypercalcemia within ten to 12 years after surgery in 40%-60% of affected individuals with MEN1, and in hypocalcemia requiring long-term therapy with vitamin D or its active metabolite calcitriol in 10%-30% [Thakker et al 2012].
- Total parathyroidectomy with autotransplantation in the forearm may use both fresh and cryopreserved parathyroid tissue. The procedure is dependent on the vitality of cryopreserved cells, which declines with the time interval from cryopreservation to autotransplantation.
    - Intraoperative monitoring of parathyroid hormone (PTH) by rapid assay during surgery to determine successful removal of hyperfunctioning parathyroid tissue and to help with the decision to implant parathyroid tissue in the forearm is recommended.
    - Recurrent hypercalcemia is present in more than 50% of affected individuals with autotransplanted parathyroid tissue, and surgical removal of the transplanted grafts is not always successful.

Subtotal parathyroidectomy is suggested as the initial treatment of PHPT in MEN1; total parathyroidectomy with autotransplantation may also be reserved for those with extensive disease either at first or at repeat surgery [Thakker et al 2012].

Parathyroidectomy may be reserved for individuals with hypercalcemia, in association with hypercalciuria, to prevent and/or reduce clinical consequences of high calcium levels.

Those with asymptomatic hypercalcemia usually can delay parathyroid surgery in favor of regular assessment for symptom onset and complications.

Parathyroidectomy is mandatory in individuals with MEN1 who have Zollinger–Ellison syndrome (ZES) to correct PHPT and hypercalcemia and, subsequently, reduce gastric acid output and the risk of peptic ulcers.

Bone antiresorptive agents administered prior to surgery help to reduce hypercalcemia and limit PTH-dependent bone resorption, thus reducing future risk of osteoporosis.

Postoperative hypoparathyroidism. Measurement of serum concentration of PTH on the first day following subtotal or total parathyroidectomy may be a good predictor of residual parathyroid function [Debruyne et al

1999, Mozzon et al 2004]. Repeated measurements of serum calcium concentration are also useful and less expensive than measurement of the serum concentration of PTH [Debruyne et al 1999].

After autotransplantation of the parathyroid glands, the serum concentration of PTH should be assessed no earlier than two months postoperatively and once a year thereafter; serum concentration of PTH should be measured simultaneously in separate blood samples, one from the arm without a parathyroid autotransplant and one from the arm with the parathyroid autotransplant. This allows assessment of the function of the transplanted parathyroid tissue and monitoring for possible recurrence of hyperparathyroidism.

Individuals with PHPT who are not considered candidates for parathyroidectomy, who failed a previous intervention, or who present with postsurgical recurrence and decline to undergo any further surgical interventions can also be treated by calcimimetics (e.g., cinacalcet), a class of calcium-sensing receptor agonists that are able to restore normal calcium homeostasis and control parathyroid cell growth. Cinacalcet is a well-tolerated, safe, and effective treatment for individuals with MEN1 [Moyes et al 2010, Giusti et al 2016].

Anterior Pituitary Adenomas

Prolactin-secreting adenomas (prolactinomas)

- Dopamine agonists such as cabergoline, bromocriptine, pergolide, and quinagolide are the preferred treatment.
- Cabergoline may be considered the current treatment of choice because of its limited side effects and greater potency [Tichomirowa et al 2009, Thakker et al 2012].
- Transsphenoidal surgery and radiotherapy are reserved for drug-resistant tumors and for macroadenomas compressing adjacent structures and generating neuroophthalmologic complications that cannot be managed through pharmacologic therapy.

Growth hormone (GH)-secreting adenomas

- Transsphenoidal surgery is the surgical treatment of choice for GH-secreting adenomas causing acromegaly and is effective in 50%-70% of individuals.
- Somatostatin analogs are the medical therapy of choice for the treatment of GH-secreting adenomas. Octreotide and lanreotide normalize serum concentration of human GH and IGF-1 in more than 50% of treated individuals [Beckers et al 2003].
- Dopamine agonists are only rarely effective in treatment of GH-secreting adenomas causing acromegaly, although they can be effective in mixed GH-PRL-secreting adenomas and 10%-20% of tumors resistant to somatostatin analogs [Varlamov et al 2019].

Adrenocorticotropic hormone (ACTH)-secreting adenomas

- In most ACTH-secreting pituitary adenomas associated with Cushing disease, the treatment is excision of the adenoma. In the series of Beckers et al [2003], 92% of individuals with an identified microadenoma and 67% with a macroadenoma were considered cured immediately after surgery.
- For those ACTH-secreting pituitary adenomas associated with Cushing disease that are not cured surgically, radiotherapy may be necessary to reduce the production of ACTH.

Nonfunctioning pituitary adenomas

- In nonfunctioning pituitary adenomas, surgery using a transsphenoidal approach is the treatment of choice. However, in rare instances of very large adenomas with considerable extracellular extension, the transfrontal approach is the only possibility [Beckers 2002].
- In 5%-15% of individuals, medical treatment with potent dopaminergic agonists or with somatostatin analogs may shrink the adenoma before surgery [Colao et al 1998].

- Published data are not sufficient to compare the treatment of sporadic versus MEN1-associated pituitary adenomas. Although opinion on this issue differs, Beckers et al [2003] suggested that aggressive therapy is more frequently needed in MEN1-associated pituitary adenomas than in sporadic tumors.

Well-Differentiated Endocrine Tumors of the Gastroenteropancreatic (GEP) Tract

Gastrinoma

- Medications that can control some of the GEP hormone excess-dependent features of MEN1 and thus prevent severe and sometimes life-threatening morbidity in MEN1 include proton pump inhibitors or H_2-receptor blockers to reduce gastric acid output [Jensen 1999].
- Surgical treatment of gastrinoma in MEN1 is controversial because these tumors are usually microscopic and scattered throughout the neuroendocrine tissue, making successful surgical outcome rare. Surgical ablation of gastrinoma is suggested only in the presence of concomitant nonfunctioning GEP tract tumors that either double their size in a six-month interval, or approach or exceed 2 cm in diameter [Thakker et al 2012, Falconi et al 2016]. There are no controlled trials comparing the efficacy of gastrinoma surgery with respect to medical treatment. The choice of therapy should be individualized according to symptoms, tumor type, and disease burden.
- Because MEN1-related gastrinomas occur most commonly in the first and second portions of the duodenum, and less commonly the third and fourth portions of the duodenum and the first jejunal loop, it is important that all these sites be examined during preoperative imaging, intraoperative exploration, and pathologic examination of surgical specimens [Tonelli et al 2005].
- Primary lymph node gastrinomas have been reported in MEN1. Long-term symptom-free follow up after the excision of a lymph node gastrinoma is the only reliable criterion for the diagnosis of a primary lymph node tumor. Thus, the findings of Zhou et al [2006] supported the possibility that any gastrinoma in persons with MEN1 should be surgically resected for cure if possible. Anlauf et al [2008] reported the presence of a primary lymph node gastrinoma or occult duodenal microgastrinoma with lymph node metastases in a person with MEN1, confirming the need for a systematic search for the primary tumor.

Pancreatic tumors. Pancreatic surgery for asymptomatic individuals with MEN1 is controversial.

- Surgery is usually indicated for insulinoma and most of the other pancreatic tumors observed in MEN1. According to Tonelli et al [2005], the best surgical approach for a MEN1-associated insulinoma is intraoperative localization of nodules >~0.5 cm in diameter by palpation or intraoperative ultrasound followed either by enucleation (removal) of these nodules or by pancreatic resection if multiple large deep tumors are present.
- The optimal therapy of gastrinoma is controversial.
  - In non-metastasizing gastrinoma within the pancreas, surgery may be curative and should be performed by an experienced endocrine surgeon. Individuals with MEN1 will have multiple small submucosal duodenal gastrinomas and in experienced surgical centers local excision of these tumors with lymph node dissection, duodenectomy, or less commonly duodenopancreatectomy may also be considered together with the affected individual's preferences, as such approaches may improve the cure rate. However, given the common multiple microadenomas typical of these tumors in individuals with MEN1, surgery is often not effective.
  - Whipple pancreaticoduodenectomy provides the greatest likelihood of cure for gastrinoma in individuals with MEN1 but can be associated with an increased operative mortality and long-term morbidity unless performed by an experienced surgeon.
- Unresectable tumors or advanced metastatic cancer can be treated with somatostatin analogs (SSAs), cytotoxic chemotherapy, inhibitors of tyrosine kinase receptors (sunitinib), or inhibitors of mammalian target of rapamycin (mTOR; everolimus). All these therapies have demonstrated an increase in the median progression-free survival in individuals with sporadic pancreatic neuroendocrine tumors; however, no

specific trials have been performed in individuals with MEN1 who have GEP tract tumors [Marini et al 2017].
- Treatment for nonfunctioning pancreatic neuroendocrine tumors is controversial; some centers consider surgical resection for lesions >1 cm in size, while other centers recommend surgery only for tumors >2 cm.
- Occult metastatic disease (i.e., tumors not detected by imaging investigations) may be present in a substantial proportion of affected individuals at the time of initial presentation.

Carcinoid Tumors

Long-acting SSAs can control the secretory hyperfunction associated with carcinoid syndrome [Tomassetti et al 2000]; however, the risk for malignant progression of the tumor remains unchanged [Schnirer et al 2003]. Therefore, the treatment of choice for carcinoid is surgical removal, if resectable.

Thymic carcinoid recurred in all individuals with MEN1 who were followed for more than one year after resection of the tumor [Gibril et al 2003].

For unresectable tumors and those individuals with metastatic disease, treatment with radiotherapy or chemotherapeutic agents (e.g., cisplatin, etoposide) may be used [Oberg et al 2008].

Adrenocortical Tumors

Consensus guidelines for the management of MEN1-associated adrenocortical tumors do not exist, since the majority of nonfunctioning tumors of the adrenal glands are benign. The risk for malignancy is increased if the tumor has a diameter >4 cm, although adrenocortical carcinomas have been identified in tumors <4 cm [Thakker et al 2012]. Surgery is suggested for adrenal tumors >4 cm in diameter, for tumors 1-4 cm in diameter with atypical or suspicious radiologic features, or for tumors that show significant measurable growth over a six-month interval [Langer et al 2002, Schaefer et al 2008, Gatta-Cherifi et al 2012]. Treatment of functioning adrenocortical tumors in individuals with MEN1 is similar to that for sporadic adrenocortical tumors.

Intraoperative hypertensive crisis. Although pheochromocytoma occurs rarely in MEN1, it is appropriate to measure urinary catecholamines prior to surgery to diagnose and treat a pheochromocytoma and thus avoid dangerous and potentially lethal blood pressure peaks during surgery.

Non-Endocrine Tumors Associated with MEN1

There are no specific treatments. Skin lesions in individuals with MEN1 are treated the same way as for the general population.

Intraoperative hypertensive crisis. Although pheochromocytoma occurs rarely in MEN1, it is appropriate to measure urinary catecholamines prior to surgery to diagnose and treat a pheochromocytoma and thus avoid dangerous and potentially lethal blood pressure peaks during surgery.

Prevention of Primary Manifestations

The organs in MEN1 at highest risk for malignant tumor development – the duodenum, pancreas, and lungs (bronchial carcinoids) – are not suitable for ablative surgery.

The only prophylactic surgery possible in MEN1 is thymectomy to prevent thymic carcinoid [Brandi et al 2001]. Prophylactic thymectomy should be considered at the time of neck surgery for primary hyperparathyroidism in males with MEN1, particularly those who are smokers or have relatives with thymic carcinoid [Ferolla et al 2005].

Surveillance

Surveillance is recommended for individuals with MEN1, including asymptomatic individuals with a heterozygous *MEN1* pathogenic variant (see Table 7a), and individuals at risk for MEN1 (i.e., those with an affected parent who have not undergone molecular genetic testing) (see Table 7b). Early detection and treatment of the potentially malignant neuroendocrine tumors should reduce the morbidity and mortality of MEN1. Such screening can detect the onset of the disease about ten years before symptoms develop, thereby providing an opportunity for earlier treatment [Bassett et al 1998].

Table 7a. Recommended Minimum Surveillance for Individuals with MEN1

System/Concern	Evaluation	Frequency
Parathyroid tumors	• Fasting total serum calcium concentration (corrected for albumin) &/or ionized-serum calcium concentration • Consider fasting serum concentration of intact (full-length) PTH.	Annually beginning at age 5 yrs [1]
Anterior pituitary adenomas	Serum concentration of prolactin, IGF-1, fasting glucose, & insulin	Annually beginning at age 5 yrs [1]
	Head MRI	Every 3-5 yrs beginning at age 5 yrs [2]
Well-differentiated endocrine tumors of the GEP tract	Chromogranin-A, pancreatic polypeptide, glucagon, vasoactive intestinal peptide for other pancreatic neuroendocrine tumors	Annually beginning at age 8 yrs [1]
	Fasting serum gastrin concentration	Annually beginning at age 20 yrs [1]
	Consider abdominal CT, MRI, or EUS exam	Every 3-5 yrs beginning at age 20 yrs [2]
Carcinoid tumors	Consider: [3] • Chest CT; • Chest MRI; • SRS octreotide scan.	Consider annually beginning at age 15 yrs.
Non-endocrine tumors	Skin exam	Consider annually or as needed.

EUS = endoscopic ultrasound; GEP = gastroenteropancreatic; PTH = parathyroid hormone; SRS = somatostatin receptor scintigraphy
1. International Guidelines for Diagnosis and Therapy of MEN Type 1 and Type 2 [Brandi et al 2001], and Clinical Practice Guidelines for MEN Type 1 [Thakker et al 2012]
2. The interval depends on whether there is biochemical evidence of a neoplasia and/or signs and symptoms of a MEN1-related tumor.
3. CT and MRI have better sensitivity than either chest x-ray or somatostatin receptor scintigraphy (SRS) scan in detecting either primary or recurrent thymic carcinoid [Gibril et al 2003, Scarsbrook et al 2007, Goudet et al 2009].

Table 7b. Recommended Surveillance for Individuals at 50% Risk for MEN1

System/Concern	Evaluation	Frequency
Parathyroid tumors	• Fasting total serum calcium concentration (corrected for albumin) &/or ionized-serum calcium concentration • Fasting serum concentration of intact (full-length) PTH	Annually beginning at age 10 yrs
Anterior pituitary adenomas	Serum concentration of prolactin	Annually beginning at age 5 yrs

Table 7b. continued from previous page.

System/Concern	Evaluation	Frequency
Well-differentiated endocrine tumors of the GEP tract	• Fasting serum gastrin concentration • EUS exam	In those w/symptoms of ZES (reflux or diarrhea) annually beginning at age 20 yrs

EUS = endoscopic ultrasound; GEP = gastroenteropancreatic; PTH = parathyroid hormone; ZES = Zollinger-Ellison syndrome

Agents/Circumstances to Avoid

Smoking is associated with a higher risk of developing carcinoid tumors in individuals with MEN1.

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of apparently asymptomatic older and younger at-risk relatives of an affected individual by molecular genetic testing of the *MEN1* pathogenic variant in the family in order to identify as early as possible those who would benefit from prompt initiation of surveillance, preventive measures, and treatment. Early detection and treatment of the potentially malignant neuroendocrine tumors should reduce the morbidity and mortality of MEN1.

When molecular genetic testing for a *MEN1* pathogenic variant is not possible or is not informative, individuals at 50% risk (i.e., first-degree relatives of an individual with MEN1) should undergo surveillance (see Surveillance, Table 7b).

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Since MEN1 is a rare condition, there are no specific guidelines regarding the clinical management and follow up of affected pregnant women.

Maternal PHPT from any cause can increase the risk of developing preeclampsia during pregnancy [Hultin et al 2009]. Approximately 50% of infants born to women with PHPT experience neonatal hypocalcemia [Kort et al 1999]. Other neonatal complications may include intrauterine growth restriction, preterm birth, and permanent hypoparathyroidism [Diaz-Soto et al 2013].

There is one report of a 29-year-old woman with molecularly confirmed MEN1 who underwent total parathyroidectomy seven years prior to conception and was maintained on calcium and vitamin D supplementation throughout pregnancy with monthly serum calcium monitoring. She also had an asymptomatic pituitary microadenoma and pancreatic islet cell tumors. Pregnancy proceeded without further complications and resulted in the delivery of a healthy infant at term. The infant did not have any neonatal complications [Daglar et al 2016].

Therapies Under Investigation

Pituitary tumors. In a MEN1 animal model with a pituitary prolactin-secreting adenoma, monotherapy with the anti-VEGF-A monoclonal antibody (mAb) G6-31 was studied. Tumor growth was evaluated by MRI and vascular density in tissue sections was assessed. Significant inhibition of the growth of the pituitary adenoma leading to an increased mean tumor-doubling-free survival and lowering of serum prolactin concentration were observed in treated animals but not controls. Additionally, the vascular density in pancreatic islet tumors was significantly reduced by the treatment. Such findings suggest that VEGF-A blockade may represent a nonsurgical treatment for benign tumors of the endocrine system, including those associated with MEN1 [Korsisaari et al 2008].

Well-differentiated tumors of the GEP tract

- **Somatostatin analogs (SSAs)** may be used to control proliferation of enterochromaffin-like cells:
  - Two clinical trials (PROMID and CLARINET) in individuals who did not have MEN1 demonstrated that treatment with SSAs had a significant positive effect on the prolongation of progression-free survival [Rinke et al 2009, Caplin et al 2014].
  - One study on octreotide long-acting release (LAR) therapy has demonstrated the same effect in individuals with MEN1. The authors suggest initiating early therapy with SSAs in those with MEN1 who had neuroendocrine tumors to reduce malignant progression and reduce morbidity [Ramundo et al 2014].
  - The European Neuroendocrine Tumor Society (ENETS) is conducting a prospective randomized controlled multicenter study in ENETS Centers of Excellence to evaluate nonfunctioning pancreatic neuroendocrine tumors in MEN1: Somatostatin Analogs Versus NO Treatment (SANO), ClinicalTrials.gov Identifier: NCT02705651.

- **Peptide receptor radionuclide therapy (PRRT),** with radio-labeled SSAs, takes advantage of the SSA specificity for somatostatin receptors to deliver cytotoxic doses of a radioactive isotope (i.e., yttrium-90 or luteticium-177) selectively to GEP neuroendocrine tumor cells.

  Response rates, reported to be 15%-35%, may vary based on the type of tumor and the radionuclide used [Kwekkeboom et al 2011, Nicolas et al 2011, Ezziddin et al 2014]. There are no studies specifically focusing on neuroendocrine tumors associated with MEN1.

Targeted molecular therapies

- **Everolimus** is an oral mTOR pathway inhibitor, used in individuals with advanced, low-grade, or intermediate-grade pancreatic neuroendocrine tumors. mTOR regulates cell survival, proliferation, and motility. An international multicenter double-blind Phase III study on 410 persons with pancreatic neuroendocrine tumors has shown that treatment with mTOR pathway inhibitors leads to an increase of median progression-free survival. This study did not provide any information about the clinical and/or genetic status of MEN1 in those who underwent treatment [Yao et al 2011].
- **Sunitinib,** an oral tyrosine-kinase inhibitor, targets the VEGF receptor. It is used for the treatment of advanced pancreatic neuroendocrine tumors since they express high levels of VEGF receptors. A multinational randomized double-blind placebo-controlled Phase III clinical trial comprising 171 individuals showed that treatment with sunitinib increases the median progression-free survival. However, the study included only two individuals with MEN1, both of whom received placebo [Raymond et al 2011].

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Multiple endocrine neoplasia type 1 (MEN1) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Approximately 90% of individuals diagnosed with MEN1 have an affected parent.
- Approximately 10% of individuals diagnosed with MEN1 have the disorder as the result of a *de novo* *MEN1* pathogenic variant that occurred in early embryogenesis.
- If the proband appears to be the only affected family member (i.e., a simplex case), molecular genetic testing is recommended for the parents of the proband to confirm their genetic status, determine their need for appropriate clinical surveillance (see Management), and allow reliable recurrence risk counseling.
- If the pathogenic variant identified in the proband is not identified in either parent, and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.
- The family history of some individuals diagnosed with MEN1 may appear to be negative because of failure to recognize the disorder in family members, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has demonstrated that neither parent is heterozygous for the pathogenic variant identified in the proband.

Sibs of a proband. The risk to the sibs of the proband depends on the clinical/genetic status of the proband's parents:

- If a parent of the proband is affected and/or is known to have the pathogenic variant identified in the proband, the risk to male and female sibs of inheriting the pathogenic variant is 50%. A high clinical variability has been described among affected members of the same families (bearing the same *MEN1* pathogenic variant) and even between identical twins.
- If the proband has a known *MEN1* pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is slightly greater than that of the general population because of the possibility of parental germline (or somatic and germline) mosaicism. Parental mosaicism for a *MEN1* pathogenic variant has been reported [Beijers et al 2019, Coppin et al 2019].
- If the parents have not been tested for the *MEN1* pathogenic variant but are clinically unaffected, sibs are still at increased risk for MEN1 because of the possibility of reduced penetrance in a heterozygous parent or parental germline mosaicism.

Offspring of a proband. Each child (regardless of sex) of an individual with MEN1 has a 50% chance of inheriting the *MEN1* pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent is affected and/or has the *MEN1* pathogenic variant, the parent's family members may be at risk.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Testing of at-risk asymptomatic individuals. Molecular genetic testing of at-risk asymptomatic family members is strongly recommended for all first-degree relatives of an affected person with an identified *MEN1* pathogenic variant. Molecular genetic testing should be performed in at-risk asymptomatic individuals as soon as possible so that individuals with a *MEN1* pathogenic variant can receive the appropriate clinical surveillance

(see Management). Education and genetic counseling of all at-risk individuals and their families prior to genetic testing is appropriate.

Genetic cancer risk assessment and counseling. For a comprehensive description of the medical, psychosocial, and ethical ramifications of identifying at-risk individuals through cancer risk assessment with or without molecular genetic testing, see Cancer Genetics Risk Assessment and Counseling – for health professionals (part of PDQ®, National Cancer Institute).

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy. Similarly, decisions about testing to determine the genetic status of at-risk asymptomatic family members are best made before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the *MEN1* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for MEN1 are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Association for Multiple Endocrine Neoplasia Disorders (AMEND)**
  United Kingdom
  Email: info@amend.org.uk
  www.amend.org.uk
- **Associazione Italiana Neoplasie Endocrine Multiple (AIMEN 1 & 2)**
  Italy
  Phone: 347 4561588
  Email: info@aimen.it
  www.aimen.it
- **MedlinePlus**
  Multiple endocrine neoplasia
- **National Endocrine and Metabolic Diseases Information Service**
  A service of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
  6 Information Way

Bethesda MD 20892–3569
Phone: 888-828-0904 (toll-free); 866-569-1162 (toll-free TTY)
Fax: 703-738-4929
Email: endoandmeta@info.niddk.nih.gov
Multiple Endocrine Neoplasia Type 1

- **Orphanet: The portal for rare diseases and orphan drugs**
  Patient organizations: Multiple endocrine neoplasia type 1
- **American Multiple Endocrine Neoplasia Support**
  Phone: 865-283-5842
  Email: Info@amensupport.org
  AMEN SUPPORT
- **AMEND Research Registry**
  Association for Multiple Endocrine Neoplasia Disorders
  United Kingdom
  amend.org.uk

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Multiple Endocrine Neoplasia Type 1: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
MEN1	11q13.1	Menin	MEN1 gene homepage	MEN1	MEN1

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Multiple Endocrine Neoplasia Type 1 (View All in OMIM)

131100	MULTIPLE ENDOCRINE NEOPLASIA, TYPE I; MEN1
613733	MENIN 1; MEN1

Molecular Pathogenesis

MEN1 encodes menin, a nuclear protein that has tissue-specific roles in DNA replication and repair and in transcriptional machinery. Menin is suspected to repress tumorigenesis through the repression of cell proliferation by:

- Directly interacting with transcription factors (e.g., JunD, NF-kB, PPARgamma, VDR) that induce or suppress gene transcription;
- Interacting with histone-modifying enzymes and the polycomb group to influence gene transcription through modification of chromatin and the accessibility to gene promoters to transcriptional factors;
- Directly interacting with gene promoters as a transcription factor;
- Interfering with or regulating cell signaling pathways, such as the transforming growth factor beta (TGF-β) and the Wnt/β-catenin signaling pathways.

A physiologic role for menin has been shown in other processes, not directly related to tumorigenesis:

- **Bone development**

- Regulation of early differentiation of osteoblasts (through interactions with Smad1 and Smad5 proteins) [Sowa et al 2003]
- Inhibition of osteoblast late differentiation (by negatively regulating the BMP2-Smad1/5-Runx2 cascade, through the TGF-β/Smad3 pathway) [Sowa et al 2004]
- Direct modulation of both SMAD1 protein and miR-26a expression during the commitment of human adipose tissue-derived mesenchymal stem cells to the osteoblast lineage [Luzi et al 2012]

- **Hematopoiesis.** Regulation of lymphoid progenitors [Naito et al 2005, Chen et al 2006, Caslini et al 2007, Maillard et al 2009]

Mechanism of disease causation. Biallelic inactivation of *MEN1*, by a germline heterozygous loss-of-function variant and an acquired somatic loss-of-function variant

***MEN1*-specific laboratory technical considerations.** The coding region of *MEN1* includes exons 2-10; all of exon 1 and parts of exons 2 and 10 are noncoding. No pathogenic variants have been found in exon 1, and this exon is usually excluded from genetic testing.

Table 8. Notable *MEN1* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_001370259.2 NP_001357188.2	c.1378C>T	p.Arg460Ter	See Genotype-Phenotype Correlations.

Variants listed in the table have been provided by the authors. GeneReviews staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Cancer and Benign Tumors

Arnold et al [2002] identified specific clonal alterations involving somatic variants and/or deletion of both *MEN1* alleles in 15%-20% of sporadic parathyroid adenomas; these pathogenic variants were scattered along the entire *MEN1* coding region with no indication of a hot spot. In addition, 5%-50% of sporadic endocrine tumors have been found to have loss of heterozygosity at the 11q13 locus, where *MEN1* is located [Friedman et al 1992, Heppner et al 1997].

Chapter Notes

Acknowledgments

This chapter has been supported by Cofin MIUR 2003 (FM), by AIRC 2000 (MLB), and by the Fondazione Ente Cassa di Risparmio di Firenze (MLB).

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Revision History

- 10 March 2022 (sw) Comprehensive update posted live

- 14 December 2017 (ma) Comprehensive update posted live
- 12 February 2015 (me) Comprehensive update posted live
- 6 September 2012 (me) Comprehensive update posted live
- 2 March 2010 (me) Comprehensive update posted live
- 31 August 2005 (me) Review posted live
- 9 September 2004 (mlb) Original submission

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