

Risk assessment and genetic counseling for multiple endocrine neoplasia type 1 (MEN1)

Thereasa A. Rich, MS, CGC, and Nancy D. Perrier, MD

Department of Surgical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, TX

The purpose of this article is to describe practical ways to identify multiple endocrine neoplasia type 1 (MEN1) at an early stage. MEN1 is a complex hereditary endocrinopathy in which early diagnosis of component tumors can help reduce morbidities associated with longstanding disease and deaths from advanced MEN1-related malignancies. Our experience has been that a diagnosis of MEN1 is often delayed until after the patient has developed a second, often more serious MEN1-related tumor. Due to the progressive nature of MEN1, its rarity, and sometimes nonspecific symptomatology, it is challenging to identify the disease early in patients presenting with MEN1-related conditions such as primary hyperparathyroidism, pituitary adenomas, pancreatic/duodenal neuroendocrine tumors, or foregut carcinoids. To make an early diagnosis of MEN1, a thorough family history and genetic testing of appropriate candidates are needed.

Multiple endocrine neoplasia type 1 (MEN1) is a hereditary condition characterized primarily by the development of tumors of the parathyroid glands (in virtually all patients), endocrine pancreas and duodenum (in up to 75% of patients), and anterior pituitary gland (in 40%–60% of patients). The prevalence of MEN1 is estimated to be 1 in 20,000–1 in 40,000, with approximately 10% of patients being the first affected person in their family.^{1,2}

Because most MEN1-related tumor growth occurs in hormone-secreting glands, tumors often become clinically evident as symptoms related to hormone overproduction. The excess hormone production causes well-defined hormonal syndromes associated with characteristic symptoms and medical sequelae; the hormone overproduction also serves as a sensitive tumor marker that is useful for diagnosing tumors, determining response to therapy, and screening asymptomatic patients.

Table 1 provides an overview of the frequency and clinical features of the most common hormonal syndromes observed in MEN1. Patients can also develop tumors that do not result in hormone overproduction. Symptoms may be due to the mass effect from growth of the tumor itself or from symptoms related to metastases from an endocrine carcinoma. In terms of the number of organ systems involved and the age at onset of tumors and symptoms, both within and between families, MEN1 is highly variable. Age at onset can

vary widely, in part due to the natural variation of the disease, but also due to the absence of symptoms despite tumor growth, as well as failure to correctly identify the cause of symptoms that are present. Most individuals with MEN1 present in late adolescence or early adulthood; however, there are reports of children as young as age 5 presenting with MEN1-related disease, and the diagnosis can be delayed to late in life.^{3,4}

Generally, a clinical diagnosis of MEN1 can be made in individuals who have developed two or more of the classic MEN1-associated tumors (parathyroid, pituitary, endocrine pancreas/duodenum) and in patients who have one classic MEN1-related tumor and a family history of MEN1.⁵ Historically, early diagnosis of MEN1 was not considered advantageous; however, this perception is changing. Diagnostic screening in individuals known to have MEN1 leads to detection of tumors approximately 10 years earlier than without screening.⁶ The aim of screening is to detect abnormalities at a presymptomatic stage, when they are most treatable, with the potential to reduce the morbidities associated with longstanding hormone excess and multiple operations and deaths from advanced malignancies.

Manuscript received May 29, 2008; accepted July 24, 2008.

Correspondence to: Thereasa A. Rich, MS, CGC, Department of Surgical Oncology, Unit 444, The University of Texas M. D. Anderson Cancer Center, 1400 Holcombe Boulevard, Houston, TX 77030; telephone: 713-563-1908; fax: 713-745-1921; e-mail: tarich@mdanderson.org.

Commun Oncol 2008;5:502–510,514 © 2008 Elsevier Inc. All rights reserved.

In 75%–90% of individuals with a clinical diagnosis of MEN1, an inactivating germline mutation of the *MEN1* gene—located on chromosome 11q13—can be identified through sequencing of the coding region (exons 2 through 10). Another 1%–4% of patients may have a large gene deletion that would require additional testing to detect.^{7–10} MEN1 is inherited in an autosomal-dominant manner. The *MEN1* gene encodes a putative tumor suppressor protein called *menin*, which is thought to be involved in the regulation of DNA replication and repair, transcriptional activation, and chromatin modification.^{11–13} The finding of loss of heterozygosity of chromosome 11 in the majority of MEN1-related tumors supports the role of *MEN1* as a tumor suppressor and is in keeping with Knudson’s “two-hit” model of hereditary tumor syndromes.¹⁴ More than 400 different germline mutations in *MEN1* have been reported and most mutations are unique to individual families.⁹ To date, no significant genotype-phenotype correlations have been identified.

Challenge of making the diagnosis

Early identification of patients with MEN1 is challenging for a number of reasons. First, MEN1 is a progressive disease dependent on age, and a clinical diagnosis may not be evident until more than one MEN1-related tumor has developed. Second, MEN1 is a rare disease and may not be recognized by all physicians and thus are not followed appropriately. Similarly, the diagnosis may have been missed in the patients’ family members. Patients may not always accurately report or know their family history, which can result in missing information that would otherwise lead to recognition and diagnosis of MEN1.

Our experience has been that a diagnosis of MEN1 is often delayed until after the patient has developed a second, often more serious MEN1-related tumor or not made at all in some patients

TABLE 1

Prevalence and clinical features of hormonal syndromes associated with multiple endocrine neoplasia type 1 (MEN1)

Source	Tumor type	Prevalence
Parathyroid gland	Hyperplasia/adenoma (primary hyperparathyroidism)	90% by age 40 ¹⁵
Anterior pituitary adenoma ²³ (30%–75%)	Prolactin-secreting (prolactinoma)	20%
	Growth hormone-secreting	5%
	ACTH-secreting	2%
	TSH-secreting	Rare
	Nonfunctioning	5%
Endocrine pancreas ⁵	Gastrinoma	40%
	Nonfunctioning/PPomas	20%
	Insulinoma	10%
	Glucagonoma	< 5%
	VIPoma	< 5%
Foregut carcinoid ⁵	Bronchial	2%
	Thymic	2%
	Gastric, duodenal	30% of patients with ZES*
Adrenal gland	Nonfunctioning adrenocortical adenoma	50% ³⁹
	Cortisol-secreting adrenocortical adenoma	Rare
	Aldosterone-secreting adrenocortical adenoma	Rare
	Pheochromocytoma	Rare

ACTH = adrenocorticotropic hormone; TSH = thyroid-stimulating hormone; PPomas = pancreatic polypeptide tumors; VIPoma = vasoactive intestinal peptide tumors (Verner-Morrison syndrome); ZES = Zollinger-Ellison syndrome

*Gibril et al. *Medicine* (Baltimore) 2004;83:43–83

who are clearly affected. Other patients present with symptomatic complaints associated with MEN1, which were not previously recognized by those providing medical care. Upon arrival at our tertiary-care center, few patients have previously had genetic counseling or testing or are aware that genetic testing for MEN1 is available. At our institution, a review of family history and genetic risk assessment and testing are integral parts of our evaluation of patients who present with MEN1-related diseases. These evaluations aid in making an early diagnosis of MEN1, so a comprehensive surveillance program can be recommended for affected patients and their at-risk relatives.

In the rest of this article, we describe practical ways to obtain informative medical and family histories, as well as genetic testing strategies to identify MEN1 patients at an early stage.

Collecting an informative medical history: focus on presenting symptoms

The first step in evaluating a patient for MEN1 is to collect pertinent medical records. The type and availability of medical records will depend on the patient’s indication for MEN1 evaluation. Unaffected patients seeking risk assessment regarding a family history of MEN1 may have no pertinent personal medical records, which makes it necessary to collect an accurate family history. Steps for assessing a personal history and the most common presenting features of MEN1 follow.

Parathyroid

Primary hyperparathyroidism is the most common MEN1-associated endocrinopathy and is the first disorder to appear in 40%–90% of MEN1 patients.^{4,15,16} Primary hyperparathyroid-

ism is often detected on routine biochemical screening and is diagnosed in the presence of an elevated or high-normal serum calcium level in concordance with an inappropriately elevated serum parathyroid hormone level. However, a significant percentage of patients report no symptoms, and the diagnosis can be delayed for decades.

In the general population, primary hyperparathyroidism occurs at an incidence of approximately 1 in 2,000, most commonly developing after age 50. Primary hyperparathyroidism is more common in women, with a female-to-male ratio of 3:1.¹⁷ The only known risk factors for hyperparathyroidism are a history of ionizing radiation to the neck, long-term lithium use, and genetic susceptibilities. MEN1 is the main syndromic hereditary susceptibility to primary hyperparathyroidism yet accounts for only about 3%–5% of apparently isolated cases of primary hyperparathyroidism and approximately 25% of cases of apparently isolated familial primary hyperparathyroidism.^{8,18,19} Factors that increase the suspicion of MEN1 are young age at diagnosis (younger than 40 years), multigland involvement, pathology revealing parathyroid hyperplasia, and male gender.^{10,20,21}

As such, it is important to obtain the pathology records for patients who have undergone surgical intervention for primary hyperparathyroidism to determine the number of parathyroid glands that were removed and the histology of parathyroid tumors present. It is also worthwhile to know whether the patient's calcium and parathyroid hormone levels normalized after surgery, as persistent postoperative hypercalcemia may indicate the presence of additional parathyroid tumors or that a normal gland, and not the tumorous gland, was inadvertently removed during the surgery.

For patients with no known history of primary hyperparathyroidism, it is extremely informative to obtain the most recent levels of serum calcium and para-

thyroid hormone. The age-related penetrance of primary hyperparathyroidism in a prospective series of MEN1 patients is approximately 90% by age 40.¹⁵ Therefore, review of laboratory records of calcium and parathyroid hormone levels is one of the most useful tools for evaluating patients for MEN1, particularly for patients who present with apparently sporadic pituitary and/or duodenal or pancreatic endocrine tumors. Evaluating a patient for hyperparathyroidism can be a more sensitive method of screening for MEN1 than genetic testing. For patients older than age 40, the penetrance of hyperparathyroidism in MEN1 is higher than the detection rate of MEN1 genetic testing.

Other hereditary conditions with primary hyperparathyroidism include multiple endocrine neoplasia type 2A and hyperparathyroidism-jaw tumor syndrome. In addition, a benign familial form of hypercalcemia called familial hypocalciuric hypercalcemia (FHH) can be confused with primary hyperparathyroidism. A 24-hour urine collection documenting no evidence of hypocalciuria (urinary calcium excretion less than 100 mg/24 hours) is useful to distinguish primary hyperparathyroidism-related hypercalcemia from FHH.

Pituitary gland

Between 20% and 60% of individuals with MEN1 develop adenomas of the anterior pituitary gland. These adenomas may be the initial manifestation in 10%–20% of MEN1 cases.^{22,23} The most common type of pituitary tumor is prolactin-secreting (ie prolactinoma); however, growth hormone (GH)- and adrenocorticotrophic hormone (ACTH)-secreting pituitary tumors are also observed and tumors may be nonfunctioning (no hormone production).² The preferred method of evaluation for pituitary tumors is MRI. Functional status is determined by biochemical evaluation of basal hormone levels. Prolactinomas are diagnosed with serum prolactin levels greater

than 250 ng/mL. GH-producing tumors are suspected in the presence of high plasma insulin-like growth factor-1 levels (growth hormone levels may be normal or elevated). ACTH-producing tumors are suspected in the presence of excess cortisol production and are best demonstrated by high 24-hour urinary free cortisol and a normal to elevated ACTH level.

In one series, up to 5% of patients with unselected pituitary tumors and up to 15% of patients with a prolactinoma were found to have coexistent primary hyperparathyroidism, and thus they met clinical diagnostic criteria for MEN1.²⁴ However, pituitary adenomas are the least predictive tumor type for classic MEN1, as up to 20% of adults in the general population may have a pituitary tumor detected on MRI²⁵ and pituitary adenomas are common in MEN1 phenocopies.^{26,27} Other known hereditary causes of pituitary tumors include Carney complex and familial isolated pituitary adenomas associated with mutations of the *AIP* gene.²⁸

Endocrine pancreas/duodenum

The prevalence of pancreatic endocrine tumors (PETs) in patients with MEN1 is approximately 80% on autopsy series. However, clinically significant tumors are diagnosed in approximately 30%–75% of patients.^{5,29} In the general population, PETs account for approximately 1%–2% of all pancreatic neoplasms and have been found in up to 1.5% of unselected cases on autopsy series.² MEN1 accounts for the large majority of hereditary cases of PETs; however, von Hippel-Lindau syndrome should also be considered for patients with clinically nonfunctioning (no hormone production) PETs. Rarely, PETs have been associated with tuberous sclerosis.³⁰

Like pituitary tumors, PETs can be functional or nonfunctional. However, unlike parathyroid and pituitary tumors, PETs are usually malignant, except for insulinomas, which are usu-

ally benign.³¹ Currently, PETs represent the most significant source of MEN1-specific morbidity and mortality.³² PETs may also be referred to as pancreatic neuroendocrine tumor, islet cell tumor, or APUDoma. However, “endocrine tumor” is currently the preferred terminology.

By far, the most common functioning PETs in patients with MEN1 are gastrinomas (affecting approximately 40% of patients) and insulinomas (affecting approximately 10% of patients).⁵ In the general population, gastrinomas may occur in the pancreas, duodenum, stomach, or other organs and are diagnosed in the presence of an elevated fasting serum gastrin level, which is usually greater than 1,000 pg/mL. Proton-pump inhibitors can falsely elevate a gastrin level and should be discontinued for at least 2 weeks prior to evaluation of the gastrin level. Insulinomas develop within the pancreas; a diagnosis is suspected in the presence of an inappropriately elevated plasma insulin level when compared with glucose levels, although confirmation of a diagnosis relies on the finding of elevated levels of insulin following a 48–72 hour fast.

Other functioning PETs, including glucagonomas, vasoactive intestinal peptide tumors (VIPomas), and somatostatinomas, are uncommon (less than 5%), even in patients with MEN1. These diagnoses are generally confirmed with fasting serum levels of 1,000 pg/mL or greater of glucagon, 200 pg/mL or greater of vasoactive intestinal polypeptide, and 100 pg/mL or greater of somatostatin, respectively.

Nonfunctioning PETs are also common in patients with MEN1, representing approximately 36% of MEN1-associated PETs in one series; by definition, they do not result in a clinically recognizable hormonal syndrome.³³ If present, symptoms may be related to tumor mass or metastases. Many nonfunctioning PETs do produce a small amount of hormone or will secrete pancreatic polypeptide

(PPoma). Nonfunctioning PETs typically require imaging studies to identify. The imaging modalities used in the evaluation of PETs vary depending on functional status but commonly include computed tomography, MRI, endoscopic ultrasonography (particularly for gastrinomas), octreotide scan, somatostatin receptor scintigraphy, and positron emission tomography.

When evaluating a patient's PET history, it is important to collect records on any presurgical laboratory studies and to ask about symptomatic presentation, which will help determine functional status. In general, the diagnosis of a functioning tumor depends on preoperative laboratory studies and clinical presentation, as histopathologic features are not reliable in distinguishing among tumor types. Functional status is an important consideration, because the risk for MEN1 depends on functional status. MEN1 accounts for approximately 20%–25% of gastrinomas, 13% of glucagonomas, and 7%–8% of insulinomas.^{34–36}

For patients who have undergone surgery for a PET, it is worthwhile to obtain the pathology record to know the type of surgery and the number of tumors present. In contrast to those with sporadic PETs, MEN1 patients typically have multifocal disease; the presence of pancreatic microadenomatosis is a hallmark of MEN1.³⁷ Another consideration is the type of surgery performed. If the patient had an enucleation of the tumor, there would be no additional pancreatic tissue available to evaluate for the possibility of additional tumors. For patients with a history or symptoms suggestive of a gastrinoma, it is important to note whether there was any evaluation of the duodenum. MEN1-related gastrinomas are almost exclusively located within the duodenum, whereas sporadic gastrinomas most commonly occur in the pancreas but may also occur in the duodenum or other locations.³⁸

For patients who have not undergone surgery, it is necessary to note whether

any biochemical evaluation for pancreatic hormones or any abdominal imaging has been performed.

Other sites

A wide variety of other tumor types have been reported in patients with MEN1. Although such tumors are not part of the diagnostic criteria for MEN1, their presence can help support or increase suspicion of a MEN1 diagnosis. These tumors include foregut carcinoids (thymic, bronchial, or gastric, found in 5%–10% of MEN1 patients); typically nonfunctioning adenomas; hyperplasia; “fullness” of the adrenal cortex (up to 50% of MEN1 patients)³⁹; facial angiofibromas (88%); collagenomas (72%)^{40,41}; lipomas (33%); leiomyomas; meningiomas; and spinal ependymomas.^{42–45} Benign thyroid disease is frequently observed in 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.⁴⁶

Because of the high prevalence of angiofibromas and collagenomas in MEN1 patients, and the fact that multiple tumors of these types are rarely seen sporadically, a dermatologic examination can be useful in the evaluation of patients for MEN1, particularly for those who have inconclusive genetic test results or for whom genetic testing is not a possibility.

Collecting an informative family history

To evaluate patients for MEN1, a detailed family history and at least a three-generation pedigree are essential. Because 90% of patients with MEN1 inherit the condition from a parent,¹ the family history must be accurate. Whenever possible, medical records confirming key diagnoses should be obtained; these diagnoses can significantly alter the risk assessment.

Accurate records on MEN1 may not always be available, particularly when the family history consists

TABLE 2

MEN1-targeted history patient questionnaire

Patient: Check all that apply to you or your biological relatives.

Me	My relatives	Condition
<input type="checkbox"/>	<input type="checkbox"/>	Hyperparathyroidism (overactive parathyroid glands)
<input type="checkbox"/>	<input type="checkbox"/>	High calcium level (hypercalcemia)
<input type="checkbox"/>	<input type="checkbox"/>	Kidney stones
<input type="checkbox"/>	<input type="checkbox"/>	Osteoporosis (weak/brittle bones)
<input type="checkbox"/>	<input type="checkbox"/>	Pituitary tumor (a type of tumor in a gland at the base of the brain)
<input type="checkbox"/>	<input type="checkbox"/>	Loss of peripheral vision (tunnel vision)
<input type="checkbox"/>	<input type="checkbox"/>	High prolactin level (hyperprolactinemia) and/or nipple discharge
<input type="checkbox"/>	<input type="checkbox"/>	Cushing's syndrome (increased steroid levels)
<input type="checkbox"/>	<input type="checkbox"/>	Acromegaly (increased growth hormone levels)
<input type="checkbox"/>	<input type="checkbox"/>	Pancreatic tumor or cancer
<input type="checkbox"/>	<input type="checkbox"/>	Gastrinoma, acid reflux, peptic ulcer disease, stomach/duodenal ulcers
<input type="checkbox"/>	<input type="checkbox"/>	Severe diarrhea
<input type="checkbox"/>	<input type="checkbox"/>	Hypoglycemia (low blood sugar level)
<input type="checkbox"/>	<input type="checkbox"/>	Other endocrine gland tumor (for example, thyroid or adrenal gland tumor)
<input type="checkbox"/>	<input type="checkbox"/>	Skin tumor(s)

MEN1 = multiple endocrine neoplasia type 1

of a constellation of MEN1-related symptoms.

As with other hereditary cancer conditions, a MEN1-focused pedigree should include basic information on all first-, second-, and third-degree relatives, including current age/age at death, cause of death if applicable, benign and malignant tumor history, and history of surgery and other major medical history.⁴⁷ By age 50, approximately 95% of affected individuals have biochemical evidence of MEN1, and approximately 80% have MEN1-related symptoms.¹⁵ Therefore, age is an important factor in the analysis of a family history. One must consider whether the patient's family members have lived long enough to have signs and symptoms of MEN1 if the condition is resented in the family and whether they have had biochemical evaluation for MEN1-related conditions.

In family members with a tumor history, it is important to characterize the organ site affected, patholo-

gy, focality, and age at diagnosis. In cases where the patient cannot recall the type of tumor that developed in a relative, it can also be helpful to ask about presenting symptomatology and method of diagnosis and treatment. It can also be helpful to ask whether apparently unaffected family members have a history of some of the more common symptoms related to MEN1 tumor development, such as kidney stones, peptic ulcer disease, chronic diarrhea, or hypoglycemia.

Another important consideration is that the same MEN1-related tumor can be referred to by several different names or symptoms. For example, parathyroid disease could be reported by patients as hyperparathyroidism or an overactive parathyroid. Hypercalcemia could be reported as a high calcium level. Gastrinomas could be reported as Zollinger-Ellison syndrome, peptic ulcer disease, reflux disease, or an intestinal tumor. A comprehensive list of targeted family history ques-

tions is provided in Table 2.

MEN1 risk assessment

Risk assessment for MEN1 involves estimating the likelihood that a given patient has MEN1 by taking into consideration data from personal and family histories as well as an assessment of the utility of genetic testing and evaluation of genetic testing results, when available. Table 3 provides an overview of the likelihood of finding a *MEN1* gene mutation in individuals with various presenting features and tumor combinations, both in index and in familial cases.^{1,4,10,18-21,27,49-59}

Genetic testing for MEN1 is available through several commercial laboratories and can be an extremely useful tool in identifying patients with MEN1 (Table 4). Unlike a clinical diagnosis of MEN1, a diagnosis identified through genetic testing is age-independent and can therefore be made before the appearance of additional MEN1-related disease. Genetic testing is useful to confirm a suspected clinical diagnosis and also to confirm or decrease suspicion of MEN1 in patients with some, but not all features of the disease. Testing is also useful in patients with atypical MEN1. Furthermore, genetic testing can be particularly helpful in young patients whose family members may still be young enough not to have developed symptoms of MEN1, and in individuals for whom the family history is not informative or not available—for example, if the patient was adopted. Table 5 lists the indications for MEN1 genetic testing or referral for MEN1 genetic counseling.

Genetic testing does not replace good clinical judgment, as not all patients with classic MEN1 will have an identifiable mutation. A positive genetic test result is easy to interpret, but a negative test result or a variant result can be more difficult to interpret. Sequencing of the coding exons (numbers 2 through 9) identifies mutations in 75%–90% of patients who meet the clinical diagnostic criteria for MEN1. Detection rates

TABLE 3

Likelihood of detecting a germline *MEN1* mutation by sequencing, based on presenting feature(s)

Study	Year	Familial presentation		Index case only						
		Classic MEN1	FIHPT	PT + PIT + PET	PT + PIT	PT + PET	PIT + PET	PT	PIT	PET
Agarwal ⁸	1997	47/50 (94%)	0/5 (0%)	2/2 (100%)	1/2 (50%)	4/4 (100%)	–	1/2 (50%)	–	–
Lemmens ⁴⁹	1997	9/10 (90%)	–	–	–	–	–	–	–	–
Bassett ¹	1998	43/57 (75%)	–	4/6 (67%)	–	–	–	–	–	–
Giraud ⁴	1998	(updated in Wautot ⁵⁷)	–	7/9 (78%)	1/1 (100%)	1/1 (100%)	–	–	–	–
Dackiw ⁵⁰	1999	8/8 (100%)	–	0/1 (0%)	0/2 (0%)	0/3 (0%)	–	–	–	–
Hai ⁵¹	1999	16/16 (100%)	–	–	–	–	–	–	–	–
Poncin ⁵²	1999	9/10 (90%)	1/1 (100%)	5/8 (63%)	1/6 (17%)	0/1 (0%)	–	–	–	–
Bergman ⁵³	2000	11/12 (92%)	1/5 (20%)	1/1 (100%)	0/4 (0%)	–	–	0/1 (0%)	–	0/1 (0%)
Hai ²⁷	2000	–	–	4/5 (80%)	1/9 (11%)	3/5 (60%)	0/1 (0%)	–	–	–
Uchino ¹⁸	2000	–	–	–	–	–	–	3/64 (5%)	–	–
Villablanca ⁵⁴	2002	–	2/7 (29%)	–	–	–	–	–	–	–
Wautot ⁵⁵	2002	165/170 (97%)	–	–	–	–	–	–	–	–
Cebrian ⁵⁶	2003	25/28 (89%)	–	4/4 (100%)	4/16 (25%)	2/7 (29%)	0/1 (0%)	–	–	–
Langer ⁵⁷	2003	–	–	–	–	–	–	2/15 (13%)*	–	0/8 (0%)*
Warner ¹⁹	2004	–	5/22 (23%)*	–	–	–	–	–	–	–
Cardinal ²¹	2005	41/49 (84%)	5/23 (22%)*	–	–	–	–	1/11 (9%)*	–	–
Klein ⁴⁸	2005	N/A (76%)	4/24 (16%)	2/2 (100%)	0/10 (0%)	4/6 (67%)	0/2 (0%)	–	–	–
Ellard ²⁰	2005	10/11 (91%)	6/17 (35%)	9/13 (69%)	3/37 (8%)	10/17 (59%)	0/3 (0%)	0/16 (0%)	0/9 (0%)	0/4 (0%)
Cetani ⁵⁸	2006	–	3/7 (43%)*	–	–	–	–	–	–	–
Mizusawa ⁵⁹	2006	–	1/11 (9%)	–	–	–	–	–	–	–
Tham ¹⁰	2007	24/33 (73%)	–	4/13 (31%)	0/27 (0%)	1/19 (5%)	–	3/48 (6%)	0/7 (0%)	0/19 (0%)
TOTAL		408/454 (90%) [†]	28/122 (23%)	42/64 (66%)	11/114 (9%)	25/63 (40%)	0/7 (0%)	10/157 (6%)	0/16 (0%)	0/32 (0%)

Index case only—no family history of MEN1-related tumors

MEN1 = multiple endocrine neoplasia type 1; FIHPT = familial isolated hyperparathyroidism; PT = parathyroid; PIT = pituitary; PET = pancreatic endocrine tumor; N/A = not available

* All positives had multiple parathyroid tumors.

† Does not include study by Klein et al⁴⁸

TABLE 4

Clinical genetic testing laboratories for MEN1 in the US

Laboratory	Sequencing of coding region (exons 2-10)	Single-site testing	Deletion/duplication analysis	Linkage prenatal/PGD
Genesis Genetics Institute				✓ PGD
Athena Diagnostics	✓			
Boston University				✓ prenatal
GeneDx	✓	✓	✓ Q-PCR	
Reproductive Genetics Institute				✓ PGD
Yale University	✓	✓		✓ prenatal

MEN1 = multiple endocrine neoplasia type 1; PGD = preimplantation genetic diagnosis; Q-PCR = quantitative polymerase chain reaction. Source: www.genetics.org

TABLE 5

Indications for MEN1 genetic evaluation

Patients with any of the following features should be offered MEN1 genetic counseling/testing:

- Two or more classic features of MEN1 (primary hyperparathyroidism, pituitary adenoma, pancreatic/duodenal endocrine tumor)
- One classic feature plus a nonclassic feature (adrenal cortical adenoma or foregut tumor such as carcinoid, lipoma, angiofibroma, or collagenoma)
- One classic feature plus a family history of a classic feature
- Familial primary hyperparathyroidism
- Multiglandular hyperparathyroidism
- Young age (younger than 30–40 years old) at hyperparathyroidism onset
- Multifocal pancreatic endocrine tumors

MEN1 = multiple endocrine neoplasia type 1

Source: Brandi et al⁵

vary, depending on the technique used and the experience of the laboratory. Mutation detection rates are also lower among patients who are the only case of MEN1 in the family (simplex cases) than in familial cases (Table 3).

A significant proportion of individuals with clinical evidence of MEN1 will not have an identifiable mutation, so a negative genetic test result does *not* necessarily rule out a diagnosis of MEN1. In patients with a high index of suspicion of MEN1, a negative genetic test result is uninformative. Most likely, the patient has a mutation of *MEN1* that could not be detected by the particular testing method used. In such cases, additional genetic testing using a different methodology (such as large dele-

tion testing) may occasionally yield a mutation. Genetic testing of the at-risk relatives of affected patients with negative genetic test results is generally not useful for discriminating affected from unaffected individuals. However, in an apparently *de novo* case of MEN1 with negative genetic test results, testing the patient's affected offspring has potential to yield a mutation if the proband has somatic mosaicism (the presence of two or more genotypes in different cell lines).⁴⁸ A strong clinical suspicion of MEN1 should warrant close follow-up regardless of genetic test results. Table 6 reviews the recommended surveillance for patients with a diagnosis of MEN1 and the clinical consequences of a missed tumor diagnosis.

In patients with a low suspicion for MEN1, a negative genetic test result is generally reassuring regarding risk for subsequent MEN1-related tumor development. In patients who do not meet classic criteria for MEN1 but who have a moderate suspicion of MEN1, determining the risk of subsequent diseases is a particular problem if MEN1 mutation testing is negative. In such cases interpretation and collection of family members' medical records become critical. What constitutes appropriate follow-up for patients with a clinical suspicion of MEN1 but negative genetic test results remains a subject of debate.

Occasionally, genetic testing may reveal a genetic variation of uncertain significance. Testing additional affected and unaffected family members sometimes helps to distinguish benign polymorphisms from disease-causing mutations, but usually a degree of uncertainty remains. The clinical management of such individuals is controversial. Interpretation of genetic test results depends on the initial risk assessment, or how likely it is that the patient actually has MEN1 before genetic testing. Genetic testing for variants of uncertain significance is not recommended for the patient's at-risk family members, as the result cannot be used to predict disease risk and therefore should not be used to dictate medical management.

Whenever possible, genetic testing should be initiated in an affected member of the family, because testing unaffected individuals can be uninformative. For example, an unaffected patient with a negative genetic test result may not have inherited MEN1; it is also possible that the patient and family could have a MEN1 mutation that cannot be detected.

Predictive genetic testing for children at risk to inherit MEN1 has been recommended as early as age 5, though there are several important considerations to discuss with parents when deciding the most appropriate age to begin

TABLE 6

MEN1 tumor surveillance recommendations

Tumor	Laboratory studies (annual)	Age to begin, yr	Imaging studies	Clinical consequences of undiagnosed tumor
Parathyroid	Calcium, Ca ²⁺ , PTH	8–20	Sestamibi, CT*	Osteoporosis, nephrolithiasis, renal disease
Gastrinoma	Fasting gastrin	20		Peptic ulcer disease, advanced malignancy
Insulinoma	Fasting glucose, insulin	5–20	CT or MRI*	Neuroglycopenic and/or hyperadrenergic symptoms
Other PETs	Chromogranin A, glucagon, proinsulin	20	Octreotide scan, CT, or MRI†	Hormonal syndrome, advanced malignancy
Pituitary	Prolactin, IGF-1	5–15	Pituitary MRI	Mass effects, reproductive problems, osteoporosis (prolactinoma), acromegaly (GH), Cushing's disease (ACTH)
Carcinoid		20	CT†	Advanced malignancy

MEN1 = multiple endocrine neoplasia type 1; PTH = parathyroid hormone; CT = computed tomography; MRI = magnetic resonance imaging; PETs = pancreatic endocrine tumors; IGF-1 = insulin-like growth factor-1; GH = growth hormone; ACTH = adrenocorticotropic hormone

* Perform if laboratory studies are positive

† Perform every 1–3 years

Source: Brandi et al⁵ and Lakhani et al: *Annu Rev Med* 2007;58:253–265.

testing. Although MEN1-related tumors have developed as young as age 5, onset most commonly occurs from late adolescence to young adulthood. Although early detection of tumors is potentially beneficial to pediatric patients, there is no proof that screening children from a young age actually reduces morbidity and mortality. Life-threatening manifestations of MEN1 are rare in children, there are no available preventive medical interventions, and there is limited experience in treating children with the disease.

Furthermore, genetic testing in children is a sensitive topic. Potentially, test results could lead to psychosocial harms: a child's self image and expectations of life could be altered; a parent's perception of the child as well as the family dynamics. Concerns about future reproduction, life planning, and potential insurance issues could become heightened. Finally, children cannot provide informed consent for genetic testing. According to the American College of Medical Genetics and the American Society of Human Genetics, the decision to undergo genetic testing in such controversial cases should be made by the parents of the child after thorough counseling regarding the risks, benefits, limitations, and special consider-

ations of such testing in children.⁶⁰

Summary

Because of the complexities and nuances of genetic testing and MEN1 risk assessment, genetic testing should be coordinated by a person with clinical expertise in MEN1. In addition, genetic testing must be preceded by thorough counseling regarding the benefits, risks, limitations, and alternatives to genetic testing (Table 7). Patients undergoing genetic testing should understand the purpose of the testing; the natural history of the disease and benefits and limitations of medical management of MEN1; the pattern of inheritance and reproductive consequences; the possible interpretations of a positive, negative, or variant result; the likelihood of a positive genetic test result; the cost of the testing; the potential psychological sequelae associated with a genetic diagnosis; and the issues related to insurance and employment discrimination.⁴⁷ Healthcare providers who are not comfortable with or who have limited experience discussing these issues should refer patients to a genetic counseling service whenever possible.

Acknowledgments: We acknowledge the support of the Roberto and Lucy Faith Fund for Endocrine Re-

search and Treatment at The University of Texas M. D. Anderson Cancer Center, Houston, TX, and the many physicians involved in the care of these patients.

TABLE 7

Benefits, risks, and limitations of genetic testing for MEN1

Benefits

- Confirm diagnosis
- More accurate risk calculation in families with equivocal features
- Early screening for tumors
- Risk assessment for relatives
- Rule out diagnosis (if mutation is known in family)
- Psychological benefit (reduced anxiety due to uncertainty)

Risks

- Potential for insurance/employment discrimination
- Change in family dynamics
- Psychological risks (anxiety, depression, fear, blame, guilt, reproductive anxiety, etc.)
- Financial cost (if not covered by insurance)

Limitations

- Detection rate is less than 100%
- Negative result does not rule out diagnosis
- No preventive options
- Inability to predict disease course
- Limited efficacy of medical interventions
- Potential for uncertain result (variant of uncertain significance)

MEN1 = multiple endocrine neoplasia type 1

References

- Bassett JH, Forbes SA, Pannett AA, et al. Characterization of mutations in patients with multiple endocrine neoplasia type 1. *Am J Hum Genet* 1998;62:232-244.
- Pathology and Genetics of Tumours of the Endocrine Organs. Lyon: IARC Press; 2004.
- Stratakis CA, Schussheim DH, Freedman SM, et al. Pituitary macroadenoma in a 5-year-old: an early expression of multiple endocrine neoplasia type 1. *J Clin Endocrinol Metab* 2000;85:4776-4780.
- Giraud S, Zhang CX, Serova-Sinilnikova O, et al. Germ-line mutation analysis in patients with multiple endocrine neoplasia type 1 and related disorders. *Am J Hum Genet* 1998;63:455-467.
- 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;86:5658-5671.
- Lairmore TC, Piersall LD, DeBenedetti MK, et al. Clinical genetic testing and early surgical intervention in patients with multiple endocrine neoplasia type 1 (MEN1). *Ann Surg* 2004;239:637-645; discussion 645-647.
- Chandrasekharappa SC, Guru SC, Manickam P, et al. Positional cloning of the gene for multiple endocrine neoplasia-type 1. *Science* 1997;276:404-407.
- Agarwal SK, Kester MB, Debelenko LV, et al. Germline mutations of the MEN1 gene in familial multiple endocrine neoplasia type 1 and related states. *Hum Mol Genet* 1997;6:1169-1175.
- Lemos MC, Thakker RV. Multiple endocrine neoplasia type 1 (MEN1): analysis of 1336 mutations reported in the first decade following identification of the gene. *Hum Mutat* 2008;29:22-32.
- Tham E, Grandell U, Lindgren E, et al. Clinical testing for mutations in the MEN1 gene in Sweden: a report on 200 unrelated cases. *J Clin Endocrinol Metab* 2007;92:3389-3395.
- Agarwal SK, Lee Burns A, Sukhodolets KE, et al. Molecular pathology of the MEN1 gene. *Ann N Y Acad Sci* 2004;1014:189-198.
- Agarwal SK, Kennedy PA, Scacheri PC, et al. Menin molecular interactions: insights into normal functions and tumorigenesis. *Horm Metab Res* 2005;37:369-374.
- Balogh K, Racz K, Patocs A, Hunyady L. Menin and its interacting proteins: elucidation of menin function. *Trends Endocrinol Metab* 2006;17:357-364.
- Pannett AA, Thakker RV. Somatic mutations in MEN type 1 tumors, consistent with the Knudson "two-hit" hypothesis. *J Clin Endocrinol Metab* 2001;86:4371-4374.
- Trump D, Farren B, Wooding C, et al. Clinical studies of multiple endocrine neoplasia type 1 (MEN1). *QJM* 1996;89:653-669.
- Schaaf L, Pickel J, Zinner K, et al. Developing effective screening strategies in multiple endocrine neoplasia type 1 (MEN 1) on the basis of clinical and sequencing data of German patients with MEN 1. *Exp Clin Endocrinol Diabetes* 2007;115:509-517.
- Heath H, 3rd, Hodgson SF, Kennedy MA. Primary hyperparathyroidism: incidence, morbidity, and potential economic impact in a community. *N Engl J Med* 1980;302:189-193.
- Uchino S, Noguchi S, Sato M, et al. Screening of the Men1 gene and discovery of germ-line and somatic mutations in apparently sporadic parathyroid tumors. *Cancer Res* 2000;60:5553-5557.
- Warner J, Epstein M, Sweet A, et al. Genetic testing in familial isolated hyperparathyroidism: unexpected results and their implications. *J Med Genet* 2004;41:155-160.
- Ellard S, Hattersley AT, Brewer CM, Vaidya B. Detection of an MEN1 gene mutation depends on clinical features and supports current referral criteria for diagnostic molecular genetic testing. *Clin Endocrinol (Oxf)* 2005;62:169-175.
- Cardinal JW, Bergman L, Hayward N, et al. A report of a national mutation testing service for the MEN1 gene: clinical presentations and implications for mutation testing. *J Med Genet* 2005;42:69-74.
- Carty SE, Helm AK, Amico JA, et al. The variable penetrance and spectrum of manifestations of multiple endocrine neoplasia type 1. *Surgery* 1998;124:1106-1113; discussion 1113-1114.
- Verges B, Boureille F, Goudet P, et al. Pituitary disease in MEN type 1 (MEN1): data from the France-Belgium MEN1 multicenter study. *J Clin Endocrinol Metab* 2002;87:457-465.
- Corbetta S, Pizzocaro A, Peracchi M, et al. Multiple endocrine neoplasia type 1 in patients with recognized pituitary tumours of different types. *Clin Endocrinol (Oxf)* 1997;47:507-512.
- Ezzat S, Asa SL, Couldwell WT, et al. The prevalence of pituitary adenomas: a systematic review. *Cancer* 2004;101:613-619.
- Sakurai A, Katai M, Yumita W, Minemura K, Hashizume K. Clinical and genetic features of patients with multiple endocrine tumors who have neither family history nor MEN1 germline mutations. *Endocrine* 2004;23:45-49.
- Hai N, Aoki N, Shimatsu A, Mori T, Kosugi S. Clinical features of multiple endocrine neoplasia type 1 (MEN1) phenocopy without germline MEN1 gene mutations: analysis of 20 Japanese sporadic cases with MEN1. *Clin Endocrinol (Oxf)* 2000;52:509-518.
- Daly AF, Vanbellinghen JF, Khoo SK, et al. Aryl hydrocarbon receptor-interacting protein gene mutations in familial isolated pituitary adenomas: analysis in 73 families. *J Clin Endocrinol Metab* 2007;92:1891-1896.
- Majewski JT, Wilson SD. The MEN-I syndrome: an all or none phenomenon? *Surgery* 1979;86:475-484.
- Verhoef S, van Diemen-Steenvoorde R, Akkersdijk WL, et al. Malignant pancreatic tumour within the spectrum of tuberous sclerosis complex in childhood. *Eur J Pediatr* 1999;158:284-287.
- Demeure MJ, Klonoff DC, Karam JH, Duh QY, Clark OH. Insulinomas associated with multiple endocrine neoplasia type I: the need for a different surgical approach. *Surgery* 1991;110:998-1004; discussion 1004-1005.
- Doherty GM, Olson JA, Frisella MM, et al. Lethality of multiple endocrine neoplasia type I. *World J Surg* 1998;22:581-586; discussion 586-587.
- Kouvaraki MA, Shapiro SE, Cote GJ, et al. Management of pancreatic endocrine tumors in multiple endocrine neoplasia type 1. *World J Surg* 2006;30:643-653.
- Roy PK, Venzon DJ, Shojamanesh H, et al. Zollinger-Ellison syndrome: Clinical presentation in 261 patients. *Medicine (Baltimore)* 2000;79:379-411.
- Service FJ, McMahon MM, O'Brien PC, Ballard DJ. Functioning insulinoma—incidence, recurrence, and long-term survival of patients: a 60-year study. *Mayo Clin Proc* 1991;66:711-719.
- Soga J, Yakuwa Y. Glucagonomas/diabetico-dermatogenic syndrome (DDS): a statistical evaluation of 407 reported cases. *J Hepatobiliary Pancreat Surg* 1998;5:312-319.
- Anlauf M, Schlenger R, Perren A, et al. Microadenomatosis of the endocrine pancreas in patients with and without the multiple endocrine neoplasia type 1 syndrome. *Am J Surg Pathol* 2006;30:560-574.
- Pipeleers-Marichal M, Somers G, Willem G, et al. Gastrinomas in the duodenum of patients with multiple endocrine neoplasia type 1 and the Zollinger-Ellison syndrome. *N Engl J Med* 1990;322:723-727.
- Waldmann J, Bartsch DK, Kann PH, et al. Adrenal involvement in multiple endocrine neoplasia type 1: results of 7 years prospective screening. *Langenbecks Arch Surg* 2007;392:437-443.
- Darling TN, Skarulis MC, Steinberg SM, et al. Multiple facial angiofibromas and collagenomas in patients with multiple endocrine neoplasia type 1. *Arch Dermatol* 1997;133:853-857.
- Asgharian B, Turner ML, Gibril F, et al. Cutaneous tumors in patients with multiple endocrine neoplasia type 1 (MEN1) and gastrinomas: prospective study of frequency and development of criteria with high sensitivity and specificity for MEN1. *J Clin Endocrinol Metab* 2004;89:5328-5336.
- McKeeby JL, Li X, Zhuang Z, et al. Multiple leiomyomas of the esophagus, lung, and uterus in multiple endocrine neoplasia type 1. *Am J Pathol* 2001;159:1121-1127.
- Vortmeyer AO, Lubensky IA, Skarulis M, et al. Multiple endocrine neoplasia type 1: atypical presentation, clinical course, and genetic analysis of multiple tumors. *Mod Pathol* 1999;12:919-924.
- Asgharian B, Chen YJ, Patronas NJ, et al. Meningiomas may be a component tumor of multiple endocrine neoplasia type 1. *Clin Cancer Res* 2004;10:869-880.
- Calender A, Giraud S, Porchet N, et al.

continued on page 514