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Multiple Endocrine Neoplasia Type 1

[*MEN1, MEN1 Syndrome, Multiple Endocrine Adenomatosis, Wermer Syndrome*]

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Summary

Disease characteristics. Multiple endocrine neoplasia type 1 (MEN1) syndrome includes a varying combination of more than 20 endocrine and non-endocrine tumors. Endocrine tumors (which become evident by overproduction of hormones by the tumor or by growth of the tumor itself) associated with MEN1 syndrome include parathyroid tumors (the main MEN1-associated endocrinopathy with onset in 90% of individuals at 20-25 years of age and manifest as hypercalcemia by age 50 years; hypercalcemia causes lethargy, depression, confusion, anorexia, constipation, nausea, vomiting, diuresis, dehydration, hypercalciuria, kidney stones, increased bone resorption and increased fracture risk, hypertension, and shortened QT interval), pituitary tumors (prolactinoma being most common and manifest as oligomenorrhea/amenorrhea and galactorrhea in females and sexual dysfunction in males), well-differentiated endocrine tumors of the gastro-entero-pancreatic (GEP) tract (manifest as Zollinger-Ellison syndrome resulting from a gastrinoma; hypoglycemia resulting from an insulinoma; hyperglycemia, anorexia, glossitis, anemia, diarrhea, venous thrombosis, and skin rash resulting from a glucagonoma; and watery diarrhea, hypokalemia, and achlorhydria syndrome resulting from a VIPoma), carcinoid tumors (non-hormone-secreting and manifest as a large mass after age 50 years), or adrenocortical tumors (associated with primary hypercortisolism or hyperaldosteronism). Non-endocrine tumors associated with MEN1 syndrome include facial angiofibromas, collagenomas, lipomas, meningiomas, ependymonas, and leiomyomas.

Diagnosis/testing. Clinical diagnostic criteria for MEN1 syndrome include the presence of two endocrine tumors that are either parathyroid, pituitary, or GEP tract tumors. Biochemical testing detects an increased serum concentration of parathyroid hormone and calcium in primary hyperparathyroidism, increased serum concentrations of prolactin from a

prolactinoma, and increased serum concentrations of gastrin, insulin, and VIP from tumors of the GEP tract. Prolactinomas are imaged by MRI, neuroendocrine tumors are detected by somatostatin receptor scintigraphy, and pancreatic endocrine tumors are detected by endoscopic ultrasound. Molecular genetic testing of *MEN1*, the only gene known to be associated with MEN1 syndrome, detects *MEN1* mutations in about 80-90% of probands with familial MEN1 syndrome and in about 65% of individuals with a single occurrence of MEN1 syndrome in the family.

Management. MEN1 syndrome-associated hyperparathyroidism is treated with subtotal parathyroidectomy and cryopreservation of parathyroid tissue or total parathyroidectomy and autotransplantation of parathyroid tissue; prior to surgery, bone anti-resorptive agents are used to reduce hypercalcemia and limit bone resorption. Prolactinomas are treated with dopamine agonists, of which cabergoline is the treatment of choice. Growth hormone-secreting tumors causing acromegaly are treated by transsphenoidal surgery; medical therapy for growth hormone-secreting tumors includes somatostatin analogues, octreotide, and lanreotide. ACTH-secreting pituitary tumors associated with Cushing syndrome are surgically removed; non-secreting pituitary adenomas are treated by transsphenoidal surgery. Proton pump inhibitors or H2-receptor blockers are used to reduce gastric acid output caused by gastrinomas. Surgery is indicated for insulinoma and most other pancreatic tumors. Long-acting somatostatin analogues can control the secretory hyperfunction associated with carcinoid syndrome. Surgical removal of adrenocortical tumors that exceed three cm in diameter can prevent malignancy. Thymectomy may prevent thymic carcinoid in males, particularly in smokers. Surveillance of individuals who have MEN1 syndrome or are at high risk includes biochemical testing of serum concentrations of calcium (from age eight years), gastrin (from age 20 years), pancreatic polypeptide (from age 10 years), and prolactin (from age five years) and abdominal CT or MRI (from age 20 years) and head MRI (from age five years). Since early detection affects medical management, molecular genetic testing is offered to at-risk members of a family in which a germline *MEN1* mutation has been identified.

Genetic counseling. MEN1 syndrome is inherited in an autosomal dominant manner. Approximately 10% of cases are caused by *de novo* mutations. Each child of an individual with MEN1 syndrome has a 50% chance of inheriting the mutation. Molecular genetic testing can be used for testing at-risk relatives if a disease-causing germline mutation has been identified in an affected family member. Prenatal diagnosis for pregnancies at increased risk is available if the disease-causing allele of an affected family member is identified or if linkage is established in the family.

Diagnosis

Clinical Diagnosis

Multiple endocrine neoplasia type 1 (MEN1) syndrome occurs with a varying combination of more than 20 endocrine and non-endocrine tumors; consequently, no simple definition can encompass all index cases or affected families.

Endocrine Tumors Associated with MEN1 Syndrome—Diagnostic criteria might be considered to be presence of two of the following three endocrine tumors. These tumors may become evident either by overproduction of polypeptide hormones or by growth of the tumor itself.

- **Parathyroid tumors** can manifest as hypercalcemia [primary hyperparathyroidism (PHPT)] as the result of the overproduction of parathyroid hormone by the parathyroid glands.

- **Pituitary tumors** can manifest as oligomenorrhea/amenorrhea and galactorrhea in females and sexual dysfunction and, more rarely, gynecomastia in males resulting from a prolactin-secreting anterior pituitary adenoma (prolactinoma).
- **Well-differentiated endocrine tumors of the gastro-entero-pancreatic (GEP) tract** (including tumors of the stomach, duodenum, pancreas, and the intestinal tract) [Klöppel et al 2004] can manifest as the following (from most frequent 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)
  - **W**atery **d**iarrhea, **h**ypokalemia, and **a**chlorhydria (WDHA syndrome) resulting from a vasoactive intestinal peptide (VIP)-secreting tumor (VIPoma)

Familial MEN1 syndrome is defined as MEN1 syndrome in an individual who has either at least one first-degree relative with at least one of these endocrine tumors **OR** only one organ involvement and an *MEN1* disease-causing germline mutation.

Note: (1) Non-functioning pancreatic endocrine tumors that are difficult to diagnose by biochemical and imaging tests are the most frequent tumors in MEN1 syndrome [Jensen 1999]. (2) Type II gastric enterochromaffin-like (ECL) cell carcinoids are included in the well-differentiated endocrine tumors of the gastro-entero-pancreatic (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].

Non-Endocrine Tumors Associated with MEN1 Syndrome

- **Skin**
  - **Facial angiofibromas:** Benign tumors comprising blood vessels and connective tissue. These consist of acneiform papules that do not regress and that may extend across the vermillion border of the lips.
  - **Collagenomas:** Multiple, skin-colored, sometimes hypopigmented, cutaneous nodules, symmetrically arranged on the trunk, neck and upper limbs. They are typically asymptomatic, roundish, and firm-elastic, from a few millimeters to several centimeters in size.
- **Lipomas:** Generally multiple benign fatty tissue tumors found anywhere that fat is located. They can be subcutaneous or, rarely, visceral.
- **Central nervous system**
  - **Meningioma** in 8% of 74 individuals [Asgharian et al 2004]; the meningiomas were mainly asymptomatic and 60% showed no growth.
  - **Ependymoma** in 1% [Kato et al 1996]
- **Leiomyomas:** Benign neoplasms derived from smooth (nonstriated) muscle [McKeeby et al 2001, Ikota et al 2004].

In 32 consecutively ascertained individuals with MEN1 syndrome, Darling et al (1997) identified multiple facial angiofibromas in 88%, collagenomas in 72%, café au lait macules in 38%, lipomas in 34%, confetti-like hypopigmented macules in 6%, and multiple gingival papules in 6%. They and Asgharian et al (2004) suggest that these cutaneous findings may be helpful in diagnosis of individuals with MEN1 syndrome before manifestations of hormone-secreting tumors appear.

Testing

Biochemical Testing—Since several parameters may influence the biochemical assessment of the secreted hormones, it is reasonable to consider the upper limit of reference values as the referring value.

Primary hyperparathyroidism (PHPT). PHPT is defined as an increased serum concentration of parathyroid hormone (PTH) (normal range: 10-60 pg/mL [Kratz & Lewandrowski 1998]) and an increased serum concentration of calcium (normal range: 8.5-10.5 mg/dL or 2.1-2.6 mmol/L [Kratz & Lewandrowski 1998]).

Note: Elevated urinary excretion of calcium may be observed, but it is not necessary to make the diagnosis of PHPT.

Prolactinoma. Prolactinoma is characterized by increased serum concentrations of prolactin (PRL). Normal ranges for PRL [Kratz & Lewandrowski 1998]:

- Premenopausal females: 0-20 ng/mL or 0-2.0 µ5g/L
- Postmenopausal females: 0-15 ng/mL or 0-1.5 µ5g/L
- Males: 0-15 ng/mL or 0-1.5 µg/L

Note: increased serum concentrations of prolactin can be observed in pregnancy and with use of dopaminergic drugs.

Well-differentiated endocrine tumors of the gastro-entero-pancreatic (GEP) tract

- **Gastrinoma** is defined as elevated basal serum concentration of gastrin (normal range: <100 ng/L [Kratz & Lewandrowski 1998]).

  Note: Elevated serum concentration of gastrin can also be observed in achlorhydria resulting from use of antibodies or medications.
- **Pancreatic insulinoma** is characterized by fasting hypoglycemia with high plasma or serum concentration of insulin (reference values 2-20 U/mL or 14.35-143.5 pmol/L) and high plasma or serum concentration of C-peptide (0.5-2.0 ng/mL or 0.17-0.66 nmol/L) **OR** proinsulin [Brandi et al 2001, Marx 2001].
- **VIPoma** is defined by high plasma concentration of VIP, as determined by immunoassay test (<75 pg/mL or <75 ng/L) [Kratz & Lewandrowski 1998].

Adrenocortex tumors are generally nonfunctioning, but may be associated with elevated serum concentrations of cortisol (reference values: fasting 8AM-noon, 5-25 µg/dL or 138-690 nmol/L; noon-8PM, 5-15 µg/dL or 138-414 nmol/L; 8PM-8AM, 0-10 µg/dL or 0-276 nmol/L).

Imaging Studies—Parathyroid disease. Imaging is not usually required for diagnosis of parathyroid disease as (1) the underlying cause of primary hyperparathyroidism in MEN1 is

usually multiglandular disease with enlargement of all the parathyroid glands rather than a single adenoma and (2) preoperative imaging does influence the surgical approach.

Prolactinoma. MRI is the imaging test of choice.

Well-differentiated endocrine tumors

- Somatostatin receptor scintigraphy (SRS) scan (performed using ^{111}Indium-diethylenetriamine pentaacetic acid-octreotide [^{111}In-DPTA octreotide]) is a proven method to image neuroendocrine tumors [Shi et al 1998], but currently lacks full evaluation in MEN1 syndrome, including its usefulness for early diagnosis of tumors.

  Note: Langer et al (2004) determined that somatostatin receptor scintigraphy is the procedure of choice for the identification of metastases of MEN1 pancreatic endocrine tumors (PETs).

- Endoscopic ultrasound (EU) 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].

  Note: (1) With the exception of endoscopic ultrasound examination, the current non-operative imaging methods are not able to identify tumors confined to the pancreas that are less than 1.5 cm diameter; this limits the detection of many primary tumors and metastases [Skogseid et al 1998]. (2) Alternative imaging methods, such as somatostatin receptor scintigraphy (SRS) scan, are being evaluated to determine their ability to localize and stage neuroendocrine tumors associated with MEN1 syndrome.

- CT and MRI are equally sensitive in detecting thymic carcinoid, at initial evaluation and during follow-up for recurrence [Brandi et al 2001].

  Note: Because both plain chest x-ray and SRS scan have lower sensitivity in detecting both primary and recurrent thymic carcinoid, SRS scan is not the first imaging study of choice [Gibril et al 2003].

- CT is useful in localizing occult bronchial carcinoid tumors and in follow-up after their successful removal.

Adrenocortical tumors. These are generally detected by CT.

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Molecular Genetic Testing—Gene. *MEN1* is the only gene known to be associated with MEN1 syndrome.

Molecular genetic testing: Clinical uses

- Confirmatory diagnostic testing
- Predictive testing
- Prenatal diagnosis

Molecular genetic testing: Clinical methods

- **Sequence analysis.** *MEN1* germline mutations are identified in about 80% to 90% of probands with familial MEN1 syndrome [Brandi et al 2001] and about 65% of individuals with simplex MEN1 syndrome (i.e., a single occurrence of MEN1 syndrome in a family) [Guo & Sawicki 2001]. Approximately 45% of germline mutations detected by sequence analysis are small deletions and approximately 15% are small insertions [Brandi et al 2001].
  - Although different mutation detection rates are reported in different series, the likelihood of detecting a *MEN1* mutation increases in individuals with more main tumors (parathyroid, pancreatic, and pituitary), especially those from families with hyperparathyroidism and pancreatic islet tumors [Ellard et al 2005, Klein et al 2005].
  - Simplex MEN1 cases (i.e., a single occurrence of MEN1 syndrome in a family) are less likely to test positive than familial cases, in part because some of these simplex cases are caused by somatic mosaicism [Klein et al 2005].
  - Individuals who have a single MEN1 related-tumor and no family history of MEN1 syndrome rarely have germline *MEN1* mutations [Ellard et al 2005].
- **Duplication/deletion testing.** In the event that sequence analysis fails to identify a germline mutation in an individual with typical MEN1 syndrome, deletions or other gross rearrangements can be tested for by Southern blot analysis. It is estimated that between 1% and 3% of *MEN1* germline mutations are large deletions that could be detected on a Southern blot analysis or by other gene dosage procedures (i. e. PCR-based) [Kishi et al 1998, Bergman et al 2000, Cavaco et al 2002, Ellard et al 2005, Klein et al 2005].
- **Linkage analysis.** In the event that a disease-causing mutation is not identified using sequence analysis or targeted mutation analysis, linkage analysis may be utilized in certain families.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in MEN1 Syndrome

Test Methods	Mutations Detected	Mutation Detection Rate		Test Availability
		Familial [1]	Simplex [2]	
Sequence analysis	*MEN1* sequence alterations	70-90%	65% [3]	Clinical Testing
Duplication/deletion testing	*MEN1* duplications/deletions	1-3%		

1. Familial MEN1 syndrome is defined as a proband meeting the diagnostic criteria of MEN1 syndrome plus a minimum of one first-degree relative with at least one of these tumors.
2. Simplex MEN1 syndrome is defined as a single occurrence of MEN1 syndrome in a family.
3. The likelihood of detecting a germline mutation may be lower in the individual who is known to be the first affected individual in the family, possibly because a *de novo* mutation has resulted in somatic mosaicism that involves the germline in that individual [Klein et al 2005].

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Genetically Related Disorders

Germline *MEN1* mutations. Another phenotype associated with germline mutations in *MEN1* is familial isolated hyperparathyroidism (FIHP). FIHP is characterized by the

occurrence of parathyroid adenoma or hyperplasia without other associated endocrinopathies. *MEN1* germline mutations have been reported in between 20% [Miedlich et al 2001, Villablanca et al 2002] and 57% [Pannett et al 2003] of families with FIHP. Of note, in one family with FIHP with no clinical evidence of hyperparathyroidism-jaw tumor syndrome and an intronic *MEN1* mutation, the mother of the proband (whose genetic status was unknown, but who likely had the mutation present in the proband) died of parathyroid carcinoma [Carrasco et al 2004]. Thus, in contrast to MEN1 syndrome, in which the risk for parathyroid carcinoma does not appear to be increased, FIHP may have an increased risk for parathyroid carcinoma. (See also Differential Diagnosis.)

Somatic *MEN1* mutations. Sporadic tumors, including parathyroid adenoma, gastrinoma, insulinoma, and bronchial carcinoid that occur as single tumors in the absence of any other findings of MEN1 syndrome, frequently harbor somatic *MEN1* mutations that are NOT present in the germline; thus, predisposition to these tumors is not heritable [Carling 2005]. Arnold et al (2002) identified specific clonal alterations involving somatic mutation and/or deletion of both *MEN1* alleles in 15-20% of sporadic parathyroid adenomas.

Clinical Description

Natural History

Endocrine tumors occurring in individuals with MEN1 syndrome are shown in Table 2.

Table 2. Endocrine Tumor Types in MEN1 Syndrome

Tumor Type	Tumor Subtype	Hormone-Secreting	Prevalence in MEN1 Syndrome	
Parathyroid	NA [1]	Yes	100% have primary hyperparathyroidism by age 50 yrs [2]	
Anterior pituitary	Prolactinoma (PRLoma)	Yes	~10-60% [3] of cases have anterior pituitary tumors	Most common anterior pituitary tumor
	Growth hormone (GH)-secreting	Yes		5% [4]
	GH/PRL-secreting	Yes		5% [4]
	TSH-secreting	Yes		Rare [5]
	ACTH-secreting	Yes		2% [4]
Well-differentiated endocrine	Gastrinoma	Yes	40% [6]	
	Insulinoma	Yes	10% [4]	
	Glucagonoma	Yes	2% [4]	
	VIPoma	Yes	2% [4]	
Carcinoid	Bronchial	No	10%	
	Thymic	No		
Adrenocortical	Cortisol-secreting	Rarely	~20-40% of cases have adrenocortical tumors	Rare
	Aldosterone-secreting	Rarely		Rare
	Pheochromocytoma	Rarely		<1% [4]

1. Not applicable
2. First clinical manifestation of MEN1 in 90% of individuals
3. First clinical manifestation of MEN1 in 10% of familial cases and 25% of simplex cases
4. Brandi et al 2001
5. Valdes-Socin et al 2003
6. Manifest as Zollinger-Ellison syndrome

The endocrine tumors of MEN1 syndrome occur in varying combinations in individuals. The only specific clustering of tumors within the MEN1 phenotype is the Burin variant in which the prevalence of prolactinoma is higher and the prevalence of gastrinoma is lower [Hao et al 2004].

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

Primary Hyperparathyroidism (PHPT)—PHPT is often mild and asymptomatic individuals with biochemical evidence of hypercalcemia are often detected in the course of evaluation of individuals known to have or be at risk for MEN1 syndrome. PHPT is the main MEN1-associated endocrinopathy, being the first clinical expression of MEN1 syndrome in 90% of individuals. Onset is typically between 20 and 25 years of age. All individuals with MEN1 syndrome can be expected to have hypercalcemia by age 50 years. Although PHPT is frequently asymptomatic for a long period of time, it may manifest as reduced bone mass in women who are hyperparathyroid as early as 35 years of age [Burgess et al 1999].

The 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 [Marx 2001].

Pathology. Individuals with MEN1 syndrome generally have multiglandular parathyroid disease with the enlargement of all the parathyroid glands, rather than a single adenoma; they are considered to be sporadic tumors of clonal origin [Marx 2001].

Cancer risk. Malignant progression of parathyroid tumors is not a clinical feature of "classic" MEN1 syndrome.

Anterior Pituitary Tumors —Pituitary tumors represent the first clinical manifestation of MEN1 syndrome in 25% of simplex cases (i.e., a single occurrence of MEN1 syndrome in a family) and in 10% of familial cases. Verges et al (2002) reported that pituitary involvement was the initial manifestation of MEN1 syndrome in 17% of individuals and that pituitary adenomas were significantly more frequent in women than in men (50% vs 31%, $P<0.001$).The occurrence of anterior pituitary tumors in MEN1 syndrome ranges between 10% and 60% depending on the study [Brandi et al 2001]. Prolactinoma is the most common pituitary tumor.

Symptoms depend on the pituitary hormone produced:

- Amenorrhea and galactorrhea occur in females with PRL-secreting tumors.
- Reduction of libido or impotence occurs in males with PRL-secreting tumors.
- Hypercortisolism occurs in ACTH-secreting tumors.
- Gigantism and acromegaly occur in children and adults, respectively, with growth hormone (GH)-secreting tumors [Stratakis et al 2000].

Symptoms may also depend on pituitary mass effects such as nerve compression, headache, and hypopituitarism, which can be clinically significant [Yoshimoto & Saito 1991, Carty et al 1998].

In some families, including four families from Newfoundland reported by Farid et al (1980) as the so-called $MEN1_{Burin}$ variant, prolactinoma is unusually common. Subsequent studies revealed that in the Burin variant, the prevalence of gastrinoma is lower as well [Hao et al 2004].

Histology. Between 65% [Brandi et al 2001] and 85% [Verges et al 2002] of pituitary tumors in MEN1 syndrome are macroadenomas.

Cancer risk. Although Verges et al (2002) reported that 32% of pituitary macroadenomas were invasive, malignant degeneration of MEN1-associated pituitary tumors is an infrequent event. However, very recently Benito et al (2005) reported the presence of a metastatic gonadotrophic pituitary carcinoma in a female individual with MEN1.

Well-Differentiated Endocrine Tumors of the Gastro-Entero-Pancreatic (GEP) Tract —Gastrinoma. Approximately 40% of individuals with MEN1 syndrome have gastrinoma, which manifests as Zollinger-Ellison syndrome (ZES). Findings can include upper abdominal pain, diarrhea, esophageal reflux, and acid-peptic ulcers; if not properly diagnosed or treated, ulcer perforation can occur from hypergastrinemia, even without prior symptoms. Heartburn and weight loss, which are less commonly reported, may be described. 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 and hematemesis or melena may result from GI bleeding.

ZES usually occurs before age 40 years [Gibril et al 2004].

- **Pathology.** Typically, multiple small (<1 cm diameter) gastrinomas are observed in the duodenal submucosa.
- **Cancer risk.** The gastrinomas of MEN1 syndrome are frequently multiple and usually include a malignant component. Half have metastasized before diagnosis [Brandi et al 2001]. Individuals with liver metastases have a poor prognosis for survival; this contrasts with nodal metastases, which do not seem to negatively influence prognosis.

  Pancreatic gastrinomas are more aggressive than duodenal gastrinomas, as suggested by their larger size and greater risk for hepatic metastasis. Eight asymptomatic individuals with pancreatic endocrine tumors (PETs) operated on at a mean age of 33 years did not have metastases [Tonelli et al 2005], whereas four out of 12 symptomatic individuals operated on for multiple PETs at a mean age of 51 years had malignant tumors, from which two individuals subsequently died [Skogseid et al 1996].

Insulinoma. The age of onset of insulinoma is generally one decade earlier than the sporadic counterpart [Marx et al 1999].

- **Pathology.** Generally a single tumor occurs in the setting of multiple islet macroadenomas [Brandi et al 2001]. Tumors responsible for hyperinsulinism are usually about 1-4 cm in diameter [Grama et al 1992].
- **Cancer risk.** Insulinomas are almost always benign [Mignon et al 1993].

Non-secreting GEP tract tumors are frequent in MEN1 syndrome. These tumors may occur in non-operated individuals as well as in the remnants that remain after resection for a GEP tract tumor. Rare functioning GEP tract tumors include VIPomas, glucagonomas, somatostatinomas, or GRFomas, usually exhibiting a large diameter (>3 cm) [Mignon et al 1993].

Carcinoid Tumors—Carcinoid tumors originating in the thymus and bronchus and type II gastric enterochromaffin-like (ECL) cell carcinoids occur in 10% of individuals with MEN1 syndrome.

Thymic, bronchial, and gastric carcinoids rarely oversecrete ACTH, calcitonin, or GHRH; similarly, they rarely oversecrete serotonin or histamine and rarely cause the carcinoid syndrome. Ectopic growth hormone production by a thymic carcinoid causing acromegaly has been reported [Boix et al 2002]; however, others have not observed hormone secretion by these tumors [Gibril et al 2003]. The clinical course of carcinoid tumors is often indolent but can also be aggressive and resistant to therapy [Schnirer et al 2003].

The retrospective study of Gibril et al (2003) supports the conclusion that thymic carcinoid tumors are generally a late manifestation of MEN1 syndrome as no affected individuals had thymic carcinoid as the initial manifestation of MEN1 syndrome. Thymic carcinoid in MEN1 syndrome 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.

Thymic carcinoids are more prevalent in males than in females [Teh et al 1997]; bronchial carcinoids are more prevalent in females than in males. These are the only MEN1 syndrome-associated neoplasms currently known to exhibit an unequal male-to-female ratio.

The mean age at diagnosis of gastric carcinoids is 50 years. In up to 15% of individuals with MEN1 syndrome, they are recognized incidentally during endoscopy [Benya et al 1993, Bordi et al 1998, Gibril et al 2000].

Cancer risk. The thymic carcinoids of MEN1 syndrome tend to be aggressive [Gibril et al 2003]. Ferolla et al (2005) determined that thymic carcinoids are highly lethal, particularly in males who are smokers.

Bronchial carcinoids, often multicentric, may exhibit both synchronous and metasynchronous occurrence. In contrast to thymic carcinoids, most bronchial carcinoids usually behave indolently, albeit with the potential for local mass effect, metastasis, and recurrence after resection [Sachithanandan et al 2005].

Adrenocortical Tumors —Adrenocortical tumors, involving one or both adrenal glands, are present in 20-40% of individuals with MEN1 syndrome [Skogseid et al 1995].

Rarely, adrenal cortex tumors are associated with primary hypercortisolism or hyperaldosteronism [Skogseid et al 1992, Beckers et al 1992, 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 benign adrenal Cushing syndrome, and one with a pheochromocytoma. Four developed adrenocortical carcinomas, three of which were functional.

Histology. Silent adrenal gland enlargement is a polyclonal or hyperplastic process, which rarely results in neoplasm [Skogseid et al 1992]. In the study of 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 or smaller.

Cancer risk. Low

Morbidity and Mortality of MEN1 Syndrome —Improved knowledge of MEN1 syndrome-associated clinical manifestations, improved early diagnosis of MEN1 syndrome-associated tumors, and improved treatment of metabolic complications of MEN1 have virtually eliminated ZES and/or complicated PHPT as causes of death.

Nonetheless, individuals with MEN1 syndrome have a significantly increased risk of premature death, justifying surveillance of those with *MEN1* mutations and/or a family history of MEN1 syndrome [Geerdink et al 2003]. (See Management.) Longer life expectancy in MEN1 syndrome is likely to result in a rising cumulative morbidity and mortality from MEN1 syndrome-associated malignancies, which currently account for approximately 30% of deaths in MEN1 syndrome.

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified in MEN1 syndrome [Kouvaraki et al 2002, Turner et al 2002, Wautot et al 2002].

Penetrance

The age-related penetrance for all clinical features rises above 50% by 20 years of age and above 95% by 40 years of age [Trump et al 1996, Bassett et al 1998, Skarulis 1998].

Anticipation

Anticipation has not been reported.

Prevalence

A prevalence of about one in 30,000 has been reported [Marx 2001].

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

The most important and common disorders to consider in the differential diagnosis:

Primary hyperparathyroidism (PHPT). Overall, PHPT has a prevalence of 3/1000 in the general population [Melton 1991] with a female-to-male ratio of approximately 3:1 [Bilezikian & Silverberg 2000].

- **Sporadic 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 of life [Bilezikian & Silverberg 2000].

  Note: Most individuals with sporadic PHPT are detected because of symptoms of

hypercalcemia, in contrast to individuals known to have or be at risk for MEN1 who are often asymptomatic when detected during evaluation for manifestations of MEN1 syndrome.

- **MEN1 syndrome-associated PHPT** represents 2-4% of all PHPT, does not exhibit sex prevalence, and has its onset three decades earlier (20-25 years of age) than its sporadic counterpart [Uchino et al 2000, Marx 2001]. PHPT caused by **multiglandular disease** in individuals younger than 40 years may represent the first manifestation of MEN1 syndrome regardless of family history [Langer et al 2003].
- **Familial isolated HPT (FIHP)** is characterized by parathyroid adenoma or hyperplasia without other associated endocrinopathies in two or more individuals in one family. Germline mutations in the following genes have been identified in FIHP:
  - *MEN1* (in a region not tested in by currently available methods) in 20% [Miedlich et al 2001] to 23% of FIHP [Warner et al 2004]. (Also see Genetically Related Disorders).
  - *CASR*, the gene encoding the calcium-sensing receptor, responsible for familial benign hypercalcemia (FBH) (also called familial hypocalciuric hypercalcemia [FHH or FBHH] and neonatal severe primary hyperparathyroidism (NSHPT) [Brown 1998, Carling et al 2000]. Between 14% [Simonds et al 2002] and 18% [Warner et al 2004] of families with FIHP have identifiable *CASR* mutations.
  - *HRPT2*, the gene encoding parafibromin, which is responsible for the hyperparathyroidism-jaw tumor (HPT-JT) syndrome [Teh, Farnebo et al 1998; Carpten et al 2002; Villablanca et al 2004]. Of note, Warner et al (2004) did not identify any *HRPT2* mutations in 22 individuals with FIHP.
  - A still unknown gene.

MEN2 syndrome, caused by mutations in *RET*, is genetically distinct from MEN1 syndrome. MEN2A, a clinical variant of MEN2 syndrome, is characterized by medullary thyroid carcinoma, pheochromocytoma, and PHPT. PHPT occurs in approximately 20-30% of individuals with MEN2A syndrome and is generally milder than MEN1 syndrome-associated PHPT [Brandi et al 2001]. Although most individuals with MEN2A syndrome and HPHPT have no symptoms, hypercalciuria and renal calculi may occur.

Pituitary tumors. Prolactinomas are more often associated with MEN1 syndrome than occur sporadically. MEN1 syndrome-associated pituitary adenomas are later onset than sporadic pituitary adenomas. MEN1 syndrome-related pituitary tumors are more likely to be macroadenomas than sporadic pituitary adenomas. Sporadic pituitary adenomas have a better response to medical therapy than MEN1 syndrome-associated pituitary tumors [Beckers et al 2003].

Note: Single pituitary adenomas in the absence of any other findings of MEN1 syndrome are not frequently associated with somatic *MEN1* mutations [Poncin et al 1999], although some data suggest that somatic *MEN1* gene mutations and deletions play a causative role in the development of a subgroup of sporadic pituitary adenomas [Zhuang et al 1997].

Familial pituitary adenomas are usually somatotropinomas and lack *MEN1* germline mutations [Tanaka et al 1998, Tsukada et al 2001]. Linkage to 11q13 has been reported in kindreds with isolated familial somatotrophinoma [Gadelha et al 2000, Luccio-Camelo et al 2004].

Zollinger-Ellison syndrome

- MEN1 syndrome-associated ZES is typically associated with multiple tumors in the duodenal mucosa, often surrounded by hyperplasia of gastrin cells [Pipeleers-Marichal et al 1990]. Twenty-five percent of all ZES can be attributed to MEN1 [Brandi et al 2001]. Moreover, 25% of individuals with MEN1 syndrome/ZES have no family history of MEN1 syndrome [Gibril et al 2004]. Without *MEN1* molecular genetic testing, the diagnosis of MEN1 syndrome is likely to be delayed or missed in individuals presenting with ZES because of the later onset and milder manifestations of the other features of MEN1 syndrome.
- Sporadically occurring gastrinomas are more commonly pancreatic in origin [Pipeleers-Marichal et al 1990, Ruszniewski et al 1993, MacFarlane et al 1995, Norton et al 2001, Tonelli et al 2005]. Symptoms of gastrinoma generally occur one decade earlier in MEN1 syndrome than in sporadic gastrinomas [Brandi et al 2001].

Insulinoma. MEN1 syndrome accounts for 10% of all sporadic and hereditary cases of hypoglycemia. MEN1 syndrome-associated hypoglycemia is generally caused by one tumor in the setting of multiple islet macroadenomas [Brandi et al 2001]. The peak age at onset of insulinoma in MEN1 syndrome is approximately one decade earlier than onset of sporadic insulinomas [Marx et al 1999, Brandi et al 2001].

Carcinoid tumors that are not associated with MEN1 syndrome usually occur in derivatives of the midgut and hindgut, are argentaffin positive, and secrete serotonin (5-hydroxytryptamine).

MEN1 syndrome-associated thymic carcinoid has a more severe course than sporadic thymic carcinoid, especially in smokers [Brandi et al 2001].

Facial angiofibromas are seen in tuberous sclerosis complex.

Leiomyomas can be seen in association with Alport syndrome.

Management

Evaluations at Initial Diagnosis

In the initial evaluation of an individual with MEN1 syndrome, attention should be directed to detection of the following most common MEN1 syndrome-associated tumors as described in the Diagnosis:

- Multiglandular parathyroid disease.
- Gastrinoma, other entero-pancreatic neuroendocrine tumors, and prolactinoma

Treatment of Manifestations

PHPT—Prior to surgery, use of bone anti-resorptive agents should be considered in order to reduce hypercalcemia and limit PTH-dependent bone resorption, thus reducing future risk of osteoporosis.

The optimal surgical approach in MEN1 syndrome-associated PHPT is controversial. MEN1 syndrome-associated hyperparathyroidism may be treated with either subtotal parathyroidectomy (removal of 7/8 of the parathyroid tissue) and cryopreservation of parathyroid tissue or total parathyroidectomy and autotransplantation of parathyroid tissue [Carling & Udelsman 2005].

- Marx (2001) determined that eight to twelve years after successful subtotal parathyroidectomy, PHPT recurred in as many as 50% of euparathyroid individuals

with MEN1 syndrome. Such recurrence was likely the result of either new neoplasia arising in residual normal tissue, or neoplasia progressing in the residual tissue.

- Elaraj et al (2003) showed that subtotal and total parathyroidectomy resulted in longer recurrence-free intervals compared with lesser resection. Cumulative recurrence rates for procedures that were less than subtotal parathyroid resection were 8%, 31%, and 63% at one, five, and ten years, respectively. For subtotal or total parathyroid resection, the cumulative recurrence rates were 0%, 20%, and 39% at one, five, and ten years, respectively.
- The high incidence of severe hypoparathyroidism after total parathyroidectomy supports the use of subtotal parathyroidectomy as the initial procedure of choice in MEN1 syndrome [Elaraj et al 2003].

Pituitary Tumors—PRL-secreting tumors (prolactinomas)

- Dopamine agonists such as cabergoline, bromocriptine, pergolide, and quinagolide are the preferred treatment of PRL-secreting tumors [Bevan et al 1992].
- Cabergoline can be considered the current treatment of choice because of its reduced side effects and greater potency.

Growth hormone-secreting tumors

- Transsphenoidal surgery, the first treatment of choice in growth hormone-secreting tumors causing acromegaly, is effective in 50-70% of cases.
- Somatostatin analogues are the medical therapy of choice for the treatment of growth hormone-secreting tumors. Octreotide and lanreotide normalize serum concentration of hGH and IGF1 in more than 50% of treated individuals [Beckers 2003].
- Dopamine agonists are only rarely efficient in treatment of growth hormone-secreting tumors causing acromegaly, although they can be effective in mixed GH-PRL-secreting adenomas and 10-20% of cases resistant to somatostatin analogues [Lamberts et al 1986, Colao et al 1997, Marzullo et al 1999, Freda 2002].

ACTH-secreting tumors

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

Non-secreting pituitary adenomas

- In non-secreting pituitary adenomas, surgical treatment using a transsphenoidal approach is the treatment of choice. However, in rare cases of very large adenomas with considerable extracellar extension, the transfrontal approach is the only possibility [Beckers 2002].
- In 5-15% of cases, medical treatment with potent dopaminergic agonists or sometimes with somatostatin analogues may shrink the adenoma before surgery [Colao et al 1998].
- Published data are not sufficient to compare the treatment of sporadic versus MEN1 syndrome-associated pituitary tumors. Although general agreement on this topic does

not exist, Beckers et al (2003) suggested that aggressive therapy is more frequently needed in MEN1-associated pituitary tumors than in sporadic tumors.

Well-Differentiated Tumors of the Gastro-Entero-Pancreatic (GEP) Tract — Gastrinoma

- Medications that can control some of the gastro-entero-pancreatic hormone excess-dependent features of MEN1 syndrome and thus prevent severe and sometimes life-threatening morbidity in MEN1 syndrome include proton pump inhibitors or H2-receptor blockers to reduce gastric acid output [Jensen 1998].
- Surgical versus nonsurgical management of gastrinoma in MEN1 syndrome is controversial as successful outcome of surgery is rare.
- Because MEN1 syndrome gastrinomas occur most commonly in the first and second portions of the duodenum, and less commonly the third and fourth duodenal portions and the first jejunal loop [Pipeleers-Marichal et al 1990], it is important that all these sites be examined during preoperative imaging, intraoperative exploration, and pathological examination of surgical specimens [Tonelli et al 2005].

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

- Surgery is usually indicated for insulinoma and most of the other pancreatic tumors observed in MEN1 syndrome. According to Tonelli et al (2005), the best surgical approach for an MEN1 insulinoma is intraoperative localization of nodules greater than approximately 0.5 cm diameter by palpation or intra-operative ultrasound followed either by enucleation (removal) of these nodules or by pancreatic resection if multiple large deep tumors are present.

  Note: Limited resection or simple enucleation of nodules is more frequently followed by persistence or recurrence of the disease [Demeure et al 1991, Lo et al 1998, Simon et al 1998, Jordan 1999].

Carcinoid Tumors—Long-acting somatostatin analogues can control the secretory hyperfunction associated with carcinoid syndrome; however, the risk for malignant progression of the tumor remains unchanged [Schnirer et al 2003].

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

Adrenocortical Tumors—Although general agreement does not exist, some suggest surgical removal of adrenocortical tumors that exceed three cm in diameter because of their malignant potential [Langer et al 2002].

Prevention of Primary Manifestations

The organs in MEN1 syndrome 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 syndrome 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 syndrome, particularly those who are smokers or have relatives with thymic carcinoid [Ferolla et al 2005].

Prevention of Secondary Complications

Post-operative hypoparathyroidism. Measurement of serum concentration of parathyroid hormone (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 post-operatively and then once a year thereafter; serum concentration of PTH should be measured in separate but simultaneous blood samples, one from the arm without a parathyroid autotransplant and one from the arm with the parathyroid autotransplant. This procedure allows the physician both to assess the function of the transplanted parathyroid tissue and monitor for possible recurrence of hyperparathyroidism.

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

Surveillance

Routine surveillance of asymptomatic individuals with an *MEN1* disease-causing mutation and others at risk for MEN1 syndrome-associated tumors (i.e., those known to have MEN1 syndrome and those with an affected parent who have not undergone molecular genetic testing) with biochemical testing and imaging beginning in early childhood and continuing for life is recommended. Early detection and treatment of the potentially malignant neuroendocrine tumors should reduce the morbidity and mortality of MEN1 syndrome. 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 3).

Table 3. Minimal Surveillance Program [1, 2] for Individuals Known to Have MEN1 Syndrome or to be at High Risk for MEN1 Syndrome [3]

For individuals known to have MEN1 syndrome or to have a family-specific mutation in *MEN1*[1, 2]
Biochemical investigations. Yearly, beginning at the specified age • Serum concentration of prolactin from age five years [1] • Fasting total serum calcium concentration (corrected for albumin) and/or ionized-serum calcium concentration from age eight years [1] • Fasting serum gastrin concentration from age 20 years [1] **To be considered:** • Fasting serum concentration of intact (full-length) PTH **Imaging.** Every 3-5 years beginning at the specified age; the interval depends on whether there is biochemical evidence of a neoplasia and/or signs and symptoms of an MEN1-related tumor [1]. • Head MRI from age five years [1] • Abdominal CT or MRI from age 20 years [1] **To be considered:** • Yearly chest CT, somatostatin receptor scintigraphy (SRS) octreotide scan
For individuals at 50% risk of having MEN1 syndrome whose genetic status is unknown
Biochemical investigations. Yearly, beginning at the specified age • Serum concentration of prolactin from age five years • Fasting total serum calcium concentration (corrected for albumin) and/or ionized-serum calcium concentration from age ten years • Fasting serum concentration of intact (full-length) PTH from age ten years • Fasting serum gastrin concentration if individual has symptoms of ZES (reflux or diarrhea) from age 20 years

1. According to the International Guidelines for Diagnosis and Therapy of MEN Type 1 and Type 2 [Brandi et al 2001]
2. Can be modified according to clinical suspicion and/or findings in an individual

Testing of Relatives at Risk

Molecular genetic testing should be offered to at-risk members of a family in which a germline *MEN1* mutation has been identified in an affected relative [Lairmore et al 2004]. When molecular genetic testing for an *MEN1* mutation is not possible or is not informative, individuals at 50% risk (first-degree relatives of an individual with MEN1 syndrome) should undergo routine evaluation (see Surveillance).

Therapies Under Investigation

Somatostatin analogues may be used to control the proliferation of enterochromaffin-like cells. In one study, long-term administration of octreotide resulted in regression of a type II gastric carcinoid tumor [Tomassetti et al 2000]. More extensive studies are needed in order to establish the efficacy of such molecules for clinical use in individuals with MEN1-ZES.

Search ClinicalTrials.gov 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, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

MEN1 syndrome is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Approximately 90% of individuals diagnosed with MEN1 syndrome have an affected parent.
- The proportion of cases caused by *de novo* mutations is approximately 10%.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* mutation include molecular genetic testing.

Note: Although approximately 90% of individuals diagnosed with MEN1 syndrome have an affected parent, the family history 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.

Sibs of a proband

- The risk to the sibs of the proband depends upon the genetic status of the proband's parents.
- If a parent of the proband is affected or has a disease-causing mutation, the risk to the sibs is 50%.
- If the disease-causing mutation found in the proband cannot be detected in the DNA of either parent, two possible explanations are germline mosaicism in a parent or a *de novo* mutation in the proband. Although no instances of germline mosaicism have been reported, it remains a possibility.

Offspring of a proband. Each child of an individual with MEN1 has a 50% chance of inheriting the mutation.

Other family members of a proband. The risk to other family members depends upon the status of the proband's parents. If a parent is found to be affected and/or to have a disease-causing mutation, his or her family members are at risk.

Related Genetic Counseling Issues

Considerations in families with an apparent *de novo* mutation. When neither parent of a proband with an autosomal dominant condition has the disease-causing mutation or clinical evidence of the disorder, it is likely that the proband has a *de novo* mutation. However, possible non-medical explanations, including alternate paternity, undisclosed adoption, or secretiveness within the family could also be explored.

Testing of at-risk asymptomatic individuals. Consideration of molecular genetic testing of at-risk asymptomatic family members is appropriate for surveillance (See Management). Molecular genetic testing can only be used for testing at-risk relatives if a disease-causing germline mutation has been identified in an affected family member. When a known disease-causing mutation is not identified, linkage or haplotype analysis can be considered in families with more than one affected family member from different generations. Because early detection of at-risk individuals affects medical management, testing of individuals during childhood who have no symptoms is beneficial [ASCO Policy Statement 2003]. Education and genetic counseling of at-risk individuals under 18 years of age and their parents prior to genetic testing is appropriate.

Genetic cancer risk assessment and counseling. For comprehensive descriptions of the medical, psychosocial, and ethical ramifications of identifying at-risk individuals through cancer risk assessment with or without molecular genetic testing, see:

- Genetic Cancer Risk Assessment and Counseling: Recommendations of the National Society of Genetic Counselors
- Elements of Cancer Genetics Risk Assessment and Counseling (part of PDQ®, National Cancer Institute)

Family planning. The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy. Similarly, decisions about testing to determine the genetic status of at-risk asymptomatic family members are best made before pregnancy.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about 10-12 weeks' gestation. The disease-causing allele of an affected family member must be identified or linkage established in the family before prenatal testing can be performed.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Requests for prenatal testing for conditions such as MEN1 syndrome that do not affect intellect and have some treatment available are not common. Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. Although most centers would consider decisions about prenatal testing to be the choice of the parents, careful discussion of these issues is appropriate.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Multiple Endocrine Neoplasia Type 1

Gene Symbol	Chromosomal Locus	Protein Name
MEN1	11q13	Menin

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Multiple Endocrine Neoplasia Type 1

131100	MULTIPLE ENDOCRINE NEOPLASIA, TYPE I; MEN1

Table C. Genomic Databases for Multiple Endocrine Neoplasia Type 1

Gene Symbol	Locus Specific	Entrez Gene	HGMD
MEN1	MEN1	4221 (MIM No. 131100)	MEN1

For a description of the genomic databases listed, click here.

Molecular Genetic Pathogenesis

Studies of loss of heterozygosity (LOH) in tumor tissues of individuals with MEN1 syndrome revealed in most of the associated neoplasms the loss of the allele derived from the unaffected parent. Thus, these findings indirectly indicated a clonal outgrowth with acquisition of a homozygous recessive state at the tissue level and suggested the inactivation of a tumor suppressor gene. Thus, the inactivating germline mutation is inherited from the affected parent or has its origin in an inactivating *de novo* mutation at an early embryonic stage, while the second mutation in a somatic cell eliminates the wild-type allele.

Normal allelic variants: *MEN1* gene consists of ten exons; about ten normal variants (polymorphisms) have been identified [Marx 2001].

Pathologic allelic variants: More than 400 different germline *MEN1* mutations are scattered in and around the open reading frame without significant clustering that corresponds to functional domains of the protein [Agarwal et al 1997; Chandrasekharappa et 1997; Heppner et al 1997; Lemmens et al 1997; Bassett et al 1998; Carling et al 1998; Farnebo et al 1998; Giraud et al 1998; Sato et al 1998; Teh, Kytola et al 1998; Vortmeyer et al 1998; Cebrian et al 1999; Morelli et al 2000; Tahara et al 2000; Sato et al 2001; Pannett & Thakker 2001; Guo & Sawicki 2001; Turner et al 2002; Verges et al 2002; Wautot et al 2002; Park et al 2003]. Of all mutations, about 25% are nonsense, about 45% are deletions, about 15% are insertions, less than 5% are splice site mutations, and about 10% are missense mutations.

Normal gene product: Menin is a protein of 610 amino acids. Menin is located in the nucleus and has two nuclear localization signals near the carboxyl terminus. Menin does not show similarity with any other known protein. The *MEN1* transcript has been detected in all human tissues.

Menin, mainly located in the nucleus [Agarwal et al 2004], is widely expressed and may play different roles in different tissues. It is probably involved in the regulation of several cell functions, including DNA replication and repair, and in transcriptional machinery. Menin may inhibit JunD-mediated transcriptional activation, as studies of deletion mutants have shown the existence of interacting regions of both the proteins. Menin could inhibit JunD-mediated transcription by modification of chromatin structure recruiting a specific histone deacetylase targeted to a promoter by binding JunD. Moreover, when compared to controls, lymphocytes from individuals with a heterozygous *MEN1* mutation show both premature division of the

centromere and hypersensitivity to alkylating agents. Thus, menin could be a negative regulator of cell proliferation after DNA damage

Abnormal gene product: Most germline or somatic mutations in the *MEN1* gene predict truncation or absence of encoded menin. Similarly, 11q13 loss of heterozygosity in tumors predicts inactivation of the other *MEN1* copy. Neither the finding of a tumor suppressor mechanism nor the identification of binding partners has established the ultimate pathways of menin action in normal tissues or in tumors [Agarwal et al 2004].

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

Medline Plus
Multiple Endocrine Neoplasia (MEN) 1

National Institute of Diabetes & Digestive & Kidney Diseases (NIDDK)
Multiple Endocrine Neoplasia Type 1

National Library of Medicine Genetics Home Reference
Multiple endocrine neoplasia type 1

NCBI Genes and Disease
Multiple Endocrine Neoplasia

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Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

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Chapter Notes

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