

Multiple Endocrine Neoplasia Syndromes

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The multiple endocrine neoplasia (MEN) syndromes are rare autosomal-dominant conditions that predispose affected individuals to benign and malignant tumors of the pituitary, thyroid, parathyroids, adrenals, endocrine pancreas, paraganglia, or nonendocrine organs. The classic MEN syndromes include MEN type 1 (MEN1) and MEN type 2 (MEN2). However, several other hereditary conditions should also be considered in the category of MEN: von Hippel-Lindau syndrome (VHL), the familial paraganglioma syndromes, Cowden syndrome, Carney complex, and hyperparathyroidism jaw-tumor syndrome. In addition, there are other familial endocrine neoplasia syndromes with an unknown genetic basis that might also fall into the category of MEN.

The MEN syndromes differ from other hereditary cancer syndromes in that most tumor growth occurs in hormone-secreting glands. This feature has two primary consequences of clinical importance. First, the excess hormone production often results in well-defined hormonal syndromes with characteristic symptoms and medical sequelae. Second, the excess hormone production serves as a sensitive tumor marker that is useful for making a diagnosis, determining response to therapy, and screening asymptomatic patients.

This article reviews the clinical features, diagnosis, and surgical management of the various MEN syndromes and genetic risk assessment for patients presenting with one or more endocrine neoplasms. [Table 1](#) provides an overview of all of the hereditary syndromes discussed in this chapter.

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Table 1
Overview of endocrine neoplasia syndromes

Syndrome	Mutated gene	Manifestations
MEN1	<i>MEN1</i>	Primary hyperparathyroidism (usually four-gland hyperplasia), anterior pituitary adenomas, tumors of endocrine pancreas and duodenum, foregut carcinoids
MEN subtype 2A	<i>RET</i> proto-oncogene	Medullary thyroid cancer, pheochromocytoma, primary hyperparathyroidism (usually single adenoma), cutaneous lichen amyloidosis, Hirschsprung disease
MEN subtype 2B	<i>RET</i> proto-oncogene	Medullary thyroid cancer, pheochromocytoma, marfanoid body habitus, facial features resulting from mucosal neuromas, ganglioneuromatosis of the gastrointestinal tract
Familial medullary thyroid cancer	<i>RET</i> proto-oncogene	Medullary thyroid cancer in at least four family members, with documented absence of other endocrinopathies
Hyperparathyroidism-jaw tumor syndrome	<i>HRPT2</i>	Primary hyperparathyroidism (usually single adenoma), ossifying fibromas of maxilla or mandible, renal cysts and hamartomas, 15% risk of parathyroid carcinoma
Familial isolated hyperparathyroidism	<i>MEN1</i> , <i>HRPT2</i> , <i>CASR</i> , other	Nonsyndromic primary hyperparathyroidism
Familial hypocalciuric hypercalcemia	<i>CASR</i>	Benign hypercalcemia; medical management only
VHL	<i>VHL</i>	Pheochromocytoma, retinal and central nervous system hemangioblastoma, renal cysts and clear cell carcinoma, pancreatic cysts and islet cell tumors, endolymphatic sac tumors, papillary cystadenomas of the epididymis and broad ligament
Familial pheochromocytoma/ paraganglioma syndrome	<i>SDHB</i> , <i>SDHC</i> , <i>SDHD</i>	Multiple paragangliomas and pheochromocytoma
Neurofibromatosis type I	<i>NFI</i>	Pheochromocytoma, characteristic physical features (eg, café-au-lait spots, neurofibromas, axillary and inguinal freckling)

Table 1
(continued)

Syndrome	Mutated gene	Manifestations
Cowden syndrome	<i>PTEN</i>	Nonmedullary thyroid cancer (usually follicular rather than papillary); benign and malignant tumors of skin, oral mucosa, breast, and uterus
Familial adenomatous polyposis	<i>APC</i>	Hundreds of adenomatous colon polyps, colon cancer, cribriform morular variant of papillary thyroid cancer
Carney complex	<i>PRKARIA</i>	Endocrine tumors (including thyroid, pituitary, primary pigmented nodular adrenocortical disease), characteristic skin pigmentation, myxomas, melanotic schwannomas
Familial nonmedullary thyroid cancer	Unknown	Nonsyndromic nonmedullary thyroid cancer

Multiple endocrine neoplasia type 1

Overview

MEN1 is characterized by tumors in the parathyroid glands, anterior pituitary, endocrine pancreas, and duodenum (see Table 1). However, a wide range of other tumors can occur in MEN1, including foregut carcinoids, adrenocortical adenomas, thyroid nodules, and such nonendocrine tumors as meningiomas, ependymomas, and leiomyomas. Lipomas, facial angiofibromas, and collagenomas are also common and can be useful in visually identifying the MEN1 syndrome in patients with otherwise equivocal features.

MEN1 is an autosomal-dominant condition that occurs as a result of inactivating mutations of the MEN1 gene (*MEN1*), located on chromosome 11q13. *MEN1* has 10 exons (the first exon is noncoding) and produces a 610-amino-acid protein called menin. Although the function of menin is still not fully understood, menin has roles in DNA replication and repair, transcription, and chromatin modification and generally behaves as a tumor suppressor [1]. No genotype-phenotype correlations have been found for MEN1.

The prevalence of MEN1 is estimated to be 1 in 20,000 to 40,000 individuals, with approximately 10% of patients being the first affected person in their family (ie, the index patient) [2,3]. MEN1 is highly variable in terms of the number of organ systems involved and age at onset of tumors and symptoms, both within and between families. Most individuals with MEN1 are

diagnosed with their first tumors in late adolescence or early adulthood. However, there are reports of tumor development in children as young as 5 years and diagnosis that is delayed until late in life [4]. The penetrance is estimated to be 80% by age 50 years, although biochemical screening detects tumors in 90% to 95% of patients by this age [5–7].

Risk assessment and surveillance

MEN1 should be considered in patients diagnosed with primary hyperparathyroidism under age 30 years, primary hyperparathyroidism resulting from multigland involvement, familial primary hyperparathyroidism, Zollinger-Ellison syndrome, multifocal pancreatic endocrine tumors, or two or more MEN1-related tumors. A clinical diagnosis of MEN1 is made in patients with tumors in two of the three most commonly affected endocrine organs (parathyroid, pituitary, and pancreatic/duodenal endocrine tumors) and in patients with one such tumor and a family history of MEN1. Of the tumors commonly seen in MEN1, pituitary adenomas are the least predictive for true MEN1 as approximately 10% of adults in the general population have a pituitary abnormality detected on MRI [8,9].

Genetic testing for MEN1 is available through several commercial laboratories and should be offered to patients in whom a diagnosis of MEN1 is being considered. The benefit of offering genetic testing is that a diagnosis of MEN1 at an early age allows patients to be monitored for the development of subsequent MEN1-related tumors. However, the sensitivity of genetic testing varies, depending on the combination of affected organs and whether the patient is an index or familial case, and mutations can be identified in only 75% to 90% of patients with a clinical diagnosis of MEN1. This is important because a negative test result cannot definitively rule out risk for further MEN1-related tumors. Follow-up screening recommendations in such cases are controversial and require careful consideration of the index of suspicion of MEN1 based on the patient's personal and family history.

Routine surveillance of presymptomatic patients and treated patients who are currently without evidence of disease involves a combination of annual biochemical testing for all tumor types and imaging studies (CT or MRI) every 1 to 3 years (Table 2) [10]. Pancreatic endocrine tumors in MEN1 patients may be nonfunctioning. Therefore, screening for these tumors with biochemical tests alone is inadequate. The goal of screening is to detect abnormalities at an early stage when tumors are most easily managed and the long-term effects of hormone hypersecretion can be avoided. The age at which screening should begin for each of the component tumors is controversial. Some advocate beginning screening as early as age 5 years. However, others advocate beginning screening in early adolescence owing to the rarity of life-threatening complications of MEN1 in young children [10]. Appropriate screening of presymptomatic MEN1 patients leads to earlier tumor detection by approximately 10 years [11].

Table 2
MEN1 screening guidelines

Tumor	Age to begin screening	Biochemical tests (annually)	Imaging (every 3 y)
Parathyroid	8 y	Serum calcium, parathyroid hormone	None
Gastrinoma	20 y	Serum gastrin	None
Insulinoma	5 y	Fasting serum glucose, insulin	None
Other enteropancreatic	20 y	Chromogranin A, glucagon, proinsulin	Octreotide scan, CT, or MRI
Anterior pituitary	5 y	Prolactin, insulinlike growth factor-1	Brain MRI
Foregut carcinoid	20 y	None	CT

Data from Brandi ML, Gagel RF, Angeli A, et al. Guidelines for diagnosis and therapy of MEN type 1 and type 2. *J Clin Endocrinol Metab* 2001; 86(12):5658–71.

Diagnosis and management of component tumors

Parathyroid tumors

Primary hyperparathyroidism resulting from benign four-gland hyperplasia is the most common presentation of parathyroid disease in MEN1 patients. Patients usually present in their early 20s and virtually all MEN1 patients are affected by parathyroid tumors by age 50 years [3]. If symptoms occur, they are similar to those of sporadic hyperparathyroidism: nephrolithiasis, decrease in bone mineral density leading to osteopenia or osteoporosis, fatigue, myopathy, peptic ulcer disease, and neurocognitive deficits, including depression and disordered sleep.

The diagnosis of hyperparathyroidism is confirmed by the presence of an elevated or high-normal serum calcium level in concordance with an inappropriately elevated serum parathyroid hormone level. A 24-hour urine collection documenting no evidence of hypocalciuria (urinary calcium excretion <100 mg/24 h) should be performed to exclude the possibility of familial hypocalciuric hypercalcemia.

Parathyroidectomy is the cornerstone of the management of primary hyperparathyroidism in MEN1 patients. According to the 2007 National Comprehensive Cancer Network guidelines, there are two surgical options: (1) subtotal parathyroidectomy (leaving 50 mg of the most normal gland in situ), parathyroid cryopreservation, and transcervical thymectomy; or (2) total parathyroidectomy with parathyroid autotransplantation into the nondominant forearm, parathyroid cryopreservation, and transcervical thymectomy [12]. Controversy exists as to which operation should be performed at the outset. Initial subtotal parathyroidectomy is associated with a 30% to 40% rate of recurrent hyperparathyroidism, which often requires cervical reoperation [13,14]. However, initial total parathyroidectomy with autotransplantation results in permanent hypoparathyroidism in up to one third of patients

because of autograft failure [14,15]. Our group has previously recommended subtotal parathyroidectomy and transcervical thymectomy with parathyroid cryopreservation but not autotransplantation at the first operation. Then, if hyperparathyroidism recurs, completion total parathyroidectomy, parathyroid autotransplantation into the nondominant forearm, and cryopreservation of the remaining parathyroid tissue are performed [16]. This approach balances the desire to avoid cervical reoperation for recurrent hyperparathyroidism with the morbidity of permanent hypoparathyroidism.

Transcervical thymectomy should always be performed during the first neck operation because MEN1 patients have an increased risk of supernumerary parathyroid glands, which are usually located ectopically, commonly in the thyrothymic ligament and in the thymus. In addition, MEN1 patients have an increased incidence of developing carcinoid tumors in the thymus.

It is important to identify MEN1 in patients presenting with apparently sporadic primary hyperparathyroidism. Unless MEN1 is recognized before the initial parathyroidectomy, the operative approach may not be appropriate. Thus, genetic testing should be offered to young patients, considered for patients presenting with suspected multigland primary hyperparathyroidism, and patients with a family history of hyperparathyroidism or any other MEN1-related disease.

Pituitary tumors

Between 20% and 60% of individuals with MEN1 develop adenomas of the anterior pituitary gland [2]. Pituitary adenomas are the initial manifestation of MEN1 in 10% to 20% of cases [17,18]. The typical age at which MEN1-related pituitary adenomas develop is in the second to fourth decade of life, with rare occurrences in children.

MEN1-related pituitary adenomas can secrete a number of different hormones. The most common functioning tumors produce prolactin, growth hormone, or corticotropin. Approximately 15% of tumors are nonfunctioning (no hormone production) [2].

MEN1-associated pituitary tumors are usually not malignant or multifocal. Most are macroadenomas (larger than 1 cm), and approximately one third are invasive and cause morbidity because of their mass effects (eg, headache, visual field defect, hypopituitarism, compression of adjacent structures, and mild hyperprolactinemia due to stalk compression) [18].

The preferred imaging modality for suspected pituitary tumors is MRI. The functional status is determined by biochemical evaluation of basal hormone levels (eg, prolactin, growth hormone, insulinlike growth factor-1, corticotropin).

Treatment of MEN1-related pituitary adenomas is the same as that of their sporadic counterparts and depends on tumor size and functional status. Treatment options include surgery (usually from a minimally invasive transsphenoidal approach), medication (for patients with prolactin- or growth-hormone-producing tumors), and radiation.

Prolactin-secreting tumors, or prolactinomas, are by far the most common functioning pituitary adenomas in MEN1. Women usually present with oligomenorrhea, amenorrhea, or galactorrhea, and men with sexual dysfunction or gynecomastia. Familial occurrences of prolactinoma are rare outside of MEN1. The diagnosis of prolactinoma is made by the presence of serum prolactin levels greater than 250 ng/mL and identification of an adenoma on MRI. When serum prolactin levels are elevated but less than 100 ng/mL, the pituitary adenomas are usually nonfunctioning, and the mild hyperprolactinemia is usually due to stalk compression.

Growth hormone-producing tumors, or somatotropinomas, are rare in MEN1 (less than 10% of functioning tumors) and result in gigantism if the tumor develops before puberty or acromegaly in adults. Acromegaly is characterized by enlargement of the hands, feet, and lower jaw; frontal bossing; and coarsening facial features. The diagnosis of growth hormone-producing tumors is established by the presence of elevated insulinlike growth factor-1. Plasma growth hormone levels may be normal or elevated.

Corticotropin-producing tumors are rare in MEN1 (accounting for less than 5% of functioning tumors) and cause cortisol overproduction, resulting in Cushing syndrome. The diagnosis of pituitary-dependent Cushing syndrome is made in the presence of excess cortisol production (best shown by a high 24-hour urinary level of free cortisol) and normal to elevated corticotropin in the presence of a pituitary abnormality on MRI. Though rare, Cushing syndrome is an important diagnosis to recognize because of the morbidities and cardiovascular complications associated with long-term cortisol excess.

Nonfunctioning pituitary tumors may present as symptoms related to their mass effect but are more typically detected incidentally or on routine screening in patients with MEN1.

Pancreatic and duodenal tumors

Approximately 75% of individuals with MEN1 develop neuroendocrine tumors of the pancreatic islet cells or duodenum, with a prevalence approaching 100% on autopsy series [19]. Pancreatic endocrine tumors are the most significant source of MEN1-specific morbidity and mortality, mainly because of their potential for malignant transformation but also from complications of hormone overproduction [20].

In contrast to sporadic pancreatic endocrine tumors, MEN1-associated pancreatic endocrine tumors develop earlier, are almost always multifocal, and occur throughout the pancreas. However, because total pancreatectomy to treat these tumors would result in insulin-dependent diabetes and pancreatic exocrine insufficiency, both of which are associated with considerable morbidity, the timing and extent of pancreatic resection for MEN1-related pancreatic endocrine tumors remain controversial.

Gastrinoma (Zollinger-Ellison syndrome) affects approximately 40% of patients with MEN1 and may present as abdominal pain, esophagitis, and

peptic ulcer disease [10]. Patients with ulcers that are multiple, found in atypical locations, fail to respond to medical therapy, recur after adequate therapy, or are discovered in association with diarrhea or hyperparathyroidism should undergo evaluation for gastrinoma. The diagnosis is made by measuring a serum gastrin level drawn when the patient has discontinued proton-pump inhibitors for at least 2 weeks. The gastrin level is usually greater than 1000 pg/mL in a patient with gastrinoma. If the gastrin level is equivocal, a secretin stimulation test can be performed, with a resulting rise in the gastrin level of more than 200 pg/mL confirming the diagnosis.

Gastrinomas are often multiple in patients with MEN1 and can occur both within the gastrinoma triangle (the area between the confluence of the cystic and common bile duct, the junction of the second and third portions of the duodenum, and the junction of the neck and body of the pancreas) and in the body of the pancreas and the distal duodenum. Tumor localization is best performed by a combination of octreotide scan, CT, and endoscopic ultrasonography. At least 40% of gastrinomas have metastasized to the lymph nodes at the time of diagnosis; liver metastases are more unusual [21–23].

Gastrinoma management is controversial, and no consensus has been achieved regarding surgical management. Medical control of acid hypersecretion has been revolutionized by the introduction of proton-pump inhibitors. When MEN1 patients have hyperparathyroidism as well as gastrinoma, parathyroidectomy is a reasonable first approach because the procedure has been shown to reduce fasting gastrin levels and basal acid output as well as parathyroid hormone levels [24,25]. However, medical management and correction of the hypercalcemia do not address the malignant potential of gastrinomas, which is considerable. Some investigators have advocated an aggressive approach, which involves early surgical intervention for any MEN1 patient with biochemical or radiographic evidence of gastrinoma [26–29]. Other investigators recommend medical management until tumors reach 2.5 to 3 cm in diameter [30,31]. The rationale for the conservative approach is that the risk of distant metastasis is small for gastrinomas less than 2.5 to 3 cm and pancreatic resection carries a high incidence of morbidity [20,23,32]. A reasonable surgical approach includes distal pancreatectomy, enucleation of lesions in the pancreatic head and uncinate process that are palpable or visible with intraoperative ultrasonography, regional lymphadenectomy, and duodenotomy with local resection of any tumors found in the duodenum.

Insulinoma affects approximately 10% of MEN1 patients and classically presents as “Whipple’s triad” of fasting or exercise-induced hypoglycemia, plasma glucose level less than 50 mg/dL, and reversal of symptoms with administration of glucose. The diagnosis is confirmed with a monitored 72-hour fast in which plasma glucose and insulin levels are measured every 4 to 6 hours. An inappropriately high insulin level in the presence of a low glucose level (insulin-to-glucose ratio greater than 0.4) is indicative of insulinoma.

Insulinomas may be multifocal and located throughout the pancreas. CT and endoscopic ultrasonography are the best tests for localization. Octreotide scanning is of limited value, as insulinomas express few somatostatin receptors. Unlike other pancreatic endocrine tumors, insulinomas are usually benign [33].

Insulinomas should be managed surgically. Although only a few small series have been reported in the literature, it seems that a rational surgical approach includes distal pancreatectomy with enucleation of any disease in the pancreatic head or uncinata process that is palpable or visible by intraoperative ultrasonography [34].

The other functioning pancreatic endocrine tumors affect less than 5% of patients with MEN1. Glucagonoma may present as the characteristic syndrome of diabetes, weight loss, anemia, and migratory necrolytic erythema. However, in MEN1 patients, glucagonomas are usually found on routine screening while they are still small and asymptomatic. A serum glucagon level greater than 1000 pg/mL confirms the diagnosis of glucagonoma, although a secretin stimulation test may be useful in equivocal situations. Glucagonomas are usually located in the pancreatic body and tail and are best localized with a combination of octreotide scan, CT, and endoscopic ultrasonography. When symptomatic, glucagonomas tend to be large and malignant [35].

Vasoactive intestinal peptide tumors (VIPomas) present as the syndrome of severe intermittent watery diarrhea, hypokalemia, and achlorhydria. Patients may also describe flushing. The diagnosis is made by fasting plasma vasoactive intestinal peptide (VIP) levels greater than 200 pg/mL. VIPomas are usually located in the body and tail of the pancreas and are localized with an octreotide scan, CT, and endoscopic ultrasonography. Their potential for malignancy is considerable [36].

Somatostatinoma presents as cholelithiasis, diabetes, and steatorrhea. The diagnosis is confirmed by a fasting somatostatin level of greater than 100 pg/mL. Somatostatinomas can be located in the pancreas or duodenum and are localized with an octreotide scan, CT, and endoscopic ultrasonography. These tumors have some potential to metastasize, although they are so rare that the incidence of metastatic disease is difficult to quantify [37].

Nonfunctioning pancreatic endocrine tumors represent up to 71% of surgically treated MEN1-associated pancreatic endocrine tumors [34]. Symptoms can arise as a result of local growth or metastatic disease. The diagnosis is made with CT, endoscopic ultrasonography, or MRI. These tumors are often malignant, metastasizing both to the lymph nodes and to the liver [37]. Pancreatic polypeptidoma is considered together with the nonfunctioning pancreatic endocrine tumors because oversecretion of pancreatic polypeptide does not produce a clinical syndrome.

Glucagonoma, somatostatinoma, VIPoma, and nonfunctioning pancreatic endocrine tumors are so unusual that it is difficult to support

management guidelines with data. However, a logical approach includes optimal medical management of any resulting syndrome and imaging studies for tumor localization. If disease cannot be localized, it seems appropriate to observe these patients with serial imaging. When disease can be localized, a reasonable surgical approach is that described by Thompson: distal pancreatectomy to the level of the superior mesenteric vein, enucleation of any palpable or ultrasonographically visible lesions in the pancreatic head or uncinate process, and regional lymphadenectomy [27]. In patients with elevated gastrin levels, duodenotomy with local excision of any visible tumors should also be performed. Although this procedure leaves behind islet cell tissue in the head and uncinate process of the pancreas, it strikes a balance between a complete oncologic operation and the morbidity associated with the insulin-dependent diabetes and pancreatic exocrine insufficiency that result from total pancreatectomy.

Other manifestations of multiple endocrine neoplasia type 1

Over 40 different tumor types have been reported in patients with MEN1. Although these are not part of the diagnostic criteria for MEN1, their presence can help to support a diagnosis of MEN1.

Foregut (thymic, bronchial, or gastric) carcinoid tumors occur in 5% to 10% of patients with MEN1. Carcinoid tumors associated with MEN1 tend to be nonfunctioning and do not usually produce the "carcinoid syndrome." Carcinoids typically develop after age 50 years and are usually detected incidentally. The exception is thymic carcinoids, which tend to be aggressive and carry a poor prognosis [38]. Carcinoid tumors represent the second-leading MEN1-specific cause of death [20].

Approximately half of MEN1 patients develop adenomas, hyperplasia, or "fullness" of the adrenal cortex [39]. In most cases, the adrenal lesions are nonfunctioning, are not malignant, and are discovered incidentally. Rarely, pheochromocytoma, hyperaldosteronism, hypercortisolism, or adrenocortical carcinomas have been reported in MEN1, so biochemical evaluation is indicated when an adrenal lesion is identified on imaging. Management of MEN1-associated adrenal lesions is the same as management in sporadic cases.

Thyroid tumors, such as follicular adenomas, goiters, and, occasionally, nonmedullary thyroid carcinoma, are observed in at least 25% of MEN1 patients. However, this observation is likely a consequence of the increased frequency of neck imaging in MEN1 patients rather than an inherent increase in risk [40].

Benign facial angiofibromas (persistent acnelike papules composed of blood vessels and connective tissue) occur in 88% of MEN1 patients. Collagenomas (elastic nonpigmented or hypopigmented raised nodules) of the neck, upper limbs, and chest occur in 72% of MEN1 patients. Such angiofibromas and collagenomas can be useful in making a diagnosis of MEN1 in patients with otherwise equivocal features, particularly because

these skin tumors are uncommon in the general population [41,42]. Subcutaneous or visceral lipomas occur in about one third of patients with MEN1, compared with about 6% of the general population. Uterine or esophageal leiomyomas, meningiomas, and spinal ependymomas also occur at a higher frequency in individuals with MEN1 than in the general population [43–46].

Multiple endocrine neoplasia type 2

Overview

The hallmark of MEN2 is a very high lifetime risk of developing medullary thyroid carcinoma (MTC)—more than 95% in untreated patients. Three clinical subtypes—MEN2A, MEN2B, and familial MTC (FMTC)—have been defined based on the risk of pheochromocytoma, hyperparathyroidism, and the presence or absence of characteristic physical features (see Table 1). The prevalence of MEN2 has been estimated at 1 in 35,000 individuals [2].

MEN2 occurs as a result of germline *activating* missense mutations of the *RET* (*RE*arranged during *Transfection*) proto-oncogene. *RET*, a 21-exon proto-oncogene located on chromosome 10q11.2, encodes a receptor tyrosine kinase that functions as a signal transducer upon interaction with the glial-derived neurotrophic factor family of ligands. Binding of these ligands induces dimerization of *RET* receptors, autophosphorylation of intracellular tyrosine residues, and ultimately cell growth and survival mediated by the mitogen-activated protein kinase intracellular signaling cascade [47]. Mutations in *RET* associated with MEN2 cause ligand-independent activation of the downstream pathways and result in unregulated cell growth and survival. MEN2-associated mutations are almost always located in exons 10, 11, or 13 through 16, although mutations in exons 5 and 8 have been reported on rare occasions [48,49]. A definitive diagnosis of MEN2 in cases of apparently sporadic MTC and in patients with an equivocal family history usually depends on the identification of a germline *RET* mutation.

Strong genotype-phenotype correlations exist with respect to clinical subtype, age at onset, and aggressiveness of MTC in MEN2. These are used to determine the age at which prophylactic thyroidectomy should occur and whether screening for pheochromocytoma or hyperparathyroidism is necessary. The presence or absence of specific *RET* mutations can also impact management in patients presenting with apparently sporadic MTC. Therefore, genetic testing should be performed before surgical intervention in all patients diagnosed with MTC.

Multiple endocrine neoplasia subtype 2A

MEN2A is the most common subtype of MEN2 and is associated with MTC and the risk of developing pheochromocytoma (approximately 50% of patients) and primary hyperparathyroidism (20%–30% of patients) [50]. The typical age at onset of biochemical evidence of MTC in untreated

patients with MEN2A is 15 to 20 years. However, MTC is frequent in children ages 10 years and younger [51–53]. Most patients with MEN2A have an affected parent. However, an apparently negative family history must be interpreted with caution as the diagnosis of MTC in family members may be delayed until late in life [54].

At least 95% of individuals with MEN2A have an identifiable *RET* mutation [55,56]. By far the most common mutation associated with MEN2A occurs at the cysteine residue at codon 634 in exon 11 (85% of MEN2A families). Mutations of cysteine residues at codons 609, 611, 618, and 620 in exon 10 account for the majority of the remainder of the MEN2A-associated mutations. However, mutations of codons 630, 666, 768, 790, 791, 804, and 891 have also been reported [51,57].

A small number of families with MEN2A have been reported to have pruritic cutaneous lichen amyloidosis or Hirschsprung disease. Cutaneous lichen amyloidosis is an itchy skin rash that develops on the upper portion of the back. Cutaneous lichen amyloidosis can be present before the onset of MTC, and identification of this skin lesion should prompt an evaluation for MEN2A. Cutaneous lichen amyloidosis has been associated only with mutations of codon 634. Hirschsprung disease is the congenital absence of the autonomic ganglia of various parts of the large intestine and results in colonic dilation, constipation, and obstruction, usually presenting in the neonatal period. Hirschsprung disease has been associated with exon 10 *RET* mutations [58].

Multiple endocrine neoplasia subtype 2B

MEN2B is the rarest subtype of MEN2 and is associated with MTC, a risk of pheochromocytoma (50% of patients), and a characteristic physical appearance that results from mucosal neuromas in the tongue, lips, and eyelids [59]. The characteristic facial features include enlarged lips, a “bumpy” tongue, and eversion of the eyelids (Fig. 1). Often patients have a thin and lanky (marfanoid) body habitus with increased joint mobility and decreased subcutaneous fat. Patients with MEN2B frequently have thickening of the corneal nerves or ganglioneuromatosis of the gastrointestinal tract, which can result in abdominal distention, megacolon, constipation, or diarrhea. The physical traits are usually evident in early childhood. The risk of hyperparathyroidism is not elevated in MEN2B.

Patients with MEN2B have the earliest onset and most aggressive type of MTC. Without prophylactic thyroidectomy at a young age (before 1 year of age), most patients with MEN2B develop metastatic MTC in childhood or adolescence [53]. Most MEN2B patients are index cases and thus do not have the benefit of early genetic screening and prophylactic thyroidectomy that would result from the identification of an affected parent. This means that the diagnosis often relies on recognition of the characteristic physical features associated with this rare subtype. Unfortunately, most

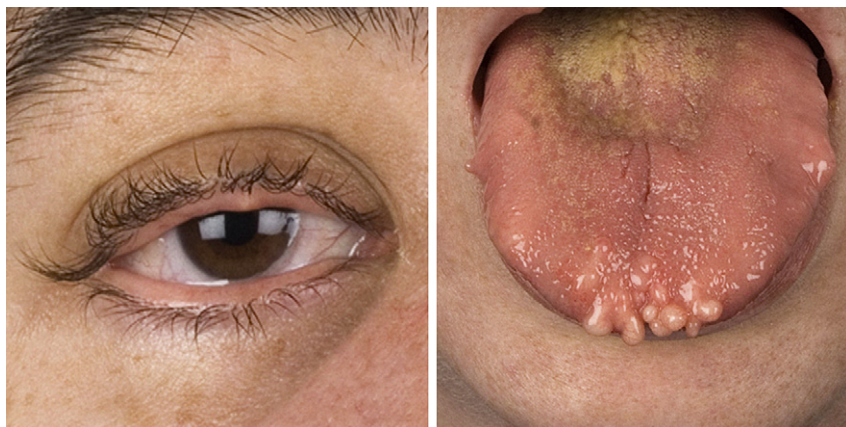


Fig. 1. MEN2B phenotype illustrating neuromas of the tongue and eyelid and eyelid eversion.

MEN2B patients experience a delay in diagnosis until palpable thyroid tumors are present, at which time MTC metastases are usually already present [60].

At least 98% of patients with MEN2B have an identifiable *RET* mutation. The mutation is almost invariably M918T. However, some individuals with MEN2B have been found to have the mutation A883F [61,62].

Familial medullary thyroid carcinoma

Patients with FMTC develop MTC but are not at increased risk for other tumors. The classification of FMTC is clinical and must be strict: Only families in which four or more cases of MTC exist with documented absence of pheochromocytoma and hyperparathyroidism should be considered to have FMTC [61]. Families with fewer than four affected members or young families without pheochromocytoma or hyperparathyroidism should be considered to have “unclassified MEN2” and screened as MEN2A patients until they meet criteria for MEN2A or FMTC. There is a broad overlap in the spectrum of *RET* mutations seen in FMTC and MEN2A, so genetic testing alone cannot always predict MEN2 subtype. In addition, mutations in codons once classified as associated with FMTC have since been found in families with MEN2A. Thus, the designation of FMTC must be used cautiously.

MTC in FMTC families tends to be the least aggressive MTC seen among all the MEN2 subtypes and tends to have the oldest age at onset, although age at onset varies considerably even among family members with the same mutation [63–65]. Certain mutations in exons 13 through 15 (except for codon 883 mutations) may be associated with reduced penetrance of MTC [63,66,67]. Mutations of codons 790, 791, or 804 may be associated with an increased risk of papillary thyroid carcinoma as well as of MTC [68].

Risk assessment and surveillance

MEN2 accounts for approximately 25% of all cases of MTC and approximately 7% of individuals presenting with apparently sporadic MTC [69]. *RET* genetic testing is considered the standard of care for newly identified MTC patients, regardless of age at diagnosis or family history. The identification of a mutation provides essential risk information for the patient's family members, and genotype-phenotype correlations can help estimate the patient's risk of developing additional endocrinopathies (eg, pheochromocytoma, primary hyperparathyroidism), provide prognostic information, and guide the surgical management of MTC.

Almost all MEN2 patients eventually develop MTC. Early detection is difficult, and the treatment options for locally advanced and metastatic disease are limited. Thus, given the acceptably low morbidity and mortality associated with thyroidectomy, it is recommended that patients at risk of inheriting a *RET* mutation undergo predictive genetic testing and that gene carriers undergo prophylactic surgical removal of the thyroid during childhood.

An international consensus conference of experts in MEN syndromes was held in 1999 to provide management guidelines for individuals with the most commonly observed *RET* codon mutations [10]. Mutations were classified into one of three levels, which are used to recommend the age at which prophylactic thyroidectomy should occur in affected patients. Level 1 mutations are associated with the least aggressive and latest onset of MTC. Some level 1 codons are also associated with reduced penetrance of MTC. Therefore, there was no consensus about at which age level 1 mutation carriers should undergo prophylactic thyroidectomy. Several panel members recommended age 5 or 10 years, whereas others felt that serial ultrasounds and calcitonin measurement could be used to delay thyroidectomy [66]. Level 2 mutations are associated with moderately aggressive MTC. Individuals with level 2 mutations should undergo prophylactic thyroidectomy by age 5 years. Codon 609 mutations were recently reclassified from level 1 to level 2 based on the diagnosis of MTC in a 5-year-old with a codon 609 mutation [70]. Level 3 mutations are associated with the most aggressive MTC and include the MEN2B-related mutations. Individuals with level 3 mutations should undergo prophylactic thyroidectomy by 6 months of age, with some experts advocating even earlier surgery. Table 3 is a summary of the most commonly observed *RET* codon mutations according to the level of risk for development of MTC as described above [10,70].

Diagnosis and management of component tumors

Medullary thyroid carcinoma

MTC is a rare cancer that develops from the calcitonin-producing cells of the thyroid (C-cells). MEN2-associated MTC typically occurs at a younger

Table 3
Genotype-phenotype correlations in MEN2

MEN2 subtype	<i>RET</i> codon mutations	Level of risk for development and aggressiveness of MTC	Age before which prophylactic thyroidectomy is recommended
MEN2A or FMTC	768, 790, 791, 804, 891	1 (lowest risk)	5–10 y
MEN2A or FMTC	609, 611, 618, 620, 630, 634	2 (intermediate risk)	5 y
MEN2B	883, 918, 922	3 (highest risk)	6 mo

Data from Brandi ML, Gagel RF, Angeli A, et al. Guidelines for diagnosis and therapy of MEN type 1 and type 2. *J Clin Endocrinol Metab* 2001; 86(12):5658–71; and Machens A, Ukkat J, Brauckhoff M, et al. Advances in the management of hereditary medullary thyroid cancer. *J Intern Med* 2005; 257(1):50–9.

age than sporadic MTC and is more often associated with C-cell hyperplasia (the precursor lesion of hereditary MTC) and multifocality or bilaterality [71]. Both C-cell hyperplasia and MTC cause an increased production of calcitonin from the C-cells, and serum measurements of calcitonin are used to monitor the presence and progression of MTC.

MTC usually presents as neck pain, a palpable neck mass, or diarrhea associated with significant hypercalcitoninemia. Approximately 50% of index patients with MEN2 have locally advanced or distant metastatic MTC by the time a thyroid mass is palpable. Diarrhea associated with hypercalcitoninemia is generally a poor prognostic indicator [72,73].

Total extracapsular thyroidectomy is indicated to manage MTC in the setting of MEN2, but the extent of neck dissection and the management of devascularized parathyroid glands differ depending upon the patient's MEN2 subtype and whether the intervention is prophylactic or therapeutic. An algorithm for management of these issues is found in Table 4 [74].

MTC associated with MEN2A and FMTC is generally less aggressive than MTC associated with MEN2B. Thus, prophylactic thyroidectomy need not include lymph node dissection in the setting of a low-risk patient with MEN2A or FMTC. Central (level VI) neck dissection should be considered based on variables such as specific *RET* mutation, age, serum calcitonin level, and preoperative cervical ultrasound findings. In the setting of MEN2B, however, central (level VI) neck dissection should be performed routinely with prophylactic thyroidectomy. In addition, strong consideration should be given to lateral (levels IIA, III, IV, and V) neck dissection, based on the estimated risk of MTC.

In patients with a malignant neuroendocrine thyroid nodule and no lymphadenopathy noted on cervical ultrasound, the extent of neck dissection that should accompany therapeutic thyroidectomy is generally determined based on the level of risk associated with their particular *RET* mutation. In MEN2A and FMTC patients with a level 1 (lowest risk)

Table 4
Operative management of MEN2-associated medullary thyroid carcinoma

Indication for surgery	Extent of neck dissection ^a	Management of devascularized parathyroid glands
Prophylactic thyroidectomy in MEN2A or FMTC	Central (level VI) neck dissection based on <i>RET</i> mutation, age, serum calcitonin level, and ultrasound	<i>RET</i> mutation consistent with MEN2A: cryopreserve/autograft in forearm <i>RET</i> mutation consistent with FMTC: autograft in neck (parathyroids normal)
Prophylactic thyroidectomy in MEN2B	Central (level VI) neck dissection routinely; lateral (levels IIA, III, IV, and V) neck dissection based on age, serum calcitonin level, and ultrasound	Autograft in neck (parathyroids normal)
Therapeutic thyroidectomy in MEN2A or FMTC ^b	Level 1 <i>RET</i> mutation: central (level VI) neck dissection routinely Level 2 <i>RET</i> mutation: central (level VI) neck dissection routinely; bilateral or ipsilateral lateral (levels IIA, III, IV, and V) neck dissection based on age, serum calcitonin level, and ultrasound	<i>RET</i> mutation consistent with MEN2A: cryopreserve/autograft in forearm <i>RET</i> mutation consistent with FMTC: autograft in neck (parathyroids normal)
Therapeutic thyroidectomy in MEN2B ^b	Central (level VI) neck dissection and bilateral lateral (levels IIA, III, IV, and V) neck dissection	Autograft in neck (parathyroids normal)
Therapeutic thyroidectomy in sporadic MTC ^b	Central (level VI) neck dissection and ipsilateral lateral (levels IIA, III, IV, and V) neck dissection	Autograft in neck (parathyroids normal)

^a Any disease visible by ultrasound in the central or lateral neck requires a central (level VI) or lateral (levels IIA, III, IV, and V) neck dissection respectively.

^b Patients with a malignant thyroid nodule and a normal ultrasound of the lateral neck.

Data from Kouvaraki M, Perrier N, Rich T, et al. The surgical treatment of MEN-1. In: Pollock R, Curley S, Ross M, et al, editors. Advanced therapy in surgical oncology, Hamilton (Canada): BC Decker Inc.; 2008. p. 449–64.

mutation, central (level VI) neck dissection should be performed routinely. In MEN2A and FMTC patients with a level 2 (intermediate risk) mutation, central (level VI) neck dissection should be performed routinely, and consideration should be given to ipsilateral or bilateral lateral (levels IIA, III, IV, and V) neck dissection, based on age and serum calcitonin level. In MEN2B patients (level 3, highest risk mutation), central (level VI), and bilateral lateral (levels IIA, III, IV, and V) neck dissection should be performed routinely.

The management of devascularized or removed parathyroid glands is fairly straightforward. If the patient's *RET* mutation is consistent with MEN2A, parathyroid glands should be cryopreserved or autografted in the forearm because these patients are at increased risk for the future development of hyperparathyroidism. Eliminating a reoperative neck procedure is ideal. If the patient's *RET* mutation is consistent with FMTC or MEN2B, devascularized parathyroid glands may be simply autografted in the neck, as patients with these MEN2 subtypes have normal parathyroid glands and are not at increased risk for future hyperparathyroidism.

Pheochromocytoma

Pheochromocytomas are rare catecholamine-secreting tumors of the adrenal medulla. MEN2-associated pheochromocytomas secrete adrenergic catecholamines and may be detected by routine biochemical screening of MEN2 patients or present as hypertension, palpitations, headache, tachycardia, or sweating. Diagnosis is confirmed by measuring 24-hour urinary levels of total metanephrines and catecholamines or plasma free metanephrines. A recent study demonstrated that plasma free metanephrines have high sensitivity and specificity for detecting pheochromocytoma and should be the test of choice in patients at high risk of pheochromocytoma, such as those with hereditary syndromes [75,76]. Imaging studies such as CT, MRI, metaiodobenzylguanidine scintiscan, or positron emission tomography are useful for localization.

Compared with sporadic pheochromocytoma, MEN2-associated pheochromocytoma is frequently bilateral and rarely malignant [77,78]. Consequently, bilateral adrenalectomy is often required, which will leave a patient dependent on replacement doses of corticosteroid drugs for life and at risk for acute adrenal insufficiency (Addisonian crisis), which can be life-threatening. A recent publication of the M.D. Anderson experience with cortex-sparing adrenalectomy in a series of hereditary pheochromocytomas found that cortex-sparing adrenalectomy led to corticosteroid independence in up to 65% of patients. Recurrent pheochromocytoma developed in only 10% of patients and metastatic disease was detected in none [79].

Based on the above findings, a reasonable approach to management of pheochromocytoma in MEN2 is as follows. A patient who presents with bilateral pheochromocytoma should undergo a unilateral cortex-sparing adrenalectomy and a total contralateral adrenalectomy. Pathologic confirmation of no medullary tissue at the margin should be considered to assure removal of the entire medulla. Preserving the cortex on only one side instead of both sides keeps the risk of recurrent pheochromocytoma low but still enables corticosteroid independence in many patients. A patient with unilateral pheochromocytoma and a normal contralateral adrenal gland should undergo unilateral total adrenalectomy. If such a patient should present later with a contralateral pheochromocytoma, a cortex-sparing

adrenalectomy should be performed. A patient who has undergone a cortex-sparing adrenalectomy requires annual biochemical screening for recurrent pheochromocytoma.

In the event that a patient is diagnosed with pheochromocytoma and concurrent MTC or primary hyperparathyroidism, it is essential that the pheochromocytoma be surgically addressed first. In addition, because the consequences of operating on a patient with an undiagnosed pheochromocytoma can be devastating, MEN2 patients undergoing preoperative evaluation for thyroidectomy, parathyroidectomy, or any other surgical procedure must be screened for pheochromocytoma with measurement of plasma free metanephrines.

Parathyroid tumors

Hyperparathyroidism occurs in 20% to 30% of patients with MEN2A and can result from a single adenoma or from hyperplasia of all parathyroid glands. The clinical presentation and diagnosis are as described above for MEN1.

MEN2A patients invariably undergo prophylactic or therapeutic cervical operation for MTC at an early age and usually before hyperparathyroidism has developed. In these patients, enlarged parathyroid glands should be resected at the initial thyroid operation, even if the patient is eucalcemic. Normal glands, however, should be left in situ. If normal parathyroid glands are inadvertently removed or devascularized during thyroidectomy, they should be cryopreserved or autografted into the forearm, but not into the neck, as there remains a risk that hyperparathyroidism will develop in the future [74]. If parathyroid glands are autotransplanted into the neck, and the patient subsequently develops hyperparathyroidism, the need for reoperation amidst scar tissue increases the morbidity of the procedure. Most cases of hyperparathyroidism in MEN2A develop many years after thyroidectomy. Such cases should be managed as sporadic primary hyperparathyroidism would be managed [74].

Genetic risk assessment of patients with endocrine neoplasias

Overview

Two basic principles guide decisions about whether patients and their families could benefit from comprehensive genetic risk assessment. First, patients with more than one endocrine tumor or a family history of endocrine tumors should have a genetic risk assessment. Unlike common diseases and common cancers that may affect multiple family members by chance, endocrine tumors are rare, and it would be unusual to see more than one endocrine tumor in a single person or in multiple members of the same family by chance. Second, there are several red flag endocrine tumors that have

a high likelihood of having an underlying genetic basis, even in the absence of a personal or family history suggestive of a particular syndrome. These red flag tumors include pheochromocytoma, paraganglioma, MTC, and parathyroid carcinoma.

Parathyroid disease

In the general population, primary hyperparathyroidism affects approximately 1 in 2000 individuals [80]. Women are diagnosed more than three times more frequently than men, with the peak incidence occurring between 50 and 60 years of age. Aside from a history of ionizing radiation, the only known risk factors for hyperparathyroidism are genetic susceptibilities, which include MEN1, MEN2A, and hyperparathyroidism-jaw tumor syndrome. A diagnosis of hyperparathyroidism, particularly in young patients (under age 30 years) and in patients with multigland disease, should prompt an assessment for features of syndromic disease and consideration of genetic testing.

MEN1 is the most common syndrome associated with hyperparathyroidism and may underlie 3% to 5% of cases of primary hyperparathyroidism. MEN1 is more prevalent in early-onset cases and in patients with multigland disease [81–83]. Genetic evaluation for MEN1 should be considered in patients with a family history of hyperparathyroidism, young onset of disease, multigland disease, or a family history of or symptoms suggestive of MEN1-associated endocrinopathies.

MEN2A accounts for a very small percentage of cases of hyperparathyroidism. Hyperparathyroidism is rarely the sentinel feature of MEN2A, so generally a diagnosis of MEN2A is considered only in hyperparathyroid patients who have a personal or family history or symptoms suggestive of MTC or pheochromocytoma.

Hyperparathyroidism-jaw tumor syndrome is an extremely rare autosomal-dominant condition associated with hyperparathyroidism (80% of patients), ossifying fibromas of the maxilla or mandible (one third of patients), kidney lesions, and risk of parathyroid carcinoma (15% of patients). Hyperparathyroidism typically presents in young adulthood and, unlike other forms of inherited hyperparathyroidism, is usually due to a single parathyroid adenoma (or carcinoma) that frequently has a cystic component. In most cases of hyperparathyroidism-jaw tumor syndrome, an inactivating germline mutation of the *HRPT2* gene (*HRPT2*) on chromosome 1q25-31 can be identified. Clinical genetic testing for *HRPT2* mutations should be offered to all patients who have hyperparathyroidism and also jaw tumors or kidney lesions and to all patients with parathyroid carcinoma. In addition, it can be considered in patients with a family history of hyperparathyroidism, particularly if a patient has a cystic or atypical parathyroid adenoma.

Approximately 5% of cases of hyperparathyroidism are familial but are not associated with an endocrine neoplasia syndrome. These cases are

termed familial isolated hyperparathyroidism. Some families with apparently isolated hyperparathyroidism have been found to harbor germline mutations in *MEN1* (10%–15%), *HRPT2* (5%–10%), or *CASR* (5%–10%) [84,85]. *CASR* mutations are typically associated with a condition called familial hypocalciuric hypercalcemia (previously referred to as benign familial hyperparathyroidism), in which the function of the extracellular calcium sensing receptors is reduced, resulting in mild to moderate hypercalcemia with inappropriately normal parathyroid hormone levels, relative hypocalciuria, and a renal calcium-to-creatinine clearance ratio of less than 0.01. In classic familial hypocalciuric hypercalcemia, the hypercalcemia is from benign causes, and parathyroidectomy is not indicated. At this time, it is unclear whether *MEN1*, *HRPT2*, and *CASR* mutations do in fact cause true isolated primary hyperparathyroidism or whether the families studied to date have incomplete or late-onset expression of the other aspects of a MEN syndrome. The majority of families with isolated hyperparathyroidism (75%–80%) do not have an identifiable mutation, although recent linkage studies suggest a new susceptibility locus on chromosome 2p13.3-14 [86].

Pheochromocytoma and paraganglioma

Pheochromocytomas and paragangliomas are histologically identical tumors. The former occur within the adrenal medulla and the latter in the sympathetic or parasympathetic paraganglia. The paraganglia are a system of neural crest-derived cells interspersed along major blood vessels and nerves from the base of the skull to the base of the pelvis; paraganglia respond to stress and changing levels of oxygen. The sympathetic paraganglia are located mainly in the chest, abdomen, and pelvis, whereas the parasympathetic paraganglia are located mostly in the head and neck, particularly near the carotid body or ganglion jugulare, vestibulare, or aortae.

Pheochromocytomas and sympathetic paragangliomas generally result in overproduction of catecholamines and cause the characteristic symptom triad of headache, palpitations, and sweating, as well as many other nonspecific symptoms. Tumor development within the parasympathetic paraganglia typically does not result in excessive catecholamine secretion, and tumors are usually asymptomatic until bulky enough to cause a visible or palpable neck mass, headaches, vocal cord disturbance, or cranial nerve deficit, such as tongue weakness, shoulder drop, hearing loss, tinnitus, or problems with balance. Parasympathetic paragangliomas of the head and neck region are also known as glomus tumors, chemodectomas, and nonchromaffin tumors. However, these terms are anatomically nonspecific. The preferred terminology is paraganglioma plus the associated anatomic position (eg, “carotid body paraganglioma”).

Pheochromocytomas and paragangliomas should be considered red flag tumors, meaning that an unusually high proportion of individuals with these tumors have an underlying genetic condition. The majority of familial and

syndromic cases of pheochromocytoma and paraganglioma can be attributed to VHL, MEN2A, MEN2B, a mutation in one of the familial pheochromocytoma/paraganglioma genes (*SDHB*, *SDHD*, and *SDHC*), or neurofibromatosis type 1. There are also familial cases in which no underlying genetic basis has been identified, suggesting the existence of additional susceptibility loci or limitations in current genetic testing techniques for the succinate dehydrogenase (SDH) genes.

Several retrospective studies have assessed the frequency of germline mutations in patients with apparently sporadic pheochromocytoma or paragangliomas (defined generally as patients without a suggestive family history and without any other clinical evidence of a particular syndrome) since the identification of *SDHD* and *SDHC* in 2000 and *SDHB* in 2001 [87–89]. Overall, the rate of detection of mutations in *SDHB*, *SDHD*, *RET*, and *VHL* in cases of apparently sporadic pheochromocytoma/paraganglioma has been estimated at approximately 25%. However, the mutation prevalence really ranges from less than 2% to nearly 70% if one takes into consideration age at diagnosis, adrenal or extra-adrenal tumor location, focality, biochemical phenotype, and presence of malignancy [90]. It is important to take these factors into consideration in providing risk information and genetic counseling for patients. Because of the multiple genes known to cause pheochromocytoma and paraganglioma, it is burdensome and expensive to evaluate each patient for all of the known genes. Fortunately, even for apparently sporadic tumors, each gene has distinguishing clinical features, so most cases can be narrowed down to one or two possible genes. Knowledge of which gene (if any) is involved enables counseling of the patient about the risk of various tumor types, risk of malignancy, and inheritance pattern. In addition, identifying a genetic basis allows for accurate risk assessment of a patient's family members.

Multiple endocrine neoplasia subtype 2A

Approximately 4% to 5% of cases of apparently sporadic pheochromocytoma occurring before age 50 years are due to mutations of *RET* and are thus associated with MEN2A [90]. MEN2A-associated pheochromocytomas almost always secrete epinephrine and may or may not secrete norepinephrines [91]. In addition, malignancy and extra-adrenal location are extremely rare in MEN2A. Therefore, all young patients presenting with apparently sporadic adrenergic pheochromocytoma should be offered testing for *RET* mutations, whereas patients with entirely noradrenergic, extra-adrenal, or malignant tumors are unlikely to benefit from *RET* testing.

Von Hippel-Lindau syndrome

VHL accounts for approximately 11% of apparently sporadic pheochromocytomas [90]. Pheochromocytomas in VHL are characterized by particularly young age at onset (often in childhood), frequent bilaterality or

multifocality, possibility of extra-adrenal abdominal location and malignancy, and noradrenergic biochemical phenotype [91–93]. In addition to pheochromocytoma, VHL is characterized by hemangioblastomas in the retina and central nervous system, renal cysts and clear cell renal cell carcinoma, pancreatic cysts and islet cell tumors, endolymphatic sac tumors, and papillary cystadenomas of the epididymis and broad ligament.

In patients presenting with pheochromocytoma, VHL should be the first consideration if the patients are particularly young at diagnosis (VHL accounts for nearly half of pheochromocytomas presenting before age 20 years) and in patients whose tumors have a noradrenergic phenotype [90]. The clinician can also look for other features of VHL in a patient, such as renal or pancreatic cysts, and ask about a family history of VHL-associated diseases. Some patients with VHL are at risk only for pheochromocytoma and not for the other features of VHL. Thus, the absence of extra-adrenal VHL features, even in an older patient, cannot by itself rule out VHL.

The underlying genetic defect is within the VHL gene (*VHL*), a three-exon tumor suppressor gene located on chromosome 3p25. Genetic testing is clinically available for VHL, and by using a combination of sequencing and large deletion testing, the detection rate is thought to be 100%. Genetic testing is the most effective method to diagnose or rule out VHL in patients with suspected VHL and in patients presenting with apparently sporadic VHL-related disease [94].

Familial paraganglioma syndromes

The familial paraganglioma syndromes are characterized by susceptibility to multiple head and neck, thoracic and abdominal paragangliomas and pheochromocytoma. Three genes encoding subunits of the mitochondrial complex II (SDH complex)—*SDHB*, *SDHC*, and *SDHD*—have recently been found to be the underlying genetic cause of most familial cases of paragangliomas and of 8% to 50% of apparently sporadic paragangliomas [95,96].

The typical age at tumor development in patients with the familial paraganglioma syndromes is in the late 20s to early 30s. However, a wide range of ages at onset have been reported, and penetrance is incomplete [97]. The risk of various tumor types and of malignancy varies, as does the inheritance pattern, depending on the gene involved.

SDHB and *SDHD* are the most common genes underlying familial forms of paraganglioma. In *SDHB* mutation carriers, paragangliomas develop most often in the abdomen, frequently in the head and neck, and less commonly in the chest and adrenal gland. Paragangliomas in *SDHD* mutation carriers tend to develop most often in the head and neck. However, abdominal and thoracic paragangliomas and adrenal pheochromocytoma are also observed at a lower frequency [97,98]. *SDHC* mutations are rare and have been identified in only a handful of families, most of which presented with benign tumors of the head and neck [99].

SDHB-related paragangliomas have a high rate of malignancy, approaching 100% in some studies; whereas the risk of malignancy in *SDHD*-related paragangliomas is low, likely less than 2% [97,100]. As for other neuroendocrine tumors, malignancy cannot reliably be predicted based on tumor histology alone and is generally identified only by the presence of metastatic disease. Therefore, the presence of an *SDH* gene mutation provides important information regarding risk of malignancy.

The inheritance pattern is also different for the three *SDH* genes. *SDHB* and *SDHC* are inherited in an autosomal-dominant manner, whereas *SDHD* exhibits autosomal-dominant inheritance with maternal imprinting [101]. This means that only those who inherit a *SDHD* mutation from their fathers are at risk for paraganglioma development. Individuals who inherit a gene mutation from their mothers are at risk of passing the mutation on to their children but do not develop paragangliomas themselves.

Neurofibromatosis type 1

Neurofibromatosis type 1 is also a significant genetic contributor to pheochromocytoma development. Patients with this condition are usually easily identified because they have manifestations that are obvious on physical examination (eg, café-au-lait spots, neurofibromas, axillary and inguinal freckling) [102]. Therefore, genetic testing is almost never necessary to establish a diagnosis of neurofibromatosis type 1.

Apparently sporadic pheochromocytomas and paragangliomas

The highest mutation prevalence rates for apparently sporadic pheochromocytoma and paraganglioma have been found in patients with multifocal tumors (approximately 80% for *MEN2*, *VHL*, *SDHB*, and *SDHD* mutations combined), individuals who are age 18 years and younger at diagnosis (approximately 56% have a mutation in *VHL*, *SDHB*, or *SDHD*), and patients with malignant extra-adrenal paragangliomas (abdominal or head and neck origin) regardless of age (the mutation detection rate for *SDHB* reaches almost 50%) [90,96,103]. A moderate detection rate of 10% to 20% is seen in patients with a single benign pheochromocytoma or paraganglioma presenting between 20 and 50 years of age with no family history. The rate is slightly higher in those with extra-adrenal tumors [90,95]. Mutations are only rarely found in patients with apparently sporadic benign pheochromocytoma or paraganglioma who present after age 50 years (<2%). Table 5 provides an overview of the mutation prevalence and characteristic features of the various pheochromocytoma/paraganglioma susceptibility syndromes.

Nonmedullary thyroid cancer

The vast majority of cases of nonmedullary thyroid cancer are sporadic. However, clinicians should be aware of several rare hereditary syndromes

Table 5
Overview of familial hyperparathyroidism syndromes

Syndrome	Gene	Parathyroid features	Additional main features
MEN1	<i>MEN1</i>	Multigland primary hyperparathyroidism; young age of onset	Pituitary adenomas Pancreatic/duodenal endocrine tumors
MEN2A	<i>RET</i>	One- or two-gland primary hyperparathyroidism	Medullary thyroid cancer Pheochromocytoma
Hyperparathyroidism-jaw tumor syndrome	<i>HRPT2</i>	Cystic glands and tumors; risk for parathyroid carcinoma	Ossifying jaw tumors Kidney tumors
Familial hypocalciuric hypercalcemia	<i>CASR</i>	Normal parathyroid glands	Hypocalciuria Low to normal parathyroid hormone levels Renal calcium-to-creatinine clearance ratio <0.01 Parathyroidectomy does not cure hypercalcemia

associated with nonmedullary thyroid cancer, as affected patients may be predisposed to additional malignancies (Table 6).

Cowden syndrome

Cowden syndrome is a rare autosomal-dominant condition in which patients are predisposed to thyroid cancer and to benign and malignant tumors of the skin and oral mucosa, breast, and uterus. A wide range of other less-common tumor types have been observed, including adult-onset dysplastic gangliocytoma of the cerebellum (Lhermitte-Duclos disease, which may be pathognomonic for Cowden syndrome), hamartomatous colon polyps, lipomas, fibromas, and renal cell carcinoma [104].

Thyroid cancer in Cowden syndrome is usually follicular and less commonly papillary, though a follicular variant of papillary thyroid cancer is increasingly being recognized as a common tumor in Cowden syndrome. The risk of thyroid cancer is thought to be approximately 10% in patients with Cowden syndrome. The risk of benign thyroid disease (follicular adenomas, multinodular goiter) is much higher, at about 70%. Cowden syndrome is important to recognize so that the patient can be screened for the more common associated malignancies, including breast cancer (25%–50% risk) and endometrial cancer (5%–10% risk). Benign breast and uterine lesions are extremely common (eg, fibrocystic breast disease, uterine fibroids).

Table 6
Overview of hereditary pheochromocytoma/paraganglioma syndromes

Syndrome	Gene	Apparently sporadic tumors	Main features
VHL	<i>VHL</i>	11%	Hemangioblastoma of brain, spinal cord, and retina Pancreatic/kidney cysts, kidney cancer Secrete norepinephrine/normetanephrine May be malignant; may be extra-adrenal
MEN2A	<i>RET</i>	5%	Medullary thyroid cancer Hyperparathyroidism Secrete epinephrine/metanephrine Usually benign; always adrenal location
Paraganglioma type 4	<i>SDHB</i>	4%	Predominantly abdominal/extra-adrenal High risk of malignancy
Paraganglioma type 1	<i>SDHD</i>	4%	Predominantly head and neck Low risk of malignancy Maternal imprinting
Paraganglioma type 3	<i>SDHC</i>	Unknown	Head and neck only Benign
Neurofibromatosis type 1	<i>NFI</i>	Not applicable	Multiple café-au-lait macules Cutaneous neurofibromas Axillary/inguinal freckling

Cowden syndrome should be considered in thyroid cancer patients whose tumors have a follicular component and who have a personal or family history of thyroid, breast, or endometrial cancer. Clinical genetic testing for Cowden syndrome is commercially available, and approximately 80% of patients with Cowden syndrome have an identifiable *PTEN* mutation. However, the best method of evaluation for the possibility of Cowden syndrome is a formal dermatologic examination. Mucocutaneous features that are almost invariably present in patients with Cowden syndrome include facial trichilemmomas and papillomatous papules, acral keratoses, and “cobblestoning” of the gums and tongue. These skin lesions are almost always present by age 30 years but can be subtle. Patients also commonly have macrocephaly. Patients without dermatologic features are unlikely to have *PTEN* mutations.

Familial adenomatous polyposis

Familial adenomatous polyposis (FAP), also known as Gardner syndrome, is an autosomal-dominant syndrome in which the hallmark feature is the development of hundreds to thousands of adenomatous polyps

in the colon starting at a young age (typically adolescence). Left untreated, FAP patients have a virtually 100% lifetime risk of colon cancer, which usually develops at a young age. Approximately 2% of FAP patients develop thyroid cancer, which is almost invariably the cribriform-morular variant of papillary thyroid cancer and usually develops by age 30 years. Thyroid cancer may be the presenting feature in FAP, so identification of papillary thyroid cancer, especially its cribriform-morular variant, in a young patient with a close relative who had early-onset colon cancer should prompt an investigation for FAP [105]. Approximately 95% of patients with FAP have an identifiable mutation of the causative gene, *APC* (Table 7).

Carney complex

Carney complex is an extremely rare autosomal-dominant condition associated mainly with characteristic spotty skin pigmentation, endocrine tumors, myxomas, and melanotic schwannomas [106]. The frequency of Carney complex in thyroid cancer patients is exceedingly low, but it should be considered in patients with suggestive skin features. The characteristic

Table 7
Overview of hereditary forms of nonmedullary thyroid carcinoma

Condition	Gene	Risk of thyroid cancer in mutation carriers	Thyroid histology	Other features
Familial adenomatous polyposis	<i>APC</i>	2%	Cribriform-morular variant of papillary	100s–1000s colon adenomas Colon, other gastrointestinal cancers Congenital hypertrophy of the retinal pigment Epithelium Desmoid tumors Osteomas, epidermoid cysts
Cowden syndrome	<i>PTEN</i>	10%	Follicular much more likely than papillary	Breast cancer, fibrocystic breasts Benign thyroid disease Uterine cancer, uterine fibroids Mucocutaneous lesions
Carney complex	<i>PRKARIA</i>	10%	Follicular or papillary	Spotty skin pigmentation Myxomas Pituitary adenomas Primary pigmented nodular adrenocortical disease Schwannomas Thyroid nodules/cysts
Familial nonmedullary thyroid cancer	Unknown	Unknown	Unknown	Unknown

skin findings include lentigines, which can range from pale brown to black, are usually slightly raised and well circumscribed, and tend to develop around the lips, eyes, and mucosal surfaces. Blue nevi and café-au-lait spots are also common, and hypopigmented areas and myxomas can occur. One or more of the skin features are almost invariably present by adolescence, are usually the first feature to develop, and are the most useful diagnostic element of Carney complex.

Although rare, Carney complex is an important entity to recognize because patients are also at risk of primary pigmented nodular adrenocortical disease, which causes clinically significant corticotropin-independent hypercortisolism–Cushing syndrome, pituitary adenomas (usually growth hormone–secreting), cardiac myxomas (which can be life-threatening), psammomatous melanotic schwannoma, and other tumor types. Carney complex is associated with *PRKARIA* mutations, which can be identified in approximately 50% of people with a clinical diagnosis.

Familial isolated nonmedullary thyroid cancer

As many as 5% of cases of nonmedullary thyroid cancer are familial but are not associated with any of the distinguishing features of the above syndromes. The genetic basis of nonsyndromic familial nonmedullary thyroid cancer is currently unknown. However, autosomal-dominant susceptibility loci for familial isolated papillary thyroid cancer and for papillary thyroid cancer with papillary renal carcinoma have been identified [107–109]. In addition, the existence of low-penetrance susceptibility genes and multigenic inheritance has been proposed.

In the absence of a known susceptibility gene, empiric data must be used to predict unaffected family members' risk of developing thyroid cancer. If the patient is the only known affected family member, the risk for siblings is approximately 3% to 6% and that for offspring is 1% to 2%. When two family members are affected, the risk for other first-degree relatives approaches 10% and, when more than two family members are affected, the risk may be as high as 50% [110]. The role of thyroid cancer screening, either by thyroid palpation or by ultrasonography, is controversial.

Summary

Clinicians need to be able to recognize the main clinical features of the MEN syndromes to ensure appropriate management. MEN patients are at risk for multiple conditions that often have a complex management and surveillance protocol involving a multidisciplinary team of endocrinologists, endocrine surgeons, and geneticists. Besides the health care management of the index patient, the risk of disease in relatives must also be adequately addressed.

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