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Clinical Guidance

American Association of Clinical Endocrinology Consensus Statement on Management of Multiple Endocrine Neoplasia Type 1

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ABSTRACT

Objective: This document presents the findings of the American Association of Clinical Endocrinology (AACE) on the diagnosis, management, and surveillance of patients with multiple endocrine neoplasia type 1 (MEN1) and associated tumors. The task force included a diverse group of experts in endocrinology, oncology, genetics, surgery, and patient representation. A comprehensive literature review was conducted to address key issues related to the evaluation, surveillance, and treatment of MEN1-related tumors.
Methods: The task force, comprised of 9 members with expertise in endocrinology, surgery, medical oncology, genetics, and patient advocacy, collaborated to develop guidance for the evaluation, surveillance, and management of MEN1-associated tumors. Consensus was defined as $\leq$1 dissenting vote and significant majority as $\geq$75%. Relevant studies were identified through a literature review process, and consensus statements were based on the available evidence.
Results: The task force deliberated on the surveillance, evaluation, and management of MEN1-related tumors including parathyroid, pituitary, and gastroenteropancreatic neuroendocrine tumors and other tumors of relevance. The document also addresses the indications for *MEN1* genetic testing.
Conclusions: This consensus statement aims to offer evidence-informed guidance for health care providers involved in the care of patients with MEN1 and associated tumors. It provides guidance on diagnostic tools, genetic testing criteria, imaging techniques, surgical interventions, and posttreatment monitoring. The practical, patient-centered approach outlined in this document is intended to improve outcomes for individuals with MEN1 and other high-risk endocrine tumors.

Abbreviations: AACE, American Association of Clinical Endocrinology; ACC, adrenocortical carcinoma; BMD, bone mineral density; CT, computed tomography; dpNETs, duodenopancreatic neuroendocrine tumors; eGFR, estimated glomerular filtration rate; GN-MEN1, genotype-negative multiple endocrine neoplasia, type 1; MEN1, multiple endocrine neoplasia type 1; MRI, magnetic resonance imaging; NET, neuroendocrine tumor; NF-pNET, nonfunctioning pancreatic neuroendocrine tumor; PEA, percutaneous ethanol ablation; PET, positron emission tomography; PHPT, primary hyperparathyroidism; pitNET, pituitary neuroendocrine tumor; pNET, pancreatic neuroendocrine tumor; PRRT, peptide receptor radionuclide therapy; PTH, parathyroid hormone; PV/LPV, pathogenic/likely pathogenic variant.

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Disclaimer: This document represents the official position of the American Association of Clinical Endocrinology on the subject matter at the time of publication. Subject matter experts who participated on the task force used their judgment and experience supported by relevant scientific evidence as available. Every effort was made to achieve consensus among the task force members.
Consensus statements are meant to provide guidance, but they are not to be considered prescriptive for any individual patient and cannot replace the judgment of a clinician. We encourage health care professionals to use this information in conjunction with their best clinical judgment. The presented guidance may not be appropriate in all situations. Any decision(s) by health care professionals to apply the guidance provided in this consensus statement must be made in consideration of local resources and individual patient circumstances.

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neuroendocrine tumor
pancreatic neuroendocrine tumor
parathyroid
parathyroid adenoma
pituitary
pituitary neuroendocrine tumor
thoracic neuroendocrine tumor

Statement of Purpose

The purpose of this consensus statement is to provide clinicians with practical evidence-informed guidance for the diagnosis, management, and surveillance of patients with multiple endocrine neoplasia type 1 (MEN1) and associated tumors.

Scope

This American Association of Clinical Endocrinology (AACE) consensus statement presents key questions to address aspects of diagnosis, management, and surveillance of patients with MEN1. Outside the scope of this consensus statement is an in-depth review of the diagnosis, surgical, and medical management, and surveillance of patients with MEN1 and their families. This statement provides practical patient-centered guidance for practitioners who care for patients with MEN1 and related endocrine tumors, some of which have a high mortality risk. This consensus statement does not address or endorse interventions of investigational nature. The statement focuses on tools for diagnosis, indications for genetic testing, biochemical and radiological guidance, surgical approaches, and follow-up. The statement also discusses evidence from randomized controlled trials to support the use of safe and effective therapies and drugs approved by the U.S. Food and Drug Administration at the time of publication for the medical management of patients with MEN1-related tumors and their complications.

Methods

The task force identified the following areas to address in the consensus statement:

1. MEN1-related parathyroid tumors
2. MEN1-related pituitary neuroendocrine tumors (pitNETs)
3. MEN1-related duodenal and pancreatic neuroendocrine tumors (dpNETs)
4. Other MEN1-related endocrine tumors (adrenal, thoracic neuroendocrine tumors [NETs], breast, cutaneous, meningioma, leiomyoma, and ependymoma)
5. *MEN1* genetic testing

The evidence team conducted several literature searches of PubMed using appropriate key words. The searches resulted in 829 abstracts for review. The task force agreed to minimize inclusion of reviews, small case studies, and pediatric populations. Through this initial screening, 182 articles were selected for full text review. Task force members reviewed search results according to the areas identified above (pituitary, parathyroid, dpNET, etc.) and selected relevant studies to support the consensus statement. Furthermore, task force members identified additional relevant studies that were not captured by the literature searches.

Panel Composition and Conflicts of Interest

The AACE membership at large was invited to apply to serve on the task force via a call for authors, in July and August of 2022, on the AACE website. Applications were reviewed by an empanelment workgroup consisting of representatives from the Clinical Practice Guidelines Oversight Committee, PGAN Disease State Network, and Diversity, Equity, and Inclusion Committee. Following selection and approval of the task force chair, the empanelment workgroup worked with the chair to propose the remaining members of the task force with attention to career level, expertise, and experience in guidance document development and diversity, equity, and inclusion considerations.

All proposed task force members were required to submit a task force disclosure of interest form, which requires disclosure of all activities and relationships (eg, speaker's bureaus, consulting, stock ownership, company ownership, research funding, etc.) within the previous 24 months. The Clinical Practice Guidelines Oversight Committee's Conflict of Interest (COI) Subcommittee reviewed all disclosures. Per the AACE COI Policy, 60% of task force members including the chair were determined to have no COI relevant to the topic of the guidance document. A minority of the task force ($\leq$40%) may have COI if deemed manageable by AACE. Further, AACE requires all task force members to avoid taking on additional conflicts during document development and for 12 months after publication.

Following disclosure review and confirmation of eligibility by the COI Subcommittee, the proposed task force was reviewed and approved by the chairs of the Clinical Practice Guidelines Oversight Committee and the AACE president. The task force was finalized in March 2023. This task force included a methodology fellow who supported the literature searches and a patient representative.

Definition of MEN1

For the purposes of developing this consensus statement, persons with MEN1 will be defined as: individuals with a diagnostic genetic test OR a parathyroid adenoma, pitNET, or dpNETs and a first-degree relative with MEN1, OR $\geq$2 endocrine gland tumors (parathyroid, pituitary, or dpNET) and negative genetic testing and no *MEN1* family history.

Introduction

MEN1 is a rare endocrine tumor syndrome prevalent in approximately 1 in 20,000 to 1 in 40,000 individuals with equal sex distribution and no ethnic or racial predilection.[1-3] The cardinal features of MEN1 are parathyroid adenomas with primary hyperparathyroidism (PHPT), dpNETs, and pitNETs. Other less frequent neoplasms seen in MEN1 syndrome include NETs of the thymus, lung, and stomach, adrenocortical tumors, skin lesions (collagenomas and angiofibromas), lipomas, leiomyomas, and meningiomas. Therefore, the phenotype of MEN1 is highly varied as many

unique combinations of endocrine and nonendocrine manifestations are possible.

MEN1 can be diagnosed in 3 ways: (1) autosomal dominant genotype-positive MEN1, defined by identification of a pathogenic or likely pathogenic germline *MEN1* gene (PV/LPV) variant leading to loss of function of the menin protein; (2) clinical MEN1, defined by the manifestation of ≥2 cardinal MEN1 features without genetic confirmation; or (3) familial MEN1, defined by presence of an MEN1-associated tumor in a patient who has a first-degree relative with MEN1. A diagnosis of MEN1 has important implications for family members because first-degree relatives have a 50% risk of inheriting the condition.

While patients with MEN1 have tended to live longer in recent years, they still have shortened overall life expectancies compared with the general population. Two-thirds of patients with MEN1 syndrome die from an MEN1-related cause, and advanced pancreatic neuroendocrine tumors (pNETs) are the most common disease-related cause of death in 40% to 45% of cases.[4] Timely identification and intervention of MEN1-associated neoplasms are needed to reduce the morbidity and mortality associated with this disease. However, the frequency and nature of interventions must also consider the direct medical costs, iatrogenic harms, and psychological burdens to affected patients and families.

Given the rarity and variety of MEN1 disease, the absence of strong medical evidence for several aspects of MEN1 care, and ever-evolving advances in diagnostic and therapeutic methods, current expert medical opinion in this area is invaluable. Yet there is a paucity of updated guidance for front-line practitioners who care for patients with MEN1. This consensus statement summarizes expert opinion for approaching MEN1 diagnosis, management, and surveillance to provide the latest guidance for clinical practice.

Patients with MEN1-Related Parathyroid Tumors

Prevalence and Presentation

PHPT, the most common MEN1 disease manifestation, occurs in approximately 95% of patients, often before 30 years of age, with an equal distribution between men and women.[5] Patients with MEN1 syndrome have a mutated copy of the *MEN1* tumor suppressor gene, which is responsible for producing the menin protein. The loss of heterozygosity results in multigland disease from independent clonal adenomas which manifest typically as 4-gland hyperplasia and PHPT.[6]

Concomitant measurement of parathyroid hormone (PTH), adjusted serum calcium, and serum phosphorus is used to screen for PHPT. PHPT is diagnosed with the combination of hypercalcemia and elevated or inappropriately normal PTH, although normocalcemic PHPT may be noted with a persistently normal serum calcium combined with an elevated PTH without a secondary cause for hyperparathyroidism.[7] An ionized calcium measurement may be considered, especially in normocalcemic PHPT.[7]

Screening

PHPT may be the initial presentation of MEN1, which should be considered in younger patients with PHPT, multiple gland disease, a family history of PHPT or other MEN1 features, and/or recurrent or persistent PHPT. Periodic biochemical screening with serum calcium and PTH may also be considered in patients with other MEN1 manifestations, such as anterior pituitary or pNETs.[8] In patients with MEN1 without PHPT, annual biochemical screening is recommended (Table 1). PHPT is highly prevalent and often the first manifestation of MEN1, and therefore patients with a genetically confirmed *MEN1* pathogenic mutation or with an immediate family history of MEN1 without genetic testing should consider annual biochemical screening for PHPT.[9] MEN1 manifestations have been identified as early as 5 years of age and PHPT has been diagnosed as early as 8 years of age; as such, some have suggested screening for PHPT in early childhood.[5]

Evaluation for Complications After Diagnosis

Once the diagnosis of PHPT is made, evaluation for related skeletal and renal disease should be considered. This would include a 3-site dual-energy X-ray absorptiometry bone mineral density (BMD) scan of the lumbar spine, hips, and distal 1/3 radius and imaging for vertebral fractures, because there is evidence suggesting that BMD is lower in patients with MEN1 versus sporadic PHPT.[10] In addition, evaluation of renal complications with an estimated glomerular filtration rate (eGFR), 24-hour urine calcium, and imaging for nephrolithiasis or nephrocalcinosis is suggested.[7]

Table 1
Screening Frequency of MEN1-Related Tumors

Type of MEN1-related tumor	Age of screening	Screening modality		Frequency
		Biochemistry	Imaging modalities	
Parathyroid	Early childhood (5-8 years)	PTH, calcium, phosphorus	Imaging may be considered if surgery is indicated but no role in diagnosis	Yearly
Pituitary	≥16 years	Prolactin and IGF-1 levels	Contrast-enhanced dynamic MRI	1-3 years
Duodenal and pancreatic neuroendocrine	≥16 years	Hormonal evaluation indicated only if symptoms	Cross-sectional imaging study (CT or MRI of abdomen and pelvis), ^{68}Ga or ^{64}Cu DOTATATE PET CT	1-3 years
Bronchopulmonary/thymic	8-15 years	Hormonal evaluation indicated only if symptoms	Cross-sectional imaging study (CT or MRI of the chest), ^{68}Ga or ^{64}Cu DOTATATE PET CT	1-3 years
Adrenal	≥16 years	Hormonal evaluation indicated if symptoms	Cross-sectional imaging study (CT or MRI abdomen)[a]	1-3 years
Breast cancer	≥40 years	Breast examination	Mammogram	Yearly

Abbreviations: CT = computed tomography; IGF-1 = insulin-like growth factor 1; MEN1 = multiple endocrine neoplasia type 1; MRI = magnetic resonance imaging; PET = positron emission tomography; PTH = parathyroid hormone.
Table 1 provides suggested frequencies of screening for various tumor types. Frequency of screenings and duration over the lifetime of a patient should consider both patient values/preferences in addition to the balance of risks/benefits of the screening modality.
[a] For masses exhibiting Hounsfield unit values between 11 and 20 and measuring <4 cm, paired with a normal hormonal work-up, immediate follow-up imaging is encouraged to preclude the necessity of subsequent imaging. If immediate additional imaging is not feasible, a noncontrast CT or MRI scan should be considered at a 12-month follow-up interval.

Treatment and Related Clinical Considerations

If patients with sporadic PHPT are <50 years of age, have significant hypercalcemia (>1 mg/dL [0.25 mmol/L] above the upper limit of normal) or hypercalciuria (>250 mg/day in women and >300 mg/day in men), have an eGFR <60 mL/min, and/or have skeletal or renal complications related to PHPT, surgery by an experienced parathyroid surgeon is recommended.[7,11] A special consideration in MEN1 is the concern of hypergastrinemia associated with hypercalcemia.[12] However, the timing of surgical intervention is less clear in PHPT associated with MEN1.

Parathyroidectomy Considerations

Imaging has no role in the diagnosis of PHPT, and negative imaging results do not preclude surgery for patients with PHPT.[11] Preoperative imaging options include cervical ultrasound, parathyroid nuclear scan, and multiphase computed tomography (CT) of the neck (4-dimensional parathyroid CT) and may be performed alone or in addition to another study for concordance.

Parathyroid imaging may be less reliable in the setting of multigland disease.[11] Therefore, preoperative localization for an initial open bilateral neck exploration may be of limited benefit given the multiglandular nature of MEN1-associated PHPT. It is estimated that only 7% of patients would have a different procedure based on preoperative localization.[13] On the other hand, many parathyroid surgeons consider 7% significant, and prefer preoperative imaging for surgical planning, including guiding resection and remnant selection given asymmetry in parathyroid gland involvement.[14] In the setting of surgery for recurrent or persistent PHPT in MEN1, preoperative localization is important to help determine the appropriate surgery, including the identification of ectopic disease sites and a better understanding of the risks and benefits of reoperative parathyroidectomy.

If parathyroid surgery is needed, referral to a high-volume center is crucial to optimize surgical outcomes with a goal to durably restore eucalcemia with avoidance of hypoparathyroidism.[14] The optimal surgery for PHPT in MEN1 is a bilateral neck exploration with identification of all 4 parathyroid glands and removal of 3.5 glands with a bilateral cervical thymectomy given the risks of parathyroid tissue within the thymus and thymic carcinoid tumors.[14-16] Of note, all-cause mortality and risk of cancer may be increased in adults with thymus removal, including subjects undergoing para(thyroid) excision (16%).[17] Additional important surgical considerations include the multiglandular nature of PHPT, possibility of asymmetric appearing glands encountered intraoperatively, risk of recurrent PHPT if less than subtotal parathyroidectomy ($\leq$3.5 glands) performed, and risk of hypoparathyroidism.[13,18] Intraoperative PTH monitoring may have limited benefit in patients with MEN1-associated PHPT undergoing initial parathyroidectomy because it will not alter the operative strategy.[19] Finally, although it is assumed that parathyroidectomy in patients with MEN1 will have similar clinical benefits to those expected in sporadic PHPT, there is only limited evidence in regard to improvement in BMD.[20]

Postoperative Surveillance and Monitoring

For MEN1-associated PHPT in which multigland disease is present, lifelong cure may not be possible, and the goal of surgery may be defined as normal calcium homeostasis and an extended time to recurrence rather than cure.[11] Postoperatively, serum calcium should be checked at 6 months to confirm normocalcemia. Although recurrent PHPT is based on hypercalcemia, some patients may have an elevated PTH with normal serum calcium after surgery, which may indicate an increased risk of recurrent PHPT.[21,22] Therefore, annual and long-term follow-up with serum calcium, serum phosphorus, and PTH may be appropriate.[11]

Nonsurgical Management

Nonsurgical management of PHPT in MEN1 includes the use of calcium-sensing receptor agonists such as cinacalcet. Cinacalcet has shown similar safety, tolerability, and efficacy in PHPT associated with MEN1 as seen with sporadic PHPT, with a significant reduction in serum calcium as the primary benefit.[23] Percutaneous ethanol ablation (PEA) is an option in patients with recurrent PHPT, especially if there is a concern for hypoparathyroidism with additional surgery or if cinacalcet is not a viable long-term treatment option. PEA is associated with normocalcemia in most patients, but recurrence of hypercalcemia is common and can require additional PEA treatment.[24]

Patients With MEN1-Related Pituitary Tumors

Prevalence and Presentation

The prevalence of pitNETs or pituitary adenomas in patients with MEN1 varies widely among series and ranges from 35% to 60% based on large cohort studies[25-29] compared with ~10% to 20% in the general population. Most patients present with microadenomas (<1 cm) and functional pitNETs, although nonfunctional pitNETs are present in 28% to 48% of patients.[26-28,30] Median age of onset is approximately 35 years of age, although pitNETs have been reported in patients 5 to 80 years of age.[26,27,31] The hormonal profile for functional pitNETs is identical in patients with MEN1 and non-MEN1 patients, with the exception of plurihormonal tumors that are more common in the former.[32] Prolactin-secreting pitNETs are the most common functional tumor (50%-75%)[26,28,30] followed by either growth hormone secreting (8%-18%)[27,28,30] or plurihormonal-secreting adenomas (5%-18%).[27,30] Adrenocorticotropic hormone-secreting tumors are less common (5%-10%).[26,28,30] Most patients with pituitary microadenomas will be asymptomatic at diagnosis. Patients with functional tumors may be asymptomatic at presentation or have typical signs and symptoms depending on the hormone produced (Table 2). pitNETs in patients with MEN1 were thought to be more aggressive and less responsive to treatment[5,32,33]; however, more recent studies refute this notion.[29] In a large Dutch cohort followed for 16 years, 38.1% of patients with MEN1 were found to have a pitNet (53% of which were diagnosed with screening; the remainder were present before diagnosis of MEN1), and 91% of patients with nonfunctioning pitNETs detected at screening did not require intervention. Furthermore, all patients with prolactinomas responded well to treatment with dopamine agonists.[34]

Screening

Screening for pitNETs is recommended in all patients with MEN1. The most sensitive imaging technique for identification of pitNETs is a contrast-enhanced dynamic magnetic resonance imaging (MRI). ^{68}Ga-DOTATATE positron emission tomography (PET)/CT has not been shown to be sensitive for detection of pitNETs in patients with MEN1.[38] Yearly hormonal testing for prolactin and insulin-like growth factor 1 (IGF-1) levels is recommended[5,27] in addition to pituitary MRI periodically, for example every 1 to 3 years.[5] For cost-effectiveness, and to minimize patient burden, some suggest that routine screening for pitNETs in asymptomatic patients with MEN1 should be delayed until $\geq$16 years of age[39] (Table 1).

Table 2
Functional Pituitary Neuroendocrine Tumors and Medical Therapy

Adenoma type	Biochemical diagnosis	Signs/symptoms	Medical treatment options	Side effects
Lactotroph (prolactinoma)[a]	Elevated prolactin	Premenopausal women: galactorrhea, amenorrhea, infertility Men: decreased libido, erectile dysfunction, infertility	Dopamine agonists: cabergoline, bromocriptine	Nausea, headache, constipation, postural hypotension, dizziness, nasal stuffiness; psychosis and impulse control disorders (rare)
Somatotroph (acromegaly)	Elevated IGF-1, GH may be normal, nadir GH ≥0.4 ng/mL during OGTT[b]	Acral enlargement, frontal bossing, prognathism, jaw malocclusion, macroglossia, headache, hyperhidrosis, arthralgias, oily skin, acne	First-generation SRLs: octreotide LAR, lanreotide depot	Nausea, diarrhea, abdominal pain or distention, cholelithiasis, bradycardia, hyperglycemia, injection site reactions
		Hypertension, type 2 diabetes or prediabetes, obstructive sleep apnea, colon polyps, thyroid nodules, carpal tunnel	Oral octreotide (patients controlled on injectable)	Same as for octreotide LAR but no injection site reaction
			Second-generation SRLs: pasireotide LAR	Hyperglycemia more frequent than first-generation SRLs; other side effects similar
			Dopamine agonists: cabergoline	Same as for prolactinoma
			GH receptor antagonist: pegvisomant	Transaminitis, injection site reaction, nausea, diarrhea, flu-like symptoms
Corticotroph (Cushing disease)	Elevated 24-hour UFC, elevated LNSC, 8 AM cortisol >1.8 mcg/dL after 1 mg dexamethasone at 11 PM	Truncal obesity, facial fullness, gonadal dysfunction, skin atrophy and easy bruising, hypertension, hirsutism, mood disorders, muscle weakness, diabetes or glucose intolerance, osteopenia or osteoporosis	Pituitary-targeted: pasireotide (LAR and SC)	Same as for acromegaly
			Cabergoline	Same as for prolactinoma
			Steroidogenesis inhibitors: Ketoconazole	GI disturbance, transaminitis, gynecomastia, skin rash, AI
			Levoketoconazole	Similar to ketoconazole
			Metyrapone	HTN, hypokalemia, hirsutism, GI disturbance, AI
			Osilodrostat	Similar to metyrapone
			Etomidate (only parenteral agent)	Nausea, vomiting, shock, apnea, AI
			Glucocorticoid receptor antagonist: mifepristone	GI disturbance, headache, hypokalemia, HTN, arthralgia, vaginal bleeding, AI

Abbreviations: AI = adrenal insufficiency; GH = growth hormone; GI = gastrointestinal; IGF-1 = insulin like growth factor 1; LAR = long-acting release; LNSC = late night salivary cortisol; OGTT = oral glucose tolerance test; SC = subcutaneous; SRL = somatostatin receptor ligand; UFC = urine free cortisol.
[a] Transsphenoidal surgery is the treatment of choice when indicated for all pituitary tumors, with the exception of prolactinomas and treatment-resistant prolactinomas.
[b] Thirty percent of patients with acromegaly have nadir GH <0.4 ng/mL during OGTT and healthy, lean individuals and females taking oral estrogen may not suppress.[35-37]

There is currently no consensus in terms of whether patients with pitNETs should be screened routinely for MEN1. It is reasonable, however, to screen for hyperparathyroidism by checking serum calcium level in all patients diagnosed with a pitNET.[40] If hyperparathyroidism is not present, the likelihood of MEN1 is low.[26]

Evaluation

Clinical manifestations of pitNET in patients with MEN1 are similar to those with sporadic cases. Endocrine testing for pituitary hormonal excess should be performed for all patients with pitNETs whether found incidentally on imaging or based on signs and symptoms (Table 2). Prolactin and IGF-1 levels should be checked to screen for prolactinoma and acromegaly, respectively. If signs or symptoms of hypercortisolemia are present, patients should be screened for Cushing disease with a 1-mg overnight dexamethasone suppression test, 24-hour urine free cortisol, and/or late-night salivary cortisol levels.[41] Patients with lesions >6 mm or symptoms should be screened for hypopituitarism with serum free T4, TSH, morning cortisol, IGF-1, testosterone (men only), and evaluation of menstrual history in premenopausal women.[42,43]

Treatment and Related Clinical Considerations

The evaluation and management of pitNETs in patients with MEN1 is similar to treatment in non-MEN1 patients. Endoscopic endonasal transsphenoidal resection remains the first-line therapy for all pitNETs requiring treatment except for prolactinomas.[44]

Patients diagnosed with large pitNETs causing mass effect, acromegaly, or Cushing disease require surgery. Nonfunctional macroadenomas confined to the sella and most microadenomas may be managed conservatively with serial imaging. Medical therapy is first-line treatment in prolactinoma and is an alternative therapy for other functional pituitary adenomas not cured by surgery or for whom surgery is not an option (Table 2).

Surgery for prolactinoma is reserved for patients who are intolerant to or who have tumors that are resistant to medical therapy and may be considered in women with macroadenomas desiring pregnancy. Bromocriptine (2.5-10 mg per day orally) and cabergoline (0.5-2 mg per week orally) are approved by the U.S. Food and Drug Administration for treating hyperprolactinemia and prolactinoma, although cabergoline is the preferred agent because of superior effectiveness and a more favorable side-effect profile. Both are safe for use in patients who are pregnant.[45]

Radiation therapy, most commonly administered to the pituitary tumor as a single fraction (radiosurgery), may be used for recurrent or aggressive nonfunctioning pituitary macroadenomas and second- or third-line treatment in patients with acromegaly or Cushing disease with residual or recurrent disease after surgery; it can also be used concomitantly with medical therapy.[46]

Treatment Risks and Benefits

Surgery for pitNETs provides the highest chance of cure and should be performed by an experienced neurosurgeon at a high-volume center. New endocrine deficiencies occur in 5% to 15% of patients postoperatively.[47] Particularly, arginine vasopressin deficiency, previously called central diabetes insipidus, may occur in ≤30% of patients, but most cases are transient. Other rare complications of surgical intervention may include cerebrospinal fluid leak, hemorrhage, and meningitis.[48]

In patients with MEN1 and in patients with sporadic disease (non-MEN1 patients), incidentally identified pituitary macroadenomas are more likely to enlarge during follow-up compared with microadenomas.[49] Although no randomized controlled clinical trials have demonstrated that serial monitoring with imaging improves outcomes, it is reasonable for macroadenomas to repeat imaging at 6 months, annually for 3 years and then less frequently if stable, and for microadenomas to repeat imaging annually for 3 years.[41,50] One could also consider reassurance without follow-up imaging for microadenomas <5 mm in size[43] because the risk of clinically significant growth is low. In patients with macroadenomas, repeat testing for hypopituitarism should also be performed. Surveillance and monitoring will be more frequent in patients with acromegaly and Cushing disease undergoing treatment to monitor for recurrence and postsurgical complications such as hypopituitarism. All patients who have pituitary surgery should be tested for hypopituitarism, and patients who receive radiation therapy should be monitored long-term because of the risk of delayed hypopituitarism (≤50%).[37]

Patients With MEN1-Related Duodenal and Pancreatic Neuroendocrine Tumors

Prevalence and Presentation

dpNETs occur in 30% to 90% of patients with MEN1.[51] dpNETs can be nonfunctional or manifest as various functional types such as gastrinoma (including in the duodenum), insulinoma, glucagonoma, VIPoma (a rare NET characterized by its secretion of elevated levels of vasoactive intestinal peptide), and somatostatinoma. In patients with MEN1 with Zollinger-Ellison syndrome, duodenal gastrinomas are frequently present, while pancreatic gastrinomas are rarer, accounting for only 25% of cases[51] Moreover, data from the Dutch MEN study group reported that >80% of patients with MEN1 have a dpNET by 80 years of age.[52,53]

The diagnosis of nonfunctioning pancreatic neuroendocrine tumors (NF-pNETs) has become more prevalent because of advancements in imaging technology, and as previously mentioned, the incidence of these tumors tends to rise with advancing age. Functioning pNETs are classified based on the predominant hormone they secrete, which leads to specific clinical syndromes (Table 3). In MEN1, they present at variable ages, with insulinomas most often presenting before 30 years of age and gastrinomas typically manifesting later in life, commonly between the ages of 30 and 51 years.[54,55] Around 15% to 30% of patients with dpNETs experience distant metastases, particularly NF-pNETs and gastrinomas.[54,56,57]

pNETs in patients with MEN1 are typically multiple, nonfunctional, and more commonly <0.5 cm in diameter. Some patients may develop larger pNETs, which, in line with previous observations, are also predominantly nonfunctional. Among functional pNETs, patients with MEN1 are most commonly diagnosed with insulinomas (30% of cases), gastrinomas (<10% are pancreatic), and others such as glucagonomas, VIPomas, and somatostatinomas <5%. Gastrinomas in most patients are generally found in the duodenum and are typically small and sometimes difficult to identify for segmental resection.[58-60] As such, they frequently require surgery to remove the duodenum and part of the pancreas (Whipple procedure) to adequately clear the disease.[61]

Surgery plays a key role in managing hormone excess and preventing the spread of cancer to other parts of the body. Recent studies have shown that pNETs >2 cm and patients >40 years of age are independently associated with an increased risk of developing distant metastasis and mortality.[56] It is agreed upon by experts that surgical intervention in NF-pNETs is warranted for those >2 cm or those showing signs of progression during observation.[51] Moreover, the rate of metastasis is higher in larger NETs related to MEN1, which consequently contributes to an increase in mortality rates. Furthermore, survival rates of patients with dpNETs with liver metastasis are lower (65% at 5 years and 50% at 10 years) compared with patients without liver metastases (95% at 5 years and 86% at 10 years).[57,62]

Occult metastatic disease is also more prevalent in MEN1 syndrome than in patients with sporadic NETs.[63,64] For example, metastases are present in ≤50% of patients with MEN1-associated insulinomas, whereas <10% of non-*MEN1* insulinomas metastasize.[64,65] Overall, two-thirds of patients with MEN1 syndrome die from a MEN1-related cause, most commonly (40%-45%) because of advanced pNETs.[66] In addition, higher mortality in MEN1 compared with the general population or with nonaffected members in MEN1 families is linked to death related to dpNETs and thymic NETs (70%).[5]

Screening

Screening should be initiated at 16 years of age.[5] Routine biochemical and imaging screenings can be extended from 1 to 3 years for asymptomatic patients. A range of 10% to 40% of dpNETs are associated with symptoms specific to the hormone(s) produced in excess. These hormones may include insulin, gastrin, glucagon, and vasoactive intestinal polypeptide, as well as, less commonly, somatostatin, adrenocorticotropin, parathormone-related protein, and growth hormone–releasing factor. Given the low likelihood of detecting elevated hormone levels in the absence of specific symptoms, it is advisable that testing for these hormonal markers be conducted only when clinical presentation indicates a potential hormone excess.[66,67] Cross-sectional imaging studies, such as MRI and CT of the chest/abdomen/pelvis, are typically performed. In addition, functional imaging such as ^{68}Ga or ^{64}Cu-DOTATATE PET/CT can be used to rule out any evidence of a NET that is not visible on anatomic imaging[68,69] (Table 1).

Treatment and Related Clinical Considerations

Medical management of hormone excess in MEN1 dpNETs is similar to the treatment approach recommended for patients with sporadic NETs. For Zollinger-Ellison syndrome, proton pump inhibitors such as omeprazole, lansoprazole, pantoprazole, and esomeprazole can be used to control gastric hypersecretion. Regular monitoring of acid-secretory control every 6 to 12 months is recommended.[70] In cases of metastatic disease, somatostatin agonists may be considered. Insulinoma should be managed by initiating treatment with diazoxide at a dose of 5 mg/kg per day, administered in divided doses every 8 to 12 hours. The typical dosage range is between 3 to 15 mg/kg per day, also administered in divided doses every 8 to 12 hours.[71] In addition, somatostatin agonists can be used as part of the treatment plan (Table 2).[51]

Given the rarity of MEN1-associated advanced dpNETs, the paucity of data available, and lack of well-powered clinical trials, treatment (or management) is based on guidelines for sporadic

Table 3
Management of Functional Neuroendocrine Tumor Syndromes Not Suitable for Primary Surgical Resection

Tumor	Peptide	Symptoms	General measures[a]	Management of advanced/metastatic disease
Insulinoma	Insulin	Hypoglycemia	Frequent small meals rich in complex carbohydrates, continuous oral glucose intake, IV dextrose; reduce insulin secretion: diazoxide; somatostatin analogs: octreotide/lanreotide, pasireotide; verapamil/phenytoin	Everolimus[b]; octreotide/lanreotide; liver-directed therapies: surgery, ablation, embolization; other systemic therapeutic approaches listed in Table 4
Gastrinoma	Gastrin	Ulcers, diarrhea, Zollinger-Ellison syndrome	Omeprazole (40 mg twice daily), pantoprazole (80 mg twice daily), radiation therapy for nonsurgical candidates	Octreotide/lanreotide; liver-directed therapies: surgery, ablation, embolization; other systemic therapeutic approaches listed in Table 4
VIPoma	VIP	Profound watery diarrhea (cholera-like), hypokalemia, hypochlorhydria or achlorhydria, abdominal pain	Repletion of fluids and electrolytes, octreotide/lanreotide, glucocorticoids: prednisone, loperamide	Octreotide/lanreotide; liver-directed therapies: surgery, ablation, embolization; other systemic therapeutic approaches listed in Table 4
Glucagonoma	Glucagon	Weight loss, skin rash (necrolytic migratory erythema), glucose intolerance, DM	Management of DM, nutritional support, infusions of aminoacids and fatty acids, octreotide/lanreotide	Octreotide/lanreotide; liver-directed therapies: surgery, ablation, embolization; other systemic therapeutic approaches listed in Table 4
Somatostatinoma	Somatostatin	DM, cholelithiasis, diarrhea/steatorrhea	Management of DM, loperamide	Octreotide/lanreotide; liver-directed therapies: surgery, ablation, embolization; other systemic therapeutic approaches listed in Table 4
ACTH-dependent, Cushing syndrome	ACTH	Cushing syndrome	Bilateral adrenalectomy, metyrapone, ketoconazole	Octreotide/lanreotide; liver-directed therapies: surgery, ablation, embolization; other systemic therapeutic approaches listed in Table 4

Abbreviations: ACTH = adrenocorticotropic hormone; DM = diabetes mellitus; IV = intravenous; VIP = vasoactive intestinal polypeptide.
[a] Surgery is the treatment of choice when indicated.
[b] Decreases insulin secretion.

dpNETs and case reports demonstrating efficiency of somatostatin agonists, targeted therapies, chemotherapy, and radiologic therapy.[5] In addition, peptide receptor radionuclide therapy (PRRT) with ^{177}Lu-DOTATATE for dpNETs, approved by the U.S. Food and Drug Administration, is an important therapy for somatostatin receptor–expressing NETs. Although the aforementioned therapeutic modalities have proven beneficial in MEN1-associated NETs, treatment options that provide improved progression-free survival over extended periods of time are limited.[51,72] Furthermore, treatment of MEN1-related NETs is more complicated compared with sporadic NETs because of the presence of multifocal tumors within multiple concurrent organs and metastatic disease that may be challenging to definitively trace back to a single primary tumor.[73]

Treatment Risks and Benefits

Treatment for advanced dpNETs in patients with MEN1 is based on the continuously evolving treatment guidelines for sporadic advanced dpNETs. Although there are limited data to inform treatment modality decisions, clinical trials have demonstrated the effectiveness of new therapies in treating advanced NETs. Emerging long-term clinical trial data allows for more accurate assessment of the risks and benefits, especially for patients requiring multimodal therapy in the absence of definitive data, treatment strategy should be based on disease-related factors, such as the origin of the tumor and the extent of the disease, as well as patient-related characteristics, including any other health conditions and patient preferences. The decision-making process for advanced NETs is complex and highly individualized, and there are gaps in evidence regarding treatment selection. Therefore, the management of advanced NETs should involve a collaborative effort between multidisciplinary teams at referring and high-volume centers. Furthermore, both short- and long-term safety should be taken into account when considering therapeutic options (Table 4).

Health care providers need both short- and long-term risk assessments information to accurately assess when choosing initial and follow-up treatments for advanced NETs. The adverse events associated with each therapy over long-term use remained consistent with those observed in the primary clinical trials, and there were no new safety concerns identified during the follow-up period.

Surveillance and Monitoring

Appropriate follow-up is necessary to prevent disease progression. The most important prognostic factors for clinical decision-making in MEN1-related dpNETs are tumor size (larger tumor size is associated with a higher rate of metastasis and decreased overall survival), histologic grading (mitotic count/Ki-67 index), and annual growth rate.[57,73,75-79] It is recommended that surveillance programs prioritize the monitoring of disease progression in patients with dpNETs. The screening frequency should be personalized based on the tumor's growth rate.

Regular follow-up and adjustments to the treatment plan based on the patient's response and disease progression are essential components of managing MEN1 dpNETs effectively. While endoscopic ultrasound is recognized for its high sensitivity in identifying pNETs, it is important to note that this procedure is invasive and may potentially overlook lesions located in the pancreatic tail.

On the other hand, MRI was found to be more sensitive than CT and offers the added benefit of no exposure to ionizing radiation, which is particularly important for a condition requiring lifelong monitoring.[68] Studies have shown that small NF-pNETs (<2 cm) typically grow at a rate of 0.1 to 1.32 mm per year.[68] Therefore, it is generally considered safe to wait 2 to 3 years for repeat imaging after an initial negative scan, unless there are specific clinical indications for earlier evaluation. While many small pNETs progress slowly, some tumors do show growth over time.[68,69,80] Therefore,

Table 4
Dosing Regimens, Tolerability Profiles, and Safety Considerations for Therapeutic Interventions in Advanced Neuroendocrine Tumors[73]

Agent	Dosage	Common AEs	Safety concerns
Octreotide LAR	30 mg every 4 weeks	Incidence >20%: back pain, fatigue, headache, abdominal pain, nausea, dizziness	Risks of cholelithiasis and its complications, hypoglycemia/hyperglycemia, hypothyroidism, cardiac dysfunction
Lanreotide	120 mg every 4 weeks	Incidence >10%: abdominal pain, musculoskeletal pain, vomiting, headache, injection site reaction, hyperglycemia, hypertension, cholelithiasis	Risks of cholelithiasis and its complications, hypoglycemia/hyperglycemia, hypothyroidism, bradycardia
Sunitinib	37.5 mg/day	Incidence ≥25%[a]: fatigue/asthenia, diarrhea, mucositis/stomatitis, nausea, decreased appetite/anorexia, vomiting, abdominal pain, hand-foot syndrome, hypertension, bleeding events, dysgeusia/altered taste, dyspepsia, thrombocytopenia	Hepatotoxicity, cardiovascular events, QT interval prolongation and torsade de pointes, hypertension, bleeding events, tumor lysis syndrome, thrombotic microangiopathy, proteinuria, skin toxicities, reversible posterior leukoencephalopathy syndrome, thyroid dysfunction, hypoglycemia, jaw osteonecrosis, impaired wound healing, embryo-fetal toxicity
Everolimus	10 mg/day	Incidence ≥30%[a]: stomatitis, infections, rash, fatigue, diarrhea, edema, abdominal pain, nausea, fever, asthenia, cough, headache, decreased appetite	Noninfectious pneumonitis, infections, severe hypersensitivity reactions, angioedema, stomatitis, renal failure, impaired wound healing, metabolic disorders, myelosuppression, risk of infection or reduced immune response with vaccination, radiation sensitization and radiation recall, and embryo-fetal toxicity
^{177}Lu-DOTATATE	7.4 GBq every 8 weeks	Grade 3-4 AEs (≥4% with a higher incidence in ^{177}Lu-DOTATATE group): lymphopenia, increased GGT, vomiting, nausea, increased AST, increased ALT, hyperglycemia, hypokalemia	Risks from radiation exposure, myelosuppression (secondary myelodysplastic syndrome and leukemia), renal toxicity, hepatotoxicity, neuroendocrine hormonal crisis, embryo-fetal toxicity, infertility risks
CAPTEM	Capecitabine 750 mg/m^2 BID (days 1-14) + temozolomide 200 mg/m^2 QD (days 10-14); temozolomide 200 mg/m^2 QD (days 1-5)	Grade 3-4 toxicities: thrombocytopenia (3.4%), neutropenia (0.7%), lymphopenia (0.7%), anemia (0.6%), mucositis (0.6%), fatigue (0.5%), diarrhea (0.5%), nausea (0.4%), transaminase elevation (0.1%)	Risks of cardiotoxicity, myelosuppression, coagulopathy, opportunistic infections, diarrhea, dehydration, renal failure, myopathy, severe adverse effects from dihydropyrimidine dehydrogenase deficiency, mucocutaneous and dermatologic toxicity, and hyperbilirubinemia

Adapted from Chauhan et al.[74]
Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyl transferase; LAR = long-acting release.
[a] Incidence reported across various tumor types.

personalized imaging intervals should be established based on individual tumor growth rates. Current evidence supports the use of somatostatin receptor PET-CT (^{68}Ga or ^{64}Cu-DOTATATE) in cases where it can impact treatment decisions, such as in detecting occult metastases in pNETs >10 mm or as part of comprehensive staging before considering further interventions.

Role of Surgery

The appropriate extent and timing of surgery in the management of dpNETs in MEN1 is not well defined. pNETs are thought to affect anywhere between 30% to 80% of patients with MEN1. Surgery is the gold standard to prevent the malignant progression of dpNETs in patients with MEN1 and prevent or resolve hormone-derived endocrine syndromes. Functioning tumors, regardless of size, should be resected. Nonfunctioning tumors can be observed if they are <20 mm, but if they are >20 mm or have significant growth while under surveillance, surgical resection should be strongly considered. Given that there are frequently multiple tumors either at the time of diagnosis or subsequent to having had surgery, pNETs in this population are difficult to treat and parenchymal-sparing surgery is preferred if feasible.

The surgical management of patients with MEN1, in contrast to that of patients with sporadic pNETs, is complicated by the frequent occurrence of multiple tumors of varying types and sizes and high rates of recurrence within a single patient. These tumors are often scattered throughout the pancreas, which may necessitate extensive surgery that poses risks of severe postoperative complications, such as exocrine gland insufficiency and diabetes. Due to the multiplicity of microadenomas, complete removal of all tumors and resolution of the disease are often unachievable through surgery alone. Moreover, given the genetic nature of MEN1 syndrome, the residual pancreas and duodenum are at high risk of development of new dpNETs. Some studies have evaluated the risk of relapse in the residual pancreas after a partial pancreatectomy in patients with MEN1, but the characteristics of the studies were heterogeneous, and the postoperative follow-up was generally <10 years.[81-84] It remains unclear from the current literature whether extensive partial resection of the pancreas has the potential to decrease malignant tumor progression or prevent the emergence of new tumors in the residual gland, especially those with malignant characteristics.

Decisions regarding pancreatic resection must be individualized with consideration of presentation, symptomatology, tumor size, tumor location, growth rates, and the patient's overall health. Studies show that patients with MEN1 who have been treated with surgery have good long-term survival. Five-year overall survival rates can range from 90% to 100% for patients with functional pNETs and 65% to 100% for NF-pNETs postresection. Disease-specific survival is also favorable, with outcomes in the >80% range.[66] As previously mentioned, local recurrence (intrapancreatic and not margin related) of pNETs after surgical resection is common in patients with MEN1 because of the multifocal nature of the disease. In the literature, recurrence rates vary widely but are reported to be ≤50%.[79,85] Local resections or enucleations are options for smaller tumors that are away from the pancreatic duct whereas formal resections, such as pancreaticoduodenectomy (Whipple procedure) or distal pancreatectomy, may be required for larger tumors that are located closer to ductal or vascular structures. In patients who undergo surgery, the risks of surgery—which can include pancreatic leak, exocrine insufficiency, and diabetes—must be discussed with the patient. In short, most studies support the proactive surgical management of pNETs in patients with MEN1, as they can control symptoms and improve outcomes, but given the high rates of recurrence, surgical approaches must be tailored to the patient's clinical presentation, with strong consideration of patient age and burden of disease.

Nonsurgical Management

Although medical therapies for MEN1 pNETs mirror those used for sporadic pNETs, they have not undergone comprehensive

evaluation in broad cohorts of patients with MEN1. Their efficacy has primarily been demonstrated through isolated case reports or small case series. These treatments primarily target hormone hypersecretion and/or tumor growth and encompass pharmacological interventions such as biotherapies and chemotherapies, as well as tumor-targeted radiotherapy like PRRT.[86]

Patients With Other Tumors Related to MEN1

Prevalence and Presentation

MEN1 encompasses a wide range of tumors, including thymic NETs and lung NETs, adrenocortical tumors, lipomas, facial angiofibromas, collagenomas, meningiomas, and others. Thymic NETs have been reported to be almost exclusively in male patients with MEN1,[87] frequently associated with smoking, with a prevalence of 3.7% and a 10-year survival rate of 30%.[88] While commonly a disease found in males, Sakurai et al[89] found a prevalence of thymic NETs in men of 7.6% compared with 3.2% in women, a majority of whom were nonsmokers, suggesting an increased risk of thymic NET in women with MEN1. Lung NETs are associated with MEN1, with a prevalence of 13% among patients who undergo thoracic imaging. The overall 10-year survival rate for thoracic/lung NETs is 71%, although cause of death has not been linked to lung NETs. The tumor volume of lung NETs increases by approximately 17% per year, resulting in an overall tumor doubling time of about 4.5 years. Interestingly, the growth rate of lung NETs is significantly higher in males compared with females.[90]

For adrenal tumors, the incidence of asymptomatic adrenocortical tumors in patients with MEN1 is reported to be 20% to 73%.[91] Adrenal tumors are more often small, nonfunctional, and arise later in the course of the disease.[92] Most of these tumors, including cortical adenomas, hyperplasia, multiple adenomas, nodular hyperplasia, cysts, or carcinomas, are nonfunctioning. Less than 10% of patients with enlarged adrenal glands have hormonal hypersecretion, and among these, primary hyperaldosteronism and cortisol are the most commonly encountered. Hyperandrogenemia may occur in association with adrenocortical carcinoma (ACC), and the occurrence of pheochromocytoma in association with MEN1 is rare. Patients with functional adrenal tumors, as well as those with tumors >1 cm in size on imaging studies, should undergo biochemical evaluation for hormone excess. Notably, the incidence of ACC in tumors >4 cm increases to 31% (ACC is rarely diagnosed, with reported incidence rates varying from 1.1%-7%).[93,94] In addition, patients diagnosed with MEN1 and adrenal tumors should receive annual imaging assessments, with careful consideration for surgical intervention if tumors are >4 cm in diameter, present with atypical radiological characteristics while being between 1 and 4 cm, or demonstrate significant growth over a 6-month period. The approach to diagnosing and managing functional adrenal tumors in individuals with MEN1 aligns with the established guidelines for adrenal incidentalomas. Consequently, it is imperative that rigorous monitoring of adrenal changes in patients with MEN1 be conducted as a standard practice.[92,94,95]

Central nervous system tumors, including ependymomas, schwannomas, and meningiomas, have been reported. Meningiomas are found in <10% of patients with MEN1. Subcutaneous lipomas may occur in >33% of patients with MEN1. In addition, visceral, pleural, or retroperitoneal lipomas may also occur in these patients. Studies of patients with MEN1 have revealed that the occurrence of multiple facial angiofibromas may range from 22% to 88%, and the occurrence of collagenomas may range from 0% to 72%. Breast cancer can occur in 7% (considered at moderately elevated risk) of female patients with MEN1.[96,97]

Screening

While MEN1-associated thymic tumors are usually asymptomatic, they are a significant determinant of survival because of their high malignant potential and accompanying recurrence and distant metastases.[89] Screening should begin at 8 to 15 years of age and should be repeated every 1 to 3 years with low-dose CT or MRI.[5] CT or MRI of the chest every 1 to 3 years is recommended for the screening of thymic and bronchopulmonary tumors.[5,98] For screening of patients with MEN1 for abdominal tumors, such as adrenal nodules, cross-sectional abdominal imaging by CT or MRI should be considered every 1 to 3 years.[98]

The evaluation of adrenal masses regarding the risk of malignancy represents an essential component in the management of adrenal tumors. A homogeneous profile with Hounsfield units (HU) of ≤10 on noncontrast CT indicates a benign adrenal mass. In such scenarios, no additional imaging is necessary. For masses exhibiting HU values between 11 and 20 and measuring <4 cm in size, paired with a normal hormonal work-up, immediate follow-up imaging is encouraged to preclude the necessity of subsequent imaging later on. If immediate additional imaging is not feasible, a noncontrast CT or MRI should be considered at a 12-month follow-up interval.[99-102]

Masses that are ≥4 cm in size or that demonstrate heterogeneous features or HU values >20 indicate a considerable risk for malignancy. In these instances, it is advisable to review the cases within a multidisciplinary team meeting. Generally, immediate surgical intervention is preferred; however, additional imaging may be warranted for certain patients. Comprehensive staging, including thoracic CT and/or fluorodeoxyglucose-PET/CT, should be ensured before surgical intervention. If surgery is deemed unnecessary, follow-up imaging should be scheduled within 6 to 12 months.[102-106] Adrenal biopsy is discouraged unless there is a known extra-adrenal malignancy that necessitates further examination. In cases where ACC is suspected based on imaging or clinical presentation, measurement of sex steroids and steroidogenesis precursors is advisable.[107,108] The use of multisteroid profiling via tandem mass spectrometry is preferred for this purpose.[109-111]

For masses that do not conform to established criteria (eg, size ≥4 cm with HU between 11-20, or size <4 cm with HU >20, or displaying heterogeneous characteristics), a multidisciplinary team discussion is recommended for tailored assessment. Although the probability of malignancy is low in these instances, follow-up imaging based on the expertise and resources of the institution may be warranted. Should an indeterminate mass be selected for observation, interval imaging should occur within 6 to 12 months.[102]

MEN1 is associated with an increased risk of early-onset breast cancer. Regular breast cancer screening, such as mammograms and clinical breast examinations, may be recommended for women with MEN1 beginning at 40 years of age to detect any potential breast tumors at an early and more treatable stage[112-114] (Table 1).

Evaluation for Complications After Diagnosis

The evaluation of adrenal tumors may be linked to various states of hormonal excess. It is imperative that all patients undergo a comprehensive clinical evaluation to identify any signs or symptoms suggestive of adrenal hormone excess, including Cushing syndrome, hyperaldosteronism, or pheochromocytoma.[115] The administration of a 1-mg overnight dexamethasone suppression

test is advocated to exclude the possibility of autonomous cortisol secretion. In cases where the patient exhibits frailty or has a limited life expectancy, the necessity for this test may be reconsidered.[116] The outcomes of the dexamethasone suppression test should be interpreted as a continuum rather than in binary terms. Specifically, a serum cortisol level measured postdexamethasone ≤50 nmol/L (≤1.8 μg/dL) serves as a threshold for excluding autonomous cortisol secretion.[117,118] It is recommended to measure plasma-free metanephrines or urinary-fractionated metanephrines for all patients with adrenal lesions that do not exhibit characteristics suggestive of benign adenomas.[115,117,119,120] In patients presenting with concomitant hypertension or unexplained hypokalemia, determining the aldosterone/renin ratio is advisable to evaluate for primary aldosteronism.[117,120] The approach to managing adrenal tumors/incidentalomas is complex and should be customized to reflect individual patient characteristics, ensuring that both biochemical evaluations and clinical contexts are integrated into the management strategy.[102]

Treatment and Related Clinical Considerations

Whether prophylactic thymectomy reduces the risk of thymic NET development or improves survival for patients with MEN1 remains unclear, and cases of thymic carcinoid arising despite previous prophylactic resection have been reported.[121] Surveillance for metastatic disease to the lungs, liver, and bone should be performed.[122] When possible, complete resection of the primary tumor and lymph node dissection is the treatment of choice for thymic and bronchial NETs. In the case of positive surgical margins or residual disease for thymic NETs, adjuvant radiation therapy may be performed. Treatments such as somatostatin analogues, mammalian target of rapamycin inhibitors, chemotherapy, and PRRT are possible therapies for unresectable or metastatic thymic NETs, and the treatment plan should be coordinated by a multidisciplinary tumor board.[122] Some studies have suggested surveillance for small MEN1-associated lung NETs, but the tumor size, location, and growth rate should prompt determination for surgery.[123]

Treatment of MEN1-associated adrenal tumors is similar to that for non-MEN1 adrenal tumors. Surgery is indicated for functioning tumors (eg, primary hyperaldosteronism or hypercortisolism) and nonfunctioning tumors with atypical features, a size >4 cm, or significant growth over a 6-month interval. Some studies suggest consideration for surgery when adrenal lesions reach a size of >3 cm.[92,102,124]

The treatment of MEN1-associated meningiomas is similar to that in non-MEN1 patients. Management of lipomas is conservative. However, when surgically removed for cosmetic reasons, they typically do not recur.

Treatment of facial angiofibromas and collagenomas is usually not required but may include surgical excision and other therapies[125-127] (Table 5).

Surveillance and Monitoring

A comprehensive surveillance strategy should be performed for early detection and intervention of MEN1-related manifestations and tumors. Long-term follow-up of patients who have undergone prophylactic thymectomy is recommended.

MEN1-associated lung NETs demonstrate benign behavior with limited tumor growth patterns and excellent long-term survival. Studies have suggested screening with chest imaging at 1 to 3 years for MEN1-associated lung NETs.[5,123]

Adrenal tumors are a common manifestation among patients with MEN1 and arise later in life. A biochemical work-up and cross-sectional imaging should be performed to evaluate for hormonally active tumors and suspicious features. All functional tumors should undergo adrenalectomy, while small, nonfunctional adrenal nodules may be surveilled with cross-sectional imaging.[92] Abdominal MRI scans are recommended every 3 years for tumors that are typically found to be benign on imaging. If there is a noticeable increase in size (>20% in 6-12 months) with an absolute size >5 mm, and the tumor does not meet criteria for being a benign adenoma on imaging, there should be concerns about malignancy. At this point, surgery should be discussed.[128]

Nonsurgical Management

Lipomas are the most common nonendocrine MEN1-associated cutaneous tumors and many cases do not require surgery.[129]

MEN1 Genetic Testing

Who Should be Evaluated for MEN1 Genetic Testing

Guidelines recommend genetic testing if an individual (1) is diagnosed with clinical or familial MEN1, (2) has a first-degree

Table 5
Summary of Management for MEN1-Associated Tumors

Primary tumor	Primary treatment	Other therapies	Benefits	Risks
Thymic NETs	Surgery	Radiation, chemotherapy	Complete resection, hormonal and/or locoregional symptom control	Bleeding, infection, anesthetic complications
Lung NETs	Surgery	Radiation, chemotherapy	Complete resection, hormonal and/or locoregional symptom control	Bleeding, infection, anesthetic complications
Adrenal Tumors	Surgery		Complete resection, hormonal control	Bleeding, infection, anesthetic complications
Cutaneous Tumors	Surgery		Complete resection, relief of local symptoms	
Meningioma	Surgery and radiation		Symptom control	Surgical complications, neurological deficits, infection, bleeding, seizures
Leiomyoma	Surgery		Locoregional symptom control	Surgical risks
Ependymoma	Surgery		Cure, relief of neurological symptoms	Surgical complications
Breast cancer	Surgery	Radiation, chemotherapy, hormone therapy	Survival benefit, remission	Lymphedema, surgical complications, cardiotoxicity, side effects of systemic treatments

Abbreviations: MEN1 = multiple endocrine neoplasia type 1; NET = neuroendocrine tumor.
Be advised that in certain cases involving these tumors, active surveillance may be warranted unless there is evidence of hormonal activity or progressive growth.

relative with a germline *MEN1* PV/LPV, or (3) has manifestations suspicious for MEN1, including PHPT before 30 years of age, multiglandular PHPT, gastrinoma or multiple pNETs at any age, or ≥2 MEN1-associated tumors that are insufficient for clinical MEN1 diagnosis.[5] Recently, increased risk (2.3-2.8 relative risk) and earlier onset of invasive breast cancer has been linked to MEN1 mutation in diverse patient cohorts; however, breast cancer is not yet incorporated into MEN1 diagnostic or testing criteria. In light of this information, we recommend adhering to the guidelines for moderate risk assessment for breast cancer.[112,113] The first MEN1-associated symptoms or biochemical abnormality rarely occur before age 5 (0.5%) or 10 years (2.2%); however, by 15 years of age ~10% of individuals have evidence of disease.[130] These data substantiate performing genetic testing and initiating tumor surveillance between the ages of 5 and 10 years (per guidelines at 5 years of age).[5]

The likelihood of identifying *MEN1* PV/LPV depends upon the number of manifestations and the presence of an affected family member; 91% to 93%, 56% to 69%, and 29% to 57% with family history versus 31% to 69%, 2% to 23%, and 0% to 4% without family history, for individuals with 3, 2, or 1 cardinal MEN1 tumor, respectively.[131,132] Although current *MEN1* genetic testing criteria provide a high diagnostic yield, they risk missing or delaying diagnosis in a subset of apparently sporadic and/or de novo *MEN1* presentations which do not meet current guideline testing criteria.[5] Therefore, germline *MEN1* testing may be considered under clinical circumstances anticipated to have a PV/LPV diagnostic yield ≥5%: (1) NET of the bronchus, thymus, or stomach (age <40 years), (2) pNET, and (3) identification of an *MEN1* PV/LPV by somatic tumor sequencing[130,133,134] (Table 6).

Benefits and Harms of Genetic Testing

Before genetic testing, all individuals should be provided genetic counseling to discuss potential benefits and harms of testing.[5] In familial MEN1, germline mutation analysis should be performed before biochemical and radiological screening tests to avoid potentially unnecessary tests and costs. Benefits of genetic testing include the identification and exoneration of at-risk individuals. Identification of unaffected at-risk family members alleviates emotional and financial burdens as these individuals, and their offspring, will not require MEN1-related follow-up care. Identification of a PV/LPV *MEN1* variant in at-risk family members leads to a reduced age at diagnosis, earlier (often presymptomatic) disease detection, and earlier intervention (before metastasis),[135-137] which is anticipated to reduce MEN1-related morbidity and mortality.[138] In addition, PV/LPV may be used for vertical transmission avoidance. Importantly, familial *MEN1* PV/LPV testing should be promptly pursued as delay has been associated with increased disease manifestation and progression.[139] The benefits of *MEN1* genetic diagnosis are primarily evidenced in at-risk family members rather than index cases, who presumably benefit from surveillance and MEN1-tailored care (Table 6).

What Genetic Testing Should be Performed if MEN1 is Suspected?

A 2012 guideline recommended a sequential genetic testing approach: *MEN1* coding sequence analysis, then *MEN1* deletion analysis, followed by consideration of additional gene testing.[5] Advances in testing methodology and awareness of overlapping genetic syndromes support a revised approach of gene panel testing with concurrent sequence and deletion analysis. The complex spectrum of *MEN1* PV/LPVs (35%-40% frameshift/truncating indels, 18%-25% missense variants, 17%-22% nonsense, 5%-10% splice junction, 6% large rearrangement, 4% mid intronic, and 2.5%-3% in-frame indels) justifies inclusion of deletion analysis and, possibly, RNA testing for splice variants.[53,140] Approximately 16% of individuals with clinical/familial MEN1 have negative *MEN1* testing, reflecting phenotypically overlapping genetic conditions and sporadic co-occurrence of MEN1-related tumors.[83] Gene panel testing for patients presenting with endocrine tumors/cancers is practical and relatively high yield (~15%).[134] Among patients presenting with early onset, multiglandular, or familial pHPT, comprehensive testing includes *AP2S1*, *CASR*, *CDC73*, *CDKN1B* (*MEN4*), *GCM2*, *GNA11*, *MAX* (*MEN5*), *MEN1*, and *RET*.[141-144] Among patients presenting with pitNET, comprehensive testing includes *AIP*, *CDKN1B* (*MEN4*), *MAX* (*MEN5*), and *MEN1*. Among patients presenting with NETs, comprehensive (not exhaustive) genetic testing includes *BRCA2*, *CDKN1B* (*MEN4*), *MAX* (*MEN5*), *MEN1*, and *VHL*.[133,145,146] Importantly, a broader testing approach increases clinically significant PV/LPV identification as well as variants of uncertain significance. Although clinical benefit and cost-effectiveness of panel testing have not been demonstrated, this approach is preferred

Table 6
MEN1 Clinical Genetics

Indications for genetic evaluation and testing	1. Clinical MEN1 diagnosis 2. First-degree relative with MEN1 PV/LPV 3. PHPT before 30 years of age 4. PHPT, dpNET, or PA and first-degree relative also with PHPT, dpNET, or PA 5. Multiglandular PHPT (any age) 6. Gastrinoma (any age) 7. Multiple pNETs (any age) 8. ≥2 MEN1-associated tumors that are insufficient for clinical MEN1 diagnosis (one of which is PHPT, dpNET, or PA) 9. NET of bronchus, thymus, or stomach (age <40 years) 10. Identified MEN1 PV/LPV on somatic testing
Timing of genetic testing	1. Genetic testing of at-risk individuals is recommended between 5-10 years of age, when tumor surveillance should be initiated 2. Genetic testing should be performed promptly in at-risk individuals beyond 10 years of age to avoid delayed diagnoses
Genetic testing methodology	Methodologies appropriate for identifying coding variants, insertions, deletions, copy number alterations and splice site mutations should be used. Gene panel testing is recommended and should (at minimum) include established genetic associations with the presenting tumor(s). PHPT: *AP2S1*, *CASR*, *CDC73*, *CDKN1B* (*MEN4*), *GCM2*, *GNA11*, *MAX* (*MEN5*), *MEN1*, and *RET* dpNET: *BRCA2*, *CDKN1B* (*MEN4*), *MAX* (*MEN5*), *MEN1*, and *VHL* PA: *AIP*, *CDKN1B* (*MEN4*), *MAX* (*MEN5*), and *MEN1*

Abbreviations: dpNET = duodenopancreatic neuroendocrine tumor; PA = pituitary adenoma; PHPT = primary hyperparathyroidism; pNET = pancreatic neuroendocrine tumor; PV/LPV = pathogenic variant/likely pathogenic variant.

based upon an increased diagnostic yield, real-world practicality, near-cost neutrality (with respect to the genetic testing itself), and utility in identifying lower-risk genotype-negative MEN1 individuals (Table 6).

Have Genotype-Phenotype Correlations Been Established for MEN1?

Genotype-phenotype correlations for MEN1 are inconsistently found and should not be used to guide patient care.[80,130,132,147-149] Missense and in-frame insertion/deletion variants are variably associated with an attenuated phenotype and may be overrepresented in familial isolated PHPT pedigrees.[150,151] However, many familial isolated PHPT–associated variants have been associated with the full disease spectrum.[53,150] Notably, familial clustering has been observed for thymic NETs, pituitary tumors, and adrenal tumors.[152] Given the strong heritability estimate of thymic NETs (97%) combined with the high morbidity/mortality of this manifestation, rigorous guideline implementation (mediastinal imaging and thymectomy with parathyroid surgery) should be emphasized in families with thymic NET.

Genotype-Negative MEN1 is a Distinct Condition

Approximately 16% of patients with MEN1 have negative or uninformative genetic testing; these individuals are said to have genotype-negative clinical MEN1 (GN-MEN1). Emerging data indicate that GN-MEN1 is a distinct condition with delayed onset (46-52 vs 33-35 years), absent-rare development of a third cardinal MEN1 tumor (compared with 48% of individuals with mutation-positive *MEN1*), and a life expectancy comparable to that of the general population.[52,153] Most patients with GN-MEN1 exhibit a combination of PHPT (usually uniglandular) and pitNET, potentially representing sporadic cooccurrence. Notably, GN-MEN1 categorization depends upon comprehensive analysis of MEN1 and overlapping genetic conditions, and consideration of MEN1 variants of uncertain significance misclassification.[153,154] A current guideline recommends uniform surveillance for all MEN1 diagnostic categories and annual clinical and biochemical screening for asymptomatic GN-MEN1 first-degree relatives.[5] Although most evidence suggests that reduced surveillance may be appropriate for patients with GN-MEN1 and their asymptomatic first-degree relatives, the data are insufficient to recommend a modified approach.

Future Directions

The presentation and clinical features of MEN1-associated tumors are widely variable even among family members. The growth of knowledge in recent years on the clinical and molecular features of MEN1 syndrome have allowed for improvements in early detection, treatment, and survival. Future studies are needed to determine the optimal screening and surveillance strategy for the MEN1 cohort. There is still a lack of high-quality evidence regarding the sequencing of treatment and the surveillance strategy of patients with certain MEN1-associated tumors, such as metastatic NETs. The care of patients with MEN1 should include a multidisciplinary team with referral to a high-volume treatment center. Future studies should be aimed at the development of clinical trials and real-world evidence to determine the optimal sequencing and timing of the available therapies for patients with MEN1-associated tumors.[81-84,122]

Future genetic testing may incorporate modified next-generation sequencing to detect low-level mosaicism (allele frequency <10%) which may be present at a meaningful frequency among genotype-negative individuals with ≥3 cardinal MEN1 tumors.[155] In addition, menin immunostaining, particularly in parathyroid adenomas, may be used in the future to support MEN1 variant pathogenicity and identify individuals who are appropriate or inappropriate for germline testing.[156] It is also anticipated that surveillance guidelines for patients with GN-MEN1 and their first-degree family members will be modified to account for the apparent reduced risk for new MEN1-related tumors. Clarification of the potential short- and long-term benefits of treatments for MEN1 on patient-important outcomes, including surgery versus active surveillance, is needed. However, given the rarity of MEN1, this would likely require larger collaborative prospective research consortia.

Conclusions

This consensus statement provides a comprehensive framework for managing patients with MEN1 and associated tumors. MEN1 is a rare hereditary condition characterized by the development of tumors in multiple endocrine glands, including the parathyroids, pancreatic islets, and anterior pituitary gland, among other tissues. This consensus statement covers a patient-centered approach on guidance regarding biochemical testing, when to perform genetic testing for MEN1, including criteria for testing relatives of affected individuals or individuals who have multiple endocrine tumors suggestive of MEN1. As MEN1 can lead to a variety of tumors within endocrine glands, detailed imaging modalities are crucial for precise localization and characterization of these tumors. Guidance includes the use of high-resolution ultrasound, CT, MRI, and nuclear medicine techniques such as somatostatin receptor PET scans, as well as guidance on surgical management for the different types of tumors associated with MEN1.

Since MEN1 is a chronic condition with potential for recurrent tumors, this consensus statement emphasizes the importance of lifelong monitoring. This could involve regular physical examinations, biochemical assessments, and repeat imaging as appropriate. Emphasis is placed on the importance of a multidisciplinary team involving endocrinologists, surgeons, genetic counselors, radiologists, pathologists, oncologists, and primary care physicians to handle the various aspects of MEN1 management. Information on support groups and educational resources for patients and their families is provided to help them understand and cope with the diagnosis and its implications.

Review Process

Drafts of this consensus statement were reviewed and approved by all task force members, the AACE Clinical Practice Guidelines Oversight Committee, the AACE Board of Directors, and peer reviewers for *Endocrine Practice*.

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