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CONSENSUS

Guidelines for Diagnosis and Therapy of MEN Type 1 and Type 2

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This is a consensus statement from an international group, mostly of clinical endocrinologists. MEN1 and MEN2 are hereditary cancer syndromes. The commonest tumors secrete PTH or gastrin in MEN1, and calcitonin or catecholamines in MEN2. Management strategies improved after the discoveries of their genes. MEN1 has no clear syndromic variants. Tumor monitoring in MEN1 carriers includes biochemical tests yearly and imaging tests less often. Neck surgery includes subtotal or total parathyroidectomy, parathyroid cryopreservation, and thymectomy. Proton pump inhibitors or somatostatin analogs are the main management for oversecretion of entero-pancreatic hormones, except insulin. The roles for surgery of most entero-pancreatic tumors present several controversies: exclusion of most operations on gastrinomas and indications for surgery on other tumors. Each MEN1 family probably has an inactivating *MEN1* germline mutation. Testing for a germline *MEN1* mutation gives useful information, but rarely mandates an intervention. The most distinctive MEN2 variants are MEN2A, MEN2B, and familial medullary thyroid cancer (MTC). They vary in aggressiveness of MTC and spectrum of disturbed organs. Mortality in MEN2 is greater from MTC than from pheochromocytoma. Thyroidectomy, during childhood if possible, is the goal in all MEN2 carriers to prevent or cure MTC. Each MEN2 index case probably has an activating germline *RET* mutation. *RET* testing has replaced calcitonin testing to diagnose the MEN2 carrier state. The specific *RET* codon mutation correlates with the MEN2 syndromic variant, the age of onset of MTC, and the aggressiveness of MTC; consequently, that mutation should guide major management decisions, such as whether and when to perform thyroidectomy. (*J Clin Endocrinol Metab* 86: 5658–5671, 2001)

THIS PAPER COVERS the diagnosis and management of MEN1 and MEN2, including important contrasts between them.[1] MEN1 is a syndrome causing combinations among many tumor types. Recent cloning of the *MEN1* gene[2] led quickly to exploring guidelines for its clinical applications. MEN2 has at least three distinct variants, with thyroidal C cell hyperfunction as the common manifestation. Each

Abbreviations: CT, Calcitonin; ECL, enterochromaffin-like; FIHPT, familial isolated hyperparathyroidism; FMTC, familial medullary thyroid cancer; HPT, hyperparathyroidism; MTC, medullary thyroid cancer; VHL, von Hippel Lindau disease; ZES, Zollinger-Ellison syndrome.

[1] This Consensus document is from the Seventh International Workshop on Multiple Endocrine Neoplasia held June 30 to July 2, 1999, in Gubbio, Italy. It also includes components from subsequent discussions.

[2] Syndromes are abbreviated as all capitals; genes are written as all capitals in *italics*. For example, MEN1 is a syndrome, and *MEN1* is a gene.

variant of MEN2 results from a *RET* gene mutation. MEN2 gives a unique model for early prevention and cure of cancer and for stratified roles of mutation-based diagnosis of carriers.[3]

MEN1 syndrome

Classification and mortality. MEN1 causes combinations of over 20 different endocrine and nonendocrine tumors (Table 1) (1–5). Thus, no simple definition of MEN1 could cover all index cases or all families. A practical definition of MEN1 is a case with 2 of the 3 main MEN1-related endocrine tumors (parathyroid adenomas, entero-pancreatic endocrine tumors, and pituitary tumor). Familial MEN1 is similarly defined as at least 1 MEN1 case plus at least 1 first degree relative with 1 of those 3 tumors. A small family that expresses 1 or more of the less common tumors of MEN1 (Table 1) would seem atypical, for example, a family reported because of 4 cases of hyperparathyroidism (HPT), 2 of whom also had ACTH oversecretion (6). However, such tumor combinations seem random, unlike syndromic variants that occur repeatedly in MEN2; the larger MEN1 families almost always show a more typical tumor spectrum. As HPT is the most frequent and usually the earliest expression of MEN1, familial isolated HPT (FIHPT) may be a prelude to typical MEN1, an atypical expression of MEN1 (1), a distinctive variant from *MEN1* mutation (7–9), or a phenocopy caused by mutation in a different gene. The prolactinoma or Burin variant of MEN1 combines HPT with an unusually high penetrance of prolactinoma and a low penetrance of gastrinomas (10). The *MEN1* mutation has been found occasionally in FIHPT and always in the prolactinoma variant of MEN1 (7–10). Each MEN1 variant lacks an informative pattern for its recognized *MEN1* mutations. In other words, the causes of the seeming organ selectivity of tumors are unknown. Consequently, carriers in a family with an MEN1 variant should be checked periodically for other, typical expressions of MEN1.

MEN1 mutation has been found in about 20% of reported FIHPT (1, 7–10). The remaining majority of FIHPT, with no detected germline *MEN1* mutation, still must have an undiscovered mutation in *MEN1* or, more likely, a mutation in other genes. Two of the genes likely to be mutated are those for familial hypocalciuric hypercalcemia (calcium-sensing receptor gene at chromosome 3q and other genes) (11, 12) and for the HPT-jaw tumor syndrome (an uncloned gene at chromosome 1q21–32) (13). Familial isolated pituitary tumor is another distinctive and incomplete mimic of MEN1 without identified *MEN1* germline mutation in more than 15 tested families (7, 8, 14).

Death from the Zollinger-Ellison syndrome (ZES) or from HPT in MEN1 have been virtually eliminated by excellent metabolic management. The consequently longer life span should result paradoxically in a rising cumulative morbidity and mortality from MEN1-associated malignancies. Approximately one third of deaths in MEN1 cases are caused mainly by MEN1-associated malignancies (15, 16). Unlike thyroid cancer in MEN2, the MEN1-related cancers have no effective prevention or cure (except prophylactic thymectomy for thymic carcinoid). This is mainly because in MEN1 the principal cancer host organs (pancreas, duodenum, and lungs) are difficult to screen for early tumors and are not appropriate for ablative surgery.

TABLE 1. Expressions of MEN1 with estimated penetrance (in *parentheses*) at age 40 yr

Endocrine features	Nonendocrine features
Parathyroid adenoma (90%)	Lipomas (30%)
Entero-pancreatic tumor	Facial angiofibromas (85%)
Gastrinoma (40%)@	Collagenomas (70%)
Insulinoma (10%)	
NF[a] including **pancreatic polypeptide** (20%[b])	Rare, maybe innate, endocrine or nonendocrine features
Other: **glucagonoma**, **VIPoma**, **somatostatinoma**, *etc.* (2%)	
Foregut carcinoid	
Thymic carcinoid NF (2%)	Pheochromocytoma (<1%)
Bronchial carcinoid NF (2%)	Ependymoma (1%)
Gastric enterochromaffin-like tumor NF (10%)	
Anterior pituitary tumor	
Prolactinoma (20%)	
Other: GH + PRL, GH, NF (each 5%)	
ACTH (2%), TSH (rare)	
Adrenal cortex NF (25%)	

Bold indicates tumor type with substantial (above 25% of cases with that tumor) malignant potential.

[a] NF, Nonfunctioning. May synthesize a peptide hormone or other factors (such as small amine), but does not usually oversecrete enough to produce a hormonal expression.

[b] Omits nearly 100% prevalence of NF and clinically silent tumors, some of which are detected incidental to pancreatico-duodenal surgery in MEN1.

Parathyroid tumors in MEN1. Primary HPT is the most common endocrinopathy in MEN1, reaching nearly 100% penetrance by age 50 yr (1–5). In contrast, MEN1 is rare in the population, representing only 2–4% of all cases of primary HPT (1, 17). HPT is usually the first clinical expression of MEN1, with a typical age of onset of 20–25 yr (1–5); this is 30 yr earlier than that from sporadic parathyroid adenoma. Bone mass in women with MEN1 and HPT is already low at age 35 yr, presumably due to early and thus long-standing HPT (18). MEN1 often causes simultaneous HPT and ZES. Hypercalcemia increases the secretion of gastrin from gastrinomas; conversely, successful parathyroidectomy lowers blood calcium and can thus decrease gastrin release in MEN1 (19). However, pharmacotherapy for ZES is so successful that ZES plus HPT does not represent a sufficient indication for parathyroidectomy in MEN1. Biochemical testing for HPT in MEN1 is central in the recognition of parathyroid tumors (Table 2), and it has occasional application in ascertainment of MEN1 carriers (Table 3).

Groups differ about the timing of parathyroid surgery in MEN1 *vs.* in sporadic cases. On the one hand, early parathyroidectomy may minimize the lifetime exposure to HPT;

[3] The term carrier is used in two similar contexts. First, it can be a case with inherited predisposition to a syndrome (such as an MEN1 carrier). Second, it can be a case that has inherited the mutated gene for a syndrome (such as an *MEN1* carrier, the latter being a shorthand for a carrier of the mutated germline *MEN1* gene). In either context the carrier state may be clinically manifested or silent.

TABLE 2. A representative program of tests and test schedules to screen for tumor expression in a highly likely carrier of *MENI* mutation (identified from *MENl* mutation or other criteria)

Tumor	Age to begin (yr)	Biochemical tests annually	Imaging tests every 3 yr
Parathyroid adenoma	8	Calcium (especially Ca++), PTH	None
Gastrinoma	20	Gastrin, gastric acid output[a]; secretin-stimulated gastrin[a]	None
Insulinoma	5	Fasting glucose; insulin	
Other enteropancreatic	20	Chromogranin-A; glucagon; proinsulin	^{111}In-DTPA octreotide scan; CAT or MRI
Anterior pituitary	5	PRL; IGF-I	MRI
Foregut carcinoid[b]	20	None	CAT

[a] Gastric acid output measured if gastrin is high; secretin-stimulated gastrin measured if gastrin is high or if gastric acid output is high (Footnote 4).

[b] Stomach best evaluated for carcinoids ("ECLomas") incidental to gastric endoscopy. Thymus removed partially at parathyroidectomy in MENl.

TABLE 3. Screening for the MEN1 carrier state by *MENl* mutation test and other methods

MEN1 carrier ascertainment by *MEN1* germline mutation test
- Indications: In an index case
  - Case meets clinical criteria for MENl (sporadic or familial)
  - Case does not meet MEN1 criteria but is suspicious/atypical of MEN1. For example, two or more MEN1-related tumors; multiple parathyroid tumors before age 30; true recurrent hyperparathyroidism; gastrinoma or multiple islet cell tumors at any age; familial isolated hyperparathyroidism.

Indications: in member of family with known familial *MEN1* mutation
- Asymptomatic relative.
- Relative expressing familial MEN1 (Mutation test would be confirmatory for this presumed carrier).

Method 1—sequence *MEN1* gene segments: sequence in and around the menin protein's open reading frame. Use DNA representing the germline. Consider DNA from a deceased carrier if no other carriers are available.

Method 2—focused test for known *MEN1* mutation: after the familial mutation is known from one index case (Method 1), test for that mutation in other members of this family by sequencing only that gene segment or by testing a restriction fragment that is introduced or removed by that mutation.

MEN1 carrier ascertainment without *MEN1* germline mutation test

Indications: same as above, plus *MEN1* mutation test not available. Including if *MEN1* mutation test has been negative in the index case of a family (10–20% of typical MEN1 index cases have presumed but undetectable *MEN1* mutation).

Method 3—determine MEN1-associated haplotype about *MEN1* locus (chromosome 11q13): requires 2 or more other MEN1-affected family members. MEN1 tumors can also be useful. Assumes correct diagnosis of syndrome and assumes correct assignment of chromosomal locus.

Method 4—kindred evaluation for genetic linkage: If there is uncertainty that the trait in a family arises at the *MEN1* locus, genetic linkage of the trait and the locus can be tested with informative DNA polymorphisms about the locus. Statistical significance requires DNA from 7–10 affected members. This analysis can also be used to examine the 11q13 haplotype of any member (Method 3).

Method 5—MEN1 initial ascertainment through tumor/biochemical expressions: calcium (prefer Ca++), PTH, and prolactin (every 3 yr after age 5). One or more other tests (glucose, gastrin, insulin, proinsulin, glucagon, chromogranin-A) may be added where resources allow this.

Method 6—kindred examination: identify undiagnosed, obligate carriers (*i.e.* they transmitted a dominant trait to an offspring).

The same principles are applicable to screening for the MEN2 carrier.

on the other hand, delay of surgery may promote a simpler operation(s). In addition, although parathyroidectomy has been performed during childhood in MEN1, surgical indications in children have not been established. Preoperative parathyroid tumor imaging has little role in the unoperated MEN1 case because of the need to examine all four glands. Preoperative imaging can be helpful before parathyroid reoperation, and the Tc^{99m} sestamibi (methoxyisobutylisonitrile) scan is the most useful among several methods that may be used alone or in combination (20).

Patients with MEN1 generally have tumors in three or all four parathyroid glands. These tumors are asymmetric in size and should be regarded as independent clonal adenomas (1); an early hyperplastic phase has been suggested, but not proven. The issue of which operation to perform remains controversial. Minimally invasive parathyroidectomy is not recommended, because it does not support the routine identification of all four parathyroid glands. Subtotal parathyroidectomy with transcervical near-total thymectomy (occasionally limited to the thymic horns) is the commonest initial neck operation performed in patients with MEN1. A viable remnant of parathyroid tissue may be left with one of several methods. These include leaving *in situ* about 50 mg of the most normal gland with or without biopsy confirmation of each gland. Alternatively, total parathyroidectomy is attempted with a fresh parathyroid autograft to the forearm. Experienced parathyroid surgeons should have similarly good results (~95% euparathyroidism) with any of these options. Because these operations carry substantial (5–10%) risk of postoperative hypoparathyroidism, parathyroid tissue may be cryopreserved to permit a subsequent autograft procedure. By 8–12 yr after successful subtotal parathyroidectomy in MEN1, HPT will have recurred in 50% of euparathyroid cases (1). This and the young age at initial operations result in frequent parathyroid reoperations as a characteristic of MEN1. To prevent late recurrence, another alternative is

intentional total parathyroidectomy and then life-long treatment by vitamin D analogs. The much higher likelihood of postoperative hypoparathyroidism from this strategy should first be discussed with the patient. Intraoperative measurement of PTH on-line during any initial or repeat surgery is a promising method to test whether parathyroid tumor remains (21).

Calcium-sensing receptor agonists (calcimimetics), a new and novel class of drugs, can act directly on the parathyroid gland, decrease PTH release, and perhaps even decrease parathyroid tumor growth. They are under investigation and might acquire an important role in treatment of HPT, possibly including HPT in MEN1 (22).

Entero-pancreatic islet tumors in MEN1. The prevalence of entero-pancreatic islet tumors in MEN1-affected individuals varies in different clinical series from 30–75% and approaches 80% in necropsy series (1, 23, 24). A pancreatic islet tumor typically can cause symptoms from hormone excess after the age of 40 yr, even though biochemical or imaging tests make it possible to diagnose some tumors in asymptomatic carriers by the third decade. The entero-pancreatic islet lesion of MEN1 is characteristically multicentric and ranges from microadenomas, to macroadenomas, to invasive and metastatic carcinomas; islet cell hyperplasia is rare (25). The lesions arise in any part of the pancreas or as foci throughout the duodenal submucosa. The majority of gastrinomas with MEN1 are in the duodenum, where they are often small (<0.5 cm in diameter) and multiple (26). The pancreatic islet tumors contain, in decreasing frequencies and in differing combinations, chromogranin A or B, pancreatic polypeptide, glucagon, insulin, proinsulin, somatostatin, gastrin, VIP, serotonin, calcitonin (CT), GH-releasing factor, and neurotensin (25). Malignant islet disease in MEN1 is rare before age 30 yr, but is present in occult form in about half of middle-aged patients. No available markers identify the cases at highest risk for development or progression of these malignant lesions.

Gastrinomas are present in about two fifths of MEN1 patients; about one fourth of all gastrinoma cases have MEN1. MEN1 gastrinomas usually include a malignant component, and half have metastasized before diagnosis (26–28). One third of sporadic and MEN1-associated ZES cases eventually die from their malignancy. The correlates of a poor prognosis are pancreatic (not duodenal) primary lesions, metastases (lymph node, liver, or bone), ectopic Cushing syndrome, or the height of the gastrin level (29). The diagnosis of gastrinoma is established when there is a combination of high serum gastrin and elevated gastric acid output (Table 2).

The number of hormonal analyses used in diagnosing entero-pancreatic tumors in MEN1 varies greatly among experienced endocrinologists. A representative biochemical screening program for tumors in likely *MEN1* mutation carriers includes fasting glucose, gastrin, insulin, proinsulin, glucagon, and chromogranin A (30) (Table 2). Some groups may include all or some among hCG α- and β-subunits, VIP, and a meal-stimulated test with measurements of gastrin and pancreatic polypeptide. False positives include high proinsulin/insulin levels in patients developing insulin resistance or hypergastrinemia in patients with hypochlorhydria. Tests with abnormal results should be repeated. Subsequently, more detailed testing may be indicated: basal acid output and/or secretin-stimulated gastrin[4] for suspected gastrinoma (31), 72-h fast protocol for insulinoma, *etc.* Somatostatin receptor scintigraphy ([^{111}In]indium-diethylenetriamine pentaacetic acid-octreotide scan) is a proven method to image neuroendocrine tumors (32); however, it is highly sensitive and to date lacks full evaluation in MEN1. It should lead to surgical consideration only after confirmation with a different test, such as computed tomography or magnetic resonance imaging. Endoscopic ultrasound has been successful as another sensitive method to evaluate the locations of islet tumors (33), but this method still needs evaluation in the complex setting of MEN1.

Except for the insulinoma syndrome, all of the various hormone excess syndromes caused by the entero-pancreatic lesions in MEN1 respond well to medication. Proton pump inhibitors or occasionally H_2 receptor blockers (for gastrin) (19) and somatostatin analogs (for several hormones other than gastrin) effectively prevent severe and sometimes life-threatening morbidity in MEN1. Surgery is the main treatment in MEN1 patients with hypoglycemia due to insulinoma. Even in the absence of positive preoperative imaging, the insulinoma is usually identified readily through intraoperative ultrasonography. There is no consensus whether one or several insulinomas cause the hypoglycemia, because patients with MEN1 often have several associated islet macroadenomas with uncertain hormonal secretions.

The use of imaging for the staging of gastrinomas must depend upon the philosophy about surgical intervention for this. Because of the small size and multiplicity of duodenal gastrinomas, the methods most sensitive for the pancreatic islets ([^{111}In]indium-diethylenetriamine pentaacetic acid-octreotide scan and endoscopic ultrasound) still have low sensitivity for MEN1 gastrinomas (32, 34). The preferred treatment of a solitary, sporadic gastrinoma is surgical excision of the gastrinoma. However, gastrinomas in MEN1 are frequently multiple and/or metastatic, and the role of surgery is controversial (28, 35, 36). For example, in one large study only 16% of MEN1 patients were free of disease immediately after gastrinoma surgery, and at 5 yr this had declined to 6%; the disease-free rates in gastrinoma without MEN1 were far better at 45% and 40%, respectively (28). Most internists favored nonsurgical management of gastrinomas in MEN1, whereas about half of the surgeons favored surgery. With few centers reporting surgical success with gastrinomas in MEN1, gastrinoma surgery aimed at cure should be limited to research settings.

There is controversy over the roles of entero-pancreatic surgery for asymptomatic patients with MEN1. Several groups advocate that MEN1 patients not undergo preventive surgery unless one tumor is more than 3 cm or is growing (36). Most groups do not require such substantial tumor burdens, and many recommend operation if the imaged lesion is 1 cm (31, 37). Several believe that as the goal in MEN1 is cancer prevention, surgery should be performed if the biochemical diagnosis is unequivocal, even without other

[4] Secretin peptide for iv testing is not currently available in any country.

signs (2). Metastatic disease is likely to be present in a substantial fraction of patients receiving even the earliest surgery without a positive imaging test (2). The standard surgical procedure, other than for gastrinoma, includes distal pancreatic resection combined with intraoperative ultrasonography and bidigital palpation for enucleation of tumors in the pancreatic head and duodenal submucosa. With improvements in intraoperative ultrasound, many surgeons limit surgery to enucleation of one or more islet macroadenomas in MEN1. Dissection of lymph nodes along the celiac trunk and hepatic ligament is also warranted (38). Duodenotomy is included mainly for patients with elevated secretin-stimulated gastrin levels (see Footnote 4) (34). If the main tumor burden is located to the head of the pancreas, a Whipple procedure may be considered (39). Extensive pancreatico-duodenal procedures are associated with substantial risks. Thus, the indications for the intervention, the potential benefit, and surgical skill must be considered in each case. The impact of liver resection or formal lobectomy on survival in MEN1 patients with metastatic entero-pancreatic lesions has not been assessed, and the experience is limited. Systemic antitumoral and radiation therapies have been examined only in preliminary ways in islet tumors, even less in tumors of MEN1 (40–42).

Pituitary tumors in MEN1. Anterior pituitary adenoma is the first clinical manifestation of MEN1 in up to 25% of sporadic cases (43), but in less than 10% of familial cases diagnosed prospectively. Its prevalence in MEN1 varies from 10–60% (1, 4, 43, 44), this wide range being mainly due to the differing patients and methods in the various studies. About two thirds of tumors are microadenomas (diameter, <1 cm). Every type of anterior pituitary adenoma, except the true gonadotropinoma, has been reported in MEN1 (1, 7, 44) (Table 1). In a likely MEN1 carrier, periodic monitoring should include serum basal levels of PRL (obtained from an indwelling venous cannula after a rest period of 2 h) and IGF-I as well as imaging of the pituitary by magnetic resonance imaging (Table 2). Undiagnosed pregnancy causes a confusingly high PRL. In patients with abnormal results, hypothalamic-pituitary testing should characterize further the nature of the pituitary lesion and its effects on the secretion of other pituitary hormones. Treatment of pituitary tumors in MEN1 varies according to the type of the adenoma and is identical to that in sporadic pituitary tumor. Finally, even in successfully treated patients, pituitary tumor screening should continue (Table 2), as the remaining pituitary tissue may cause recurrence.

Less common expressions of MEN1. All or most MEN1 carcinoids originate in the foregut. MEN1 thymic carcinoid is seen predominantly in males (45). Patients can be asymptomatic until a late stage. The course of thymic carcinoid appears more aggressive with MEN1 than without it. MEN1 bronchial carcinoid is mainly in females. Computed tomography or magnetic resonance imaging is recommended similarly for early diagnosis of thymic or bronchial carcinoid. Type II gastric enterochromaffin-like (ECL) cell carcinoids are recognized mainly incidental to gastric endoscopy for ZES in MEN1, and they are common in MEN1 (46, 47) (Table 1). The tumors are usually multiple, smaller than 1.5 cm, and associated with proliferation of extratumoral ECL cells, from which the tumors (gastric carcinoids = ECLomas) are presumed to originate (48). Compared with other MEN1-related tumors, little is known about their malignant potential (49). Foregut carcinoids in MEN1 rarely hypersecrete hormones. Little is known about the optimum treatment for MEN1 carcinoids, because of the rarity of reported cases and trials.

Adrenal cortical lesions are common (20–40%) in MEN1; the majority are bilateral, hyperplastic, and nonfunctional (2, 5, 50, 51). Adrenal pathology may include cortical adenoma, diffuse hyperplasia, nodular hyperplasia, or even carcinoma. Hyperaldosteronism has been reported (52). Most of the adrenal enlargements exhibit an indolent clinical course (50, 51). Consensus has not been reached about management of MEN1-associated adrenocortical lesions.

Lipomas, both cutaneous and visceral, are observed in up to one third of MEN1 patients (1, 4, 53). Lipomas in MEN1 are encapsulated (nodular). Small or large lesions are usually multicentric and cosmetically disturbing (54). When removed, they typically do not recur. Large visceral lipomas are noted occasionally. Multiple facial angiofibromas occur in 40–80% of MEN1 patients, with half the cases having five or more; collagenomas are also common (53, 55). Cutaneous tumors have been suggested as possibly helpful for presymptomatic diagnosis of MEN1 carriers (53).

Screening of DNA OR of tumor expressions in diagnosis of the MEN1 carrier. The *MEN1* gene is located at chromosome 11ql3 and consists of 10 exons with a 1830-bp coding region that encodes a novel 610-amino acid protein, referred to as menin (1, 56–58). Menin resides mainly in the nucleus (59). Its first documented interaction partner was the activating protein 1 transcription factor JunD (60). Other proteins that interact with menin are under investigation. Genetic linkage studies have suggested that the familial MEN1 trait always arises from the same chromosomal locus at chromosome 11q13 and thus always from the same gene (61). Studies of *MEN1* germline mutation have supported this (1, 8, 10, 62, 63).

MEN1 mutations are scattered in and around the open reading frame of menin and are diverse in their types; approximately 25% are nonsense, approximately 45% are small deletions, approximately 15% are small insertions, less than 5% are donor-splice mutations, and approximately 10% are missense mutations, predicted to change one to three amino acids in menin (1, 8, 10, 62–64). *MEN1* mutation usually predicts menin protein absence or truncation (the "first hit"). The presumed unifying mechanism for tumor formation in MEN1 involves loss of menin functions in a tumor precursor cell. The first hit is inherited and therefore is present in every cell of the body; it is generally silent until the first tumor develops. It conveys an autosomal dominant predisposition to neoplasia in certain tissues. When the first hit is combined with a somatic or postnatal loss of the other copy of *MEN1* (named the second hit and frequently involving the loss of a large segment or all of chromosome 11) in one cell, neoplastic clonal expansion from that cell is initiated. These findings represent biallelic *MEN1* gene inactivation, synonymous with a tumor suppressor mechanism for oncogenesis

by the *MEN1* gene (1, 56). Similar loss of function of both *MEN1* copies is also important in the development of about one fourth of sporadic or common variety tumors of the types seen in MEN1 (1, 64–66). In this latter situation both the first hit and the second hit occur in somatic cells and independently. The finding of similar inactivation mechanisms for both *MEN1* copies in virtually all MEN1 tumors and in many sporadic tumors has established a central role for the *MEN1* gene in these tumors. Unlike the *RET* gene, the *MEN1* gene shows no relation between the detailed sequence of the mutation (either the first hit or the second hit) and the tumor behavior sporadically or in MEN1 (1, 8, 10, 62, 67).

Several analytic approaches to the *MEN1* locus have been used, but most laboratories currently use direct DNA sequencing strategies (Table 3). The first step in the analysis of a sporadic case or patients in a kindred with suspected or proven hereditary MEN1 is to identify the specific *MEN1* mutation in germline DNA derived from a peripheral blood sample from one affected index case. In a kindred with suspected MEN1 but with no living affected member, consideration should be given to obtaining germline DNA from one deceased, presumably affected member. Because *MEN1* somatic mutation is found in common endocrine tumors (1, 64–66), tumor DNA is rarely useful as an index of the uncommon *MEN1* germline mutation. *MEN1* carrier testing should be performed preferably with specimens, such as blood leukocytes, that better represent the germline. In most index cases of familial MEN1, a mutation of *MEN1* will be identified. Subsequent analysis of other family members at risk will be simplified by testing selectively for the *MEN1* mutation that has already been found to be specific for that family (Table 3).

Most larger series have failed to find *MEN1* germline mutation in 10–20% of index cases for familial MEN1 (1, 8, 10, 62, 63). Such failures are likely to reflect mutation in the untested parts of the *MEN1* gene or large deletions that are transparent to PCR amplification methods. In an MEN1 family with no identifiable germline *MEN1* mutation, haplotype analysis around the *MEN1* locus at chromosome 11q13 can allow screening for the MEN1 carrier status (Table 3). Haplotype analysis requires the strong presumption that the familial trait arises in the *MEN1* gene (61) as well as the availability of DNA from at least two more affected members. An MEN1 tumor can contribute to haplotype analysis, as loss of the wild-type alleles at 11q13 results in the tumor displaying only the mutation-linked 11q13 alleles (68). In contrast, in haplotype analysis of the *RET* locus for MEN2 carriers, tumors are usually not applicable because of the different ways in which the *MEN1* and *RET* genes contribute to tumors. Specifically, loss of the normal *RET* allele in tumors of MEN2 is uncommon (69). If there is uncertainty about the nature of the syndrome in a family, then genetic linkage between the trait and the *MEN1* locus can be tested. Statistical significance of the linkage result requires DNA from 7–10 affected members. Linkage or haplotype analysis is predictably more difficult in the 10% of families in whom the *MEN1* germline mutations are newly arisen (62).

When DNA-based testing for the MEN1 carrier state is not helpful, individuals at 50% risk (first degree relatives of an MEN1 case) of being an MEN1 carrier should have compressed biochemical testing [calcium (preferably ionized), PTH, and PRL] for MEN1 carrier ascertainment every 3 yr (Table 3). MEN1-specific skin tumors need more exploration as indicators of the MEN1 carrier state (53, 55).

Indications for MEN1 mutation testing. Indications for germline *MEN1* testing are under development. Testing can be offered to index cases with MEN1 or with atypical MEN1 and to their relatives; other cases have indications for testing that derive from their possibly high likelihood of germline *MEN1* mutation in as yet untested categories (Table 3). A careful assessment of sporadic cases must first exclude those that prove unexpectedly to have familial MEN1. Candidates for testing should include any sporadic case with two or more MEN1-related tumors. Some cases with sporadic tumor combinations, such as parathyroid and somatotroph, have unexpectedly low frequency of *MEN1* mutation (70). There are limited data on the frequency of an *MEN1* germline mutation among the common cases with apparently sporadic tumor in one organ. The frequency of *MEN1* germline mutation with a tumor, presumed to be sporadic based on family evaluations, is speculated as follows: parathyroid adenoma (1%), gastrinoma (5%), prolactinoma (1%), foregut carcinoid (2%), lipoma (0.1%), and angiofibroma (1%) (1, 17). The likelihood of *MEN1* mutation is higher with younger onset age for the tumor or with tumor multiplicity in that organ. These estimates suggest that a high importance would go to testing the presumably sporadic gastrinoma case due to higher mutation yield and the special impact of a discovered *MEN1* mutation on decisions about gastrinoma surgery.

Protocols for periodic screening of tumor expressions in MEN1 carriers. Periodic screening for endocrine tumor manifestations in definite or probable *MEN1* mutation carriers seems likely to help improve management, but, unlike in MEN2, this has not been proven. The age-related penetrance for all features (*i.e.* the proportion of gene carriers manifesting symptoms or signs of the disease by a given age) is near zero below age 5 yr, rising to above 50% by 20 yr, and above 95% by 40 yr (4, 5, 62). Periodic screening for tumors should include assessments of symptoms from the principal tumors. Screening for tumor signs in MEN1 can be difficult and expensive because of large numbers of potentially useful tests. Biochemical screening is recommended yearly, with tumor imaging recommended less frequently (every 3–5 yr; Table 2). The earliest morbid and potentially treatable feature in MEN1 has been an aggressive pituitary macroadenoma at the age of 5 yr (71). Thus, screening should commence in early childhood, and it should continue for life (4, 62). Choices of biochemical tests and imaging modalities should depend on utility, cost, and availability (Table 2).

MEN1 consensus summary statements. 1) MEN1 tumors cause important morbidity through hormone excess (PTH, gastrin, *etc.*) and through malignancies (gastrinoma/islet cell or foregut carcinoid).

2) Medications should control most features of hormone excess (gastrin, PRL, *etc.*). Surgery should control features of excess of some other hormones (PTH and insulin). Surgery has not been shown to prevent or cure MEN1-related cancers.

3) Hyperparathyroidism develops in over 90% of MEN1

carriers. There is controversy over whether parathyroid surgery should be performed for different indications in MEN1 than in sporadic HPT.

4) The preferred parathyroid operation in the HPT of MEN1 is subtotal parathyroidectomy with or without autograft; transcervical, near-total thymectomy is performed simultaneously. Parathyroid tissue can be cryopreserved to retain the possibility of subsequent autograft.

5) Successful surgery for gastrinoma in MEN1 is rare. There is controversy over the primacy of surgical or of nonsurgical management for gastrinomas in MEN1.

6) Surgery in MEN1 is indicated and is usually successful for insulinoma. For most other pancreatic islet tumors, except gastrinomas, surgery is also indicated; however, there was no consensus over tumor criteria for the latter operations.

7) The management of pituitary tumor in MEN1 should be similar to that in sporadic cases.

8) The *MEN1* germline mutation test is recommended for MEN1 carrier identification. All kindreds with MEN1 are likely to have a mutation in the *MEN1* gene.

9) However, *MEN1* germline mutation tests fail to detect 10–20% of those mutations. If a family lacks an identifiable *MEN1* mutation, 11q13 haplotype testing about the *MEN1* locus or genetic linkage analysis can identify MEN1 carriers. Periodic biochemical testing is a less effective alternative when DNA-based tests are not possible.

10) The main candidates for *MEN1* mutation analysis include index cases with MEN1, their unaffected relatives, and some cases with features atypical for MEN1.

11) MEN1 carrier analysis should be used mainly for information. It should rarely determine a major intervention.

12) MEN1 tumor patterns in families do not have clear variants or specific correlations with an *MEN1* germline mutation pattern. Thus, the MEN1 carriers in a family with either typical or atypical expression of MEN1 should be monitored similarly for typical expressions of MEN1 tumors.

13) Biochemical and imaging tests should be carefully chosen from among many options for periodic screening of tumors in MEN1 carriers. Selected biochemical tests are recommended annually, and selected imaging tests less often.

MEN2 syndrome

Classification and mortality. MEN2 is an autosomal dominant syndrome identified to date in 500-1000 kindreds (72, 73). All variants of MEN2 show a high penetrance for medullary thyroid carcinoma (MTC); in fact, 90% of MEN2 carriers will eventually show evidence for MTC (a palpable nodule or a blood CT abnormality) (74, 75). MEN2A is a syndrome of MTC in 90% of adult gene carriers, unilateral or bilateral pheochromocytoma in 50%, and multigland parathyroid tumors in 20–30% (Table 4) (76–79). MEN2A accounts for over 75% of MEN2 (72, 73). Several rare variants of MEN2 include familial MTC (FMTC) (80), MEN2A with cutaneous lichen amyloidosis (81, 82), and MEN2A or FMTC with Hirschsprung's disease (83) (Table 4). MTC is the first neoplastic manifestation in most MEN2 kindreds because of its earlier and overall higher penetrance. Consequently, some small kindreds with MEN2A manifest only MTC and thus have a high probability of being incorrectly designated FMTC, with a resulting danger that pheochromocytoma will not be considered. Categorization of a kindred as FMTC should, therefore, depend on the following rigorous criteria: more than 10 carriers in the kindred, multiple carriers or affected members over the age of 50 yr, and an adequate medical history, particularly in older members. These conservative criteria deliberately misplace small FMTC kindreds in the MEN2A category. MEN type 2B (MEN2B) is the most distinctive and aggressive of the MEN2 variants. MEN2B is characterized by the major neoplasms of MEN2A (MTC and pheochromocytoma), plus decreased upper/lower body ratio, a marfanoid habitus, and mucosal and intestinal ganglioneuromatosis, but not HPT (84, 85). All MEN2 variants are caused by germline mutation in the *RET* gene (72, 73, 86). Furthermore, there are important correlations of MEN2A and MEN2B with selected *RET* codon mutations (87, 88).

In older MEN2A series, with treatment initiated after the identification of a thyroid nodule, MTC progressed and showed 15–20% cancer mortality (89). Carrier diagnosis before adulthood has an impact (proven in long-term studies with measurement of serum CT) that is only now evident. Early thyroidectomy may have lowered the mortality from hereditary MTC to less than 5%, well below the cancer mortality in MEN1; however, the longest follow-up period for prospective CT screening is less than 25 yr (78). Before the recognition of MEN2, sudden death from pheochromocytoma was frequent in these families, perhaps as frequent as death from progression of MTC (76, 77). Sudden death from pheochromocytoma in MEN2 has also been reported more recently (90, 91). However, it is probable that improved management of pheochromocytoma has decreased the rate of premature mortality in MEN2 even more than has the improved management of MTC. Syndromic morbidity is more severe, and mortality is earlier in MEN2B than in MEN2A. Recognition of the most highly aggressive MTC in MEN2B

TABLE 4. MEN2 and its clinical variants or syndromes

Syndrome	Characteristic features
MEN2A	MTC
	Adrenal medulla (pheochromocytoma)
	Parathyroid glands
FMTC	MTC
MEN2A with cutaneous lichen amyloidosis	MEN2A and a pruritic cutaneous lesion located over the upper back
MEN2A or FMTC with Hirschsprung's disease	MEN2A or FMTC with Hirschsprung's disease
MEN2B	MTC
	Adrenal medulla (pheochromocytoma)
	Intestinal and mucosal ganglioneuromatosis
	Characteristic habitus, marfanoid

and recognition of the possibility for early carrier detection have led to thyroidectomy in MEN2B far earlier than before (see below). The two major comorbid MEN2B conditions are MTC (89) and intestinal ganglioneuromatosis (85). Diarrhea from humoral factors produced by MTC combined with gastrointestinal dysmotility from intestinal ganglioneuromatosis can reduce the quality of life to a very low level. Like pheochromocytoma in MEN2A, pheochromocytoma in MEN2B has been virtually eliminated as a major cause of death because of improved management.

MTC in MEN2. MTC is a rare CT-producing tumor of the parafollicular or C cells of the thyroid gland (89, 92). Multifocal C cell hyperplasia is a precursor lesion to hereditary MTC; the progression from C cell hyperplasia to microscopic MTC is undoubtedly variable and may take many years (92). Metastasis may be in the central and lateral, cervical, and mediastinal lymph nodes or more distantly in lung, liver, or bone. The aggressiveness of MTC correlates with the MEN2 variant syndrome and with the mutated *RET* codon (see below). The primary secretory product of MTC is CT, which is important only as an excellent tumor marker (78, 93). CT values (basal or stimulated by pentagastrin,[5] calcium, or both) are nearly always elevated with MTC (94–98). Similarly, elevated CT values after surgery are generally the first sign of persistent or recurrent disease.

Prevention or cure of MTC is by surgery; success is mainly dependent upon the adequacy of the initial operation (99, 100). Therefore, surgery for MTC should be performed, if possible, before the age of possible malignant progression (see below) (73, 78, 101). Family screening sometimes results in MEN2 carrier diagnosis in an adult. If the first operation for MTC is performed in a teenager or an adult, the likelihood of metastasis is necessarily higher. In this situation the physician should be guided by the presentation. If there is an elevated basal or stimulated CT value, the minimum surgical procedure should be total thyroidectomy with central lymph node dissection. A more aggressive neck dissection should be performed if there is evidence of involved lymph nodes in the lateral neck. If the basal or stimulated plasma CT levels are high after primary thyroid surgery, it is important to define the extent of local and distant metastatic disease (102–107). Then, a decision regarding reoperation must be made (108–111). If there is no evidence of distant metastases and if local disease is found or suspected in the neck and/or upper mediastinum, then reoperation is advocated. A successful cure, even years after primary thyroidectomy, is possible by meticulous lymph node dissection of all compartments of the neck and perhaps of the mediastinum. Exploration of the mediastinum is controversial because of the greater morbidity and the few examples of cures. If distant metastases are found, there is no indication for surgical intervention unless the patient develops diarrhea, for which tumor debulking may be beneficial. Unfortunately, standard chemotherapeutic regimens have not proven beneficial in patients with metastatic MTC (112–114), and the tumors are not very sensitive to x-ray or thermal radiation therapy (115, 116). Above all it should be remembered that some patients with substantial burdens of metastatic MTC can remain asymptomatic and live for many years.

Pheochromocytoma in MEN2. Pheochromocytoma in MEN2 may be unilateral or bilateral (117–119). Special problems include the patient who eschews routine screening and the potential of a hypertensive crisis from an unsuspected pheochromocytoma, activated during pregnancy, labor, or delivery. The latter issue can be addressed by routine chemical screening of all female *RET* mutation carriers before or early in the pregnancy. Screening for pheochromocytoma is by measurement of plasma metanephrines or measurement of 24-h collections for urinary catecholamines or metanephrines (120). Analysis of all three will provide the greatest sensitivity and specificity; there was no consensus choice if expense limited the analysis to one test. With high catecholamine or metanephrine levels or symptoms consistent with a pheochromocytoma, a retroperitoneal imaging study (computed tomography and magnetic resonance imaging) should be performed. A majority also uses meta-iodobenzyl guanidine scanning for preoperative localization.

All patients with evidence of excessive catecholamine production should receive appropriate pharmacotherapy (α-with/without β-adrenergic antagonist and/or α-methyl tyrosine) before adrenal surgery. Even patients with demonstrated adrenal tumors but no evidence of biochemical abnormalities should undergo adrenergic blockade. Further advances in adrenal surgery over the past 5 yr have improved the management of pheochromocytoma (119–123). Laparoscopic adrenalectomy is the procedure of choice for patients with unilateral pheochromocytoma (121). With bilateral abnormalities, bilateral adrenalectomy should be performed by open or laparoscopic approach.

Adrenal insufficiency remains a significant problem in patients who have had bilateral adrenalectomy (123). There have been at least four deaths from adrenal insufficiency in MEN2 patients who have had both adrenal glands removed. Patients must be instructed about the parenteral administration of corticosteroids. Furthermore, all patients should be provided with an emergency card or bracelet, indicating the possibility of adrenal insufficiency and the requirement for parenteral corticoid therapy in an emergency. Adrenal cortical-sparing adrenalectomy is a promising technique for preventing adrenal insufficiency (123), but there is limited long-term experience, leading to cautious enthusiasm for the approach.

HPT in MEN2. Primary HPT occurs in 20–30% of MEN2A patients, the highest frequency being with any codon 634 mutation (79). Most cases have no symptoms, although hypercalciuria and renal calculi may occur. HPT is milder in MEN2A than in MEN1. The indications for surgical intervention and the diagnostic criteria are similar to those in sporadic primary HPT (124–127). Although often fewer than four parathyroid glands are enlarged, all glands should be identified at parathyroid surgery. Indications and operation (resection of only enlarged glands, subtotal parathyroidectomy, parathyroidectomy with autotransplantation) should be similar to those in other patients with potential for mul-

[5] Pentagastrin peptide for parenteral testing is currently in very restricted availability.

tiple parathyroid tumors. During thyroid surgery in a normocalcemic patient with MEN2A, the surgeon may encounter one or more parathyroid tumors; these operations should be performed as if there is biochemical evidence of mild HPT.

Testing to diagnose the MEN2 carrier. The *RET* gene is near the centromere of chromosome 10 and encodes a plasma membrane-bound tyrosine kinase enzyme, termed ret. Some mutations activate ret kinase activity, causing oncogenic or transforming properties. *RET* mutation contributes to many papillary thyroid cancers via a nonhereditary somatic rearrangement (termed *RET-PTC* genes), in which promoter sequence from one of eight other genes replaces the *RET* promoter and activates *RET* by causing *RET* overexpression. In contrast, MEN2 results from hereditary *RET* mutations that change one amino acid. The *RET* activation is either by causing ret homodimerization (extracellular domain mutants in most MEN2A) or by activating the ret kinase enzyme's catalytic site (intracellular domain mutants in MEN2B) (73). Some tumors in MEN2 display a second hit, a somatic mutation involving the *RET* gene in the tumor clone precursor cell; the activated *RET* allele is amplified by chromosome 10 duplication in some tumors, or the normal *RET* allele is deleted in some others (69).

MEN2 carrier determination is one of the few examples of a genetic test that mandates a highly effective clinical intervention (73, 78, 101, 128). Consensus was reached at the MEN97 Workshop that the decision to perform thyroidectomy in MEN2 should be based predominately on the result of *RET* mutation testing, rather than on CT testing (129). Several unique features of MEN2 support this recommendation. First, early detection and intervention can alter the clinical course of MTC (78). The development of provocative screening tests based on CT measurement 25 yr ago made it possible to identify routinely and treat early MTC. Follow-up of children operated upon in their teenage years has shown evidence for long-term cure in most. Second, treatment of early MTC by thyroidectomy is well tolerated even by most infants. This contrasts with the complex issues involved in surgical removal of organs in breast-, colon-, or MEN1-associated malignancy. Third, the use of abnormal CT tests to dictate thyroidectomy led to a low, but still problematic, incidence (as high as 5–10%) of false positive tests, with lower incidence in some current immunometric CT assays; false positivity was determined by retrospective testing for *RET* mutation. Fourth, the *RET* test has a higher rate of true positives and lower rates of false negatives and false positives than the CT tests, and it facilitates earlier thyroidectomy.

Indications for RET mutation testing. Sequencing of DNA for *RET* mutation is effective and widely available. The general issues for carrier screening have been reviewed in the context of MEN1 (above) (Table 3). Special points particularly relevant to testing for MEN2 carriers are presented here. Ninety-eight percent of MEN2 index cases have an identified *RET* mutation (130, 131), and testing in no MEN2 family has excluded the *RET* locus. A limited number of MEN2-associated mutations, involving *RET* exons 10, 11, 13, 14, 15, and 16, have been identified. Thus, only these exons must be tested routinely. If this is negative, the remaining 15 exons should be sequenced. This latter analysis is currently available only in research laboratories. If this extended *RET* mutation testing is negative in the index case of a family, the family pattern of MEN2 can give a strong presumption of undiscovered *RET* mutation. Haplotype or genetic linkage testing about the *RET* locus should be considered (Table 3). Periodic tumor monitoring should be performed in some cases with suspected, but unconfirmable, MEN2 carrier state, based on the belief that MEN2 carrier state is plausible and that incorrect exclusion of the diagnosis could be unacceptable. CT testing remains applicable for diagnosis of the carrier state in these unusual situations (see Footnote 5).

The likelihood of a *RET* germline mutation in a patient with apparently sporadic MTC is 1–7% (132). A *RET* germline mutation is more likely if apparently sporadic MTC, such as sporadic pheochromocytoma, has an early age of onset or multiplicity within the thyroid. Because of the modest mutation yield but the critical implications of finding a *RET* mutation, all cases of sporadic MTC should be tested for germline *RET* mutation. This should be performed through a laboratory that analyzes exons 10, 11, 13, 14, 15, and 16. It is particularly important to examine exons 13, 14, and 15, because mutations in these exons are most likely to cause MTC with a low prevalence of pheochromocytoma and, therefore, likely to escape detection as a familial disorder. If this testing is negative the remaining 15 *RET* exons should be sequenced. If no germline *RET* mutation is found, a small risk of hereditary MTC remains [calculated from Bayes' theorem to be the *a priori* probability that an individual with sporadic MTC has a germline mutation (0.07) $\times$ the probability of not identifying a *RET* mutation in a known kindred (0.05) $\times$ the probability that a first degree relative will inherit an autosomal dominant gene (0.5) = 0.00175 or 0.18%]. If the family or the clinician is not reassured by the low probability of hereditary MTC in this clinical situation, provocative CT screening (see Footnote 5) of family members should be considered. Analysis for *RET* mutations in tumor tissue from apparently sporadic cases of MTC has limited value. First, if there has been no peripheral blood available, analysis of DNA from tissue blocks may provide a substitute for germline analysis; however, tissue other than tumor is preferable because A883F (rare) and M918T (25%) mutations occur somatically in sporadic MTC. Second, sporadic tumors with a somatic codon 918 mutation may metastasize earlier and be more lethal (133–136). Whether the availability of a *RET* mutation analysis in the tumor for staging will improve management is unclear.

Heritable causes of pheochromocytoma include MEN2A, MEN2B, von Hippel Lindau disease (VHL), neurofibromatosis type 1, paraganglioma syndrome, and hereditary pheochromocytoma. Estimates of hereditary etiology among apparently sporadic cases of pheochromocytoma range from 5–15% (73). This modest probability and especially the importance of an abnormal mutation finding support performing germline *RET, VHL*, and *NF1* analysis and other screening studies for MEN2 or VHL in any patient with a tumor in this category. If this testing is negative, the remaining 15 *RET* exons should be sequenced. If testing is negative, mutation likelihood can be estimated by Bayes' theorem exactly as

with pheochromocytoma (above). *RET* testing is not indicated in apparently sporadic HPT in the absence of other clinical suspicion for hereditary MEN2. Even in those subjects with a family history of HPT, early onset, or multiglandular HPT, several other hereditary disorders are more likely (see above section on MEN1).

RET protooncogene inactivating mutations account for approximately half the cases of familial Hirschsprung's disease. It is thus surprising that activating mutations of *RET* codons 609, 618, and 620 have also been associated, albeit rarely, with MEN2A and Hirschsprung's disease. In addition, there have been rare cases of Hirschsprung's disease with exon 10 mutations identical to those found in hereditary MTC. Germline mutation analysis of *RET* exon 10 (containing codons 609, 618, and 620) is indicated in all children with Hirschsprung's disease. In those rare cases with potential activating mutation at one of these codons, consideration should be given to prophylactic thyroidectomy, and parents and other first degree relatives should be screened. *RET* codon 918 mutations, like those in MEN2B, have been reported in several children with colonic ganglioneuromatosis. In children with this disorder and a codon 918 mutation or other *RET* activating mutation, consideration should be given to prophylactic thyroidectomy.

Thyroid management based on stratified genetic information. The specifically mutated codon of *RET* correlates with the MEN2 variant, including the aggressiveness of MTC. Thus, the mutated *RET* codon and the features within the family should receive careful attention in planning thyroid management. This discussion stratifies MTC risk, according to the known *RET* mutation. Children with MEN2B and/or *RET* codon 883, 918, or 922 mutation are classified as level 3 or as having the highest risk from aggressive MTC and should have thyroidectomy within the first 6 months and preferably within the first month of life. The finding of microscopic MTC within the first year of life in this setting is common, and metastasis during the first year of life has been described (137–141). Thyroid surgery for MEN2B should include a central node dissection. If metastases are identified, a more extensive node dissection may be appropriate.

Children with any *RET* codon 611, 618, 620, or 634 mutation are classified as level two or as having a high risk for MTC and should have thyroidectomy performed before the age of 5 yr. Total thyroidectomy, including removal of the posterior capsule, should be performed. Early thyroidectomy, with a codon 634 mutation, has helped identify microscopic MTC in a child as young as 2 yr of age (107) and nodal metastasis from MTC in another child at age 5 yr (142). Despite these findings, there was little consensus regarding the need for prophylactic dissection of the central lymph nodes in MEN2A, with differences of opinion between surgeons and internists. Most surgeons favored a central lymph node dissection during the primary operative procedure because of the higher morbidity associated with reentry into the central compartment during a second procedure. Internists were concerned about the higher rate of hypoparathyroidism and recurrent laryngeal nerve damage associated with primary central node dissection. A minority relied on the magnitude of the CT rise after a provocative test, reserving central lymph node dissection for children with abnormal responses. There are no data available regarding the use of radioactive iodine to ablate residual thyroid tissue in early MTC, and there was little enthusiasm for its use.

Children with *RET* codon 609, 768, 790, 791 804, and 891 mutations are classified as level 1 or as having the least high risk among the three *RET* codon mutation stratification categories. They, too, should have a total thyroidectomy. The biological behavior of MTC in patients with these mutations is variable, but, in general, MTC grows more slowly and develops at a later age than with the high risk mutations. However, lymph node metastasis and death caused by MTC have been observed for mutation in each of these except codons 790 and 791. There was little consensus on the management of patients with these mutations. Some recommended a strategy similar to that in the high risk group, with thyroidectomy by the age of 5 yr. Others suggested that thyroidectomy by age 10 yr is appropriate. Still others recommended periodic pentagastrin-stimulated CT testing (see Footnote 5) with thyroidectomy at the first abnormal test result.

Screening for tumor expressions in MEN2 carriers. Because of DNA-based testing, many MEN2 carriers should undergo total thyroidectomy before expressing MTC. However, basal and stimulated CT testing (see Footnote 5) are still useful indexes of tumor mass to screen for or monitor MTC before or after thyroid surgery.

Pheochromocytoma has been found in kindreds with all *RET* protooncogene mutations except those in codons 609, 768, val804met, and 891. Pheochromocytomas have been identified with codon 634 mutations as early as 5 and 10 yr of age. In high and highest risk codons, screening should begin at the age thyroidectomy would be considered or by the age of 5–7 yr, and it should be performed annually. In families with mutation in less high risk codons, especially codons 609, 768, val804met, and 891, screening may be initiated at a later age, and less frequent biochemical screening may be appropriate. The familial pattern of pheochromocytoma should be considered during the development of a screening plan. There was no consensus on the best imaging procedure, although the majority use computed tomographic scanning. A sizable minority thought that imaging studies should be performed every 3–5 yr after the age of 15 yr even in patients with normal biochemical indexes.

With mutation causing any amino acid substitution in *RET* codon 634, patients are more likely to develop HPT (79) and should be screened for this annually. Mutations at codons 609, 611, 618, 620, 790, and 791 are less frequently associated with HPT. Serum PTH and calcium, preferably ionized calcium, should be measured every 2–3 yr or more frequently if there is a family history of HPT. Individuals with codon 768, val804met, and 891 mutations rarely develop HPT, and those with MEN2B (mutation in codon 883, 918, or 922) do not develop HPT.

MEN2 consensus summary statements. 1) MEN2 has distinctive variants. MEN2A and MEN2B are the MEN2 variants with the greatest syndromic consistency.

2) FMTC is the mildest variant of MEN2. To avoid missing

a diagnosis of MEN2A with its risk of pheochromocytoma, physicians should diagnose FMTC only from rigorous criteria.

3) Morbidity from pheochromocytoma in MEN2 has been markedly decreased by improved recognition and management. The preferred treatment for unilateral pheochromocytoma in MEN2 is laparoscopic adrenalectomy.

4) HPT is less intense in MEN2 than in MEN1. Parathyroidectomy should be the same as in other disorders with multiple parathyroid tumors.

5) The main morbidity from MEN2 is MTC. MEN2 variants differ in aggressiveness of MTC, in decreasing order as follows: MEN2B>MEN2A>FMTC.

6) MEN2 carrier detection should be the basis for recommending thyroidectomy to prevent or cure MTC. This carrier testing is mandatory in all children at 50% risk.

7) Compared with *RET* mutation testing, immunoassay of basal or stimulated CT results in more frequent false positive diagnoses and delays of the true positive diagnosis of the MEN2 carrier state. However, the CT test still should be used to monitor the tumor status of MTC. It can be the first index of persistent or recurrent disease.

8) *RET* germline mutation testing has replaced CT testing as the basis for carrier diagnosis in MEN2 families. When performed rigorously, it reveals a *RET* mutation in over 95% of MEN2 index cases.

9) The *RET* codon mutations can be stratified into three levels of risk from MTC (see text). These three categories predict the MEN2 syndromic variant, the age of onset of MTC, and the aggressiveness of MTC.

10) Detailed recommendations about aggressiveness of interventions for MTC are derived from knowledge about the specific *RET* codon mutated and/or from a clear familial pattern.

11) Thyroidectomy should be performed before age 6 months in MEN2B, perhaps much earlier, and before age 5 yr in MEN2A. Policies about central lymph node dissection at initial thyroidectomy are controversial and may differ among the MEN2 variants.

12) Testing (in blood leukocytes) for germline *RET* mutation should be performed in all cases with apparently isolated and nonfamilial (*i.e.* sporadic) MTC or with apparently isolated and nonfamilial pheochromocytoma. A germline mutation is found only occasionally, but such a discovered mutation is important.

13) Tests (in tumor tissue) for somatic *RET* mutation in sporadic MTC or in sporadic pheochromocytoma are generally not recommended for clinical use.

14) Periodic screening for tumors in MEN2 carriers is based upon the MEN2 variant, as characterized by the *RET* codon mutation and by manifestations in the rest of the family.

Issues in genetic counseling of MEN1 of MEN2

Pretest genetic counseling. The counseling issues are similar among all familial cancer syndromes. Before giving or authorizing blood or other tissue for genetic testing, children, adults or the parents of children at risk should be counseled about the implications of genetic testing (143). The counseling session should include a simple discussion about genetic transmission and the probability of inheritance of an autosomal dominant disorder. Risks and benefits should be discussed, including the potential for genetic discrimination in employment and in life or health insurance, privacy issues (including among relatives) related to genetic testing, the potential for genetic testing errors, and potentials for future technologies (*in vitro* fertilization and antenatal testing). Additional topics should include therapy of specific malignancies, therapy of endocrine-metabolic disorders, and the roles of life-long surveillance. Psychological and spiritual support mechanisms should be available. Written consent (assent from children) should be obtained. Posttest counseling should include a review and update of similar issues. If the clinician is not knowledgeable or comfortable discussing these issues, an appropriate referral should be sought. Some issues and some answers will depend on social and national considerations.

Contrasts between mutation tests of the MEN1 gene and the RET gene. MEN1 and MEN2 syndromes have similar names and some similar clinical features. In either setting the properly used germline mutation test will usually establish the presence or absence of the mutation carrier state; this information can be beneficial to the patient and the physician. For example, the exclusion of *MEN1* or *RET* mutation in a family member also precludes periodic screening for tumors in that member. Many other genetic aspects differ strikingly between MEN1 and MEN2 testing (Table 5). The main differences center around two issues. First is the urgency of the test to guide an effective intervention. The decision for a major intervention (in this case, cancer prevention or cancer cure)

TABLE 5. Contrasts between *MEN1* and *RET* germline mutation tests

Test feature	*MEN1* gene	*RET* gene
Information to patient and physician	Yes	Yes
Guides intervention to prevent cancer	No	Yes
Guides intervention to cure cancer	No	Yes
Recommended for child	Maybe[a]	Yes
Chromosomal locus of gene	11q13	10cen
Mutation type to cause tumor	Inactivate	Activate
Genotype/phenotype correlation	No	Yes
Mutation test shortcuts	No	Yes
False negative rate	10–20%	2–5%

[a] Use in child depends partly on philosophy about using a nonessential genetic test in a subject that is not old enough to make an important long-term decision (71, 143). 10 cen, Chromosome 10, centromeric region.

can be clearly mandated by the *RET* mutation test, but almost never by the *MEN1* test. This mandate is due to the tractable biological properties of MTC as well as the completeness and low morbidity of thyroid surgery. The second difference concerns mutation test properties and is less important. MEN2 results from an activating or transforming mutation of the *RET* gene (73); activating mutations can only occur in selected vulnerable *RET* codons and are thus relatively easy to screen for. MEN1 results from inactivating mutations in and around the menin protein's long open reading frame, without major hot spots for mutation. *MEN1* mutations are thus more difficult to screen for (1) unless the mutation in that family is known (Table 3). The combination of greater clinical benefit and greater test simplicity results in more widely recommended application of the *RET* test than the *MEN1* test.

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