



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 from the American Association of Clinical Endocrinology (AACE) consensus meeting on the diagnosis, management, and surveillance of patients with Multiple Endocrine Neoplasia Type 1 (MEN1) and associated tumors. The panel 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.

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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 utilized 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.

Methods: The expert panel, comprising 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 no more than 1 dissenting vote and significant majority as 75% or higher threshold. Relevant studies were identified through a literature review process, and consensus statements were based on the available evidence.

Results: The panel 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 healthcare 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 post-treatment 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.

Keywords

Multiple Endocrine Neoplasia Type 1; MEN1; pituitary; parathyroid; neuroendocrine tumor; pituitary neuroendocrine tumor; duodenal neuroendocrine tumor; pancreatic neuroendocrine tumor; duodenopancreatic neuroendocrine tumor; parathyroid adenoma; adrenal; neuroendocrine tumor; thoracic neuroendocrine tumor; breast tumor; cutaneous tumor; meningioma; leiomyoma; ependymoma; MEN1 genetic testing

Introduction

Multiple Endocrine Neoplasia, type 1 (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 predilection¹⁻³. The cardinal features of MEN1 are parathyroid adenomas with primary hyperparathyroidism (PHPT), duodenal and pancreatic neuroendocrine tumors (dpNETs), and anterior pituitary adenomas (pitNETs). Other less frequent neoplasms seen in MEN1 syndrome include neuroendocrine tumors 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 non-endocrine manifestations are possible.

MEN1 can be diagnosed three ways: (i) autosomal dominant genotype-positive MEN1, defined by identification of a pathogenic or likely pathogenic germline MEN1 gene variant leading to loss of function of the menin protein, (ii) clinical MEN1, defined by the manifestation of two or more cardinal MEN1 features without genetic confirmation, or (iii) 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 are living longer in recent years, they still have a shortened overall life expectancy compared to the general population. Two-thirds of patients with MEN1 syndrome die from an MEN1-related cause, and advanced pancreatic neuroendocrine tumors are the most common disease-related cause of death in 40% to 45% of cases⁴. 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

Primary hyperparathyroidism (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 women⁵. 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 four gland hyperplasia and primary hyperparathyroidism⁶.

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 hyperparathyroidism⁷. An ionized calcium measurement may be considered, especially in normocalcemic PHPT⁷.

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 pancreatic neuroendocrine tumors⁸. In MEN1 patients without PHPT, annual biochemical screening is recommended (see Table 1). Since PHPT is highly prevalent and often the first manifestation of MEN1, 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 PHPT⁹. 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 childhood⁵.

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 three-site dual-energy X-ray absorptiometry bone mineral density (BMD) of the lumbar spine, hips, and distal 1/3 radius and imaging for vertebral fractures since there is evidence suggesting that BMD is lower in patients with MEN1 versus sporadic PHPT¹⁰. In addition, evaluation of renal complications with an estimated glomerular filtration rate (eGFR), 24-hour urine calcium, and imaging for nephrolithiasis or nephrocalcinosis is suggested⁷.

Treatment and Related Clinical Considerations

In sporadic PHPT if the patient is < 50 years of age, has 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), eGFR < 60 mL/min, and/or has skeletal or renal complications related to PHPT, surgery by an experienced parathyroid surgery is recommended^{7,11}. A special consideration in MEN1 is the concern of hypergastrinemia associated with hypercalcemia¹². However, in PHPT associated with MEN1 the timing of surgical intervention is less clear.

Parathyroidectomy Considerations

Imaging has no role in the diagnosis of PHPT, and negative imaging results do not preclude surgery for patients with PHPT¹¹. Pre-operative imaging options include cervical ultrasound, parathyroid nuclear scan, and multiphase computed tomography of the neck (4D 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 disease¹¹. Therefore, preoperative localization for an initial open bilateral neck exploration (BNE) 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 localization¹³. 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 involvement¹⁴. In the setting of surgery for recurrent or persistent PHPT in MEN1 preoperative localization is important to help determine the appropriate surgery including identification of ectopic disease sites and better understand risk and benefits of re-operative 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 hypoparathyroidism¹⁴. The optimal surgery for PHPT in MEN1 is a BNE with identification of all four 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 tumors¹⁴⁻¹⁶. Of note, all-cause mortality and risk of cancer may be increased in adult patients with thymus removal, including subjects (16%) undergoing para(thyroid) excision¹⁷. 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 ($\leq 3 \frac{1}{2}$ glands) performed,

and risk of hypoparathyroidism^{13,18}. Intraoperative parathyroid hormone monitoring may have limited benefit in patients with MEN1 associated PHPT undergoing initial parathyroidectomy since it will not alter the operative strategy¹⁹. Finally, although it is assumed that parathyroidectomy in MEN1 will have similar clinical benefits to those expected in sporadic PHPT, there is only limited evidence in regard to improvement in BMD²⁰.

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 cure¹¹. 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}. Hence, annual and long-term follow-up with serum calcium, serum phosphorus, and PTH may be appropriate¹¹.

Nonsurgical Management

Nonsurgical management of PHPT in MEN1 includes the use of calcium-sensing receptor (CaSR) 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 benefit²³. 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 treatment option long term. PEA is associated with normocalcemia in the majority of patients, but recurrence of hypercalcemia is common and can require further PEA treatment²⁴.

Patients with MEN1-related pituitary tumors

Prevalence and Presentation

The prevalence of pituitary neuroendocrine tumors (pitNETs) or pituitary adenomas in patients with MEN1 varies widely among series with ranges from 35 to 60% based on large cohort studies,^{25–29} as compared to ~10–20% in the general population. Most patients present with microadenomas (< 1 cm) and functional pitNETs, although non-functional 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 MEN1 and non-MEN1 patients with the exception of plurihormonal tumors which are more common in the former³². 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}. ACTH 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 (see 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 notion²⁹. 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 agonists³⁴.

Screening

Screening for pitNETs is recommended in all patients with MEN1. The most sensitive imaging technique for identification of pitNet is a contrast-enhanced dynamic MRI. ⁶⁸Ga-DOTATATE PET/CT has not been shown to be sensitive for detection of pitNet in patients with MEN1³⁸. Yearly hormonal testing for prolactin and IGF-1 levels is recommended^{5,27} in addition to pituitary MRI periodically, for example every 1 to 3 years⁵. For cost-effectiveness, and to minimize burden on patients, some suggest that routine screening of asymptomatic MEN1 patients for pitNET should be delayed until age ≥ 16 years of age³⁹ (see Table 1).

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 pitNet⁴⁰. If hyperparathyroidism is not present, the likelihood of MEN1 is very low²⁶.

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 and/or symptoms of hypercortisolemia are present, patients should be screened for Cushing disease with a 1mg overnight dexamethasone suppression test, 24-hour urine free cortisol and/or late-night salivary cortisol levels⁴¹. Patients with lesions > 6 mm and/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

Evaluation and management of pitNETs in patients with MEN1 is similar to treatment in non-MEN1 patients. Endoscopic endonasal transsphenoidal resection (EETS) remains the first-line therapy for all pitNETs requiring treatment except for prolactinomas⁴⁴.

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 (see Table 2).

Surgery for prolactinoma is reserved for patients intolerant to or with 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 FDA 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 pregnancy⁴⁵.

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 2nd or 3rd line in patients with acromegaly or Cushing disease with residual or recurrent disease after surgery; it can also be used concomitantly with medical therapy⁴⁶.

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 5–15% of patients postoperatively⁴⁷. Particularly, arginine vasopressin deficiency (AVP-D), previously called central diabetes insipidus may occur in up to 30% of patients but majority of cases are transient. Other rare complications of surgical intervention may include CSF leak, hemorrhage, and meningitis⁴⁸.

In sporadic and MEN1 patients, incidentally identified pituitary macroadenomas are more likely to enlarge during follow-up compared to microadenomas⁴⁹. 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 three years^{41,50}. One could also consider reassurance without follow up imaging for microadenomas < 5 mm in size⁴³ since the risk of clinically significant growth is very 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 (up to 50%)³⁷.

Patients with MEN1-related duodenal and pancreatic neuroendocrine tumors

Prevalence and Presentation

Duodenal and pancreatic neuroendocrine tumors (dpNETs) occur in 30–90% of patients with MEN1⁵¹. dpNETs can be non-functional or manifest as various functional types such as gastrinoma (including in the duodenum), insulinoma, glucagonoma, VIPoma, and somatostatinoma. In MEN1 patients with Zollinger-Ellison syndrome, duodenal gastrinomas are frequently present, while pancreatic gastrinomas are rarer, accounting for only 25% of cases⁵². Moreover, data from the Dutch MEN study group reported that >80% of the patients with MEN1 have a dpNET by the age of 80^{53,54}.

The diagnosis of non-functioning pancreatic neuroendocrine tumors (NF-pNETs) has become more prevalent due to advancements in imaging technology, and as previously mentioned, the incidence of these tumors tends to rise with advancing age. Functioning pancreatic neuroendocrine tumors (F-pNETs) are classified based on the predominant hormone they secrete, which leads to specific clinical syndromes (see 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^{55,56}. Around 15% to 30% of dpNET patients experience distant metastases, particularly NF-pNETs and gastrinomas^{55,57,58}.

pNETs in patients with MEN1 are typically multiple, non-functional (NF) and more commonly <0.5 cm in diameter. Some patients may develop larger pNETs, which, in line with the previous observation, are also predominantly NF. Among functional pNETs, MEN1 patients 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^{59–61}. As such, they frequently require surgery to remove the duodenum and part of the pancreas (Whipple procedure) to adequately clear the disease⁶².

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 larger than 2 cm and patients over the age of 40 are independently associated with an increased risk of developing distant metastasis and mortality⁵⁷. It is agreed upon by experts that surgical intervention in NF-pNETs is warranted for those larger than 2 cm or those showing signs of progression during observation⁵¹. Moreover, the rate of metastasis is higher in larger NETs related to MEN1, which consequently contributes to an increase mortality rates. Furthermore, survival rates of dpNET patients with liver metastasis are lower (65% at 5 years and 50% at 10 years) as compared to patients without liver metastases (95% at 5 years and 86% at 10 years)^{58,63}.

Occult metastatic disease is also more prevalent in *MEN1* syndrome than in patients with sporadic neuroendocrine tumors^{64,65}. For example, metastases are present in up to 50% of patients with *MEN1*-associated insulinomas, whereas less than 10% of non-*MEN1* insulinomas metastasize^{65,66}. Overall, two-thirds of patients with *MEN1* syndrome die from a *MEN1*-related cause, most commonly (40–45%) due to advanced pancreatic neuroendocrine tumors (pNETs)⁶⁷. In addition, higher mortality in MEN1 as compared to the general population or to 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 age⁵. Routine biochemical and imaging screenings can be extended from 1–3 years for asymptomatic patients. A range of 10–40% 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^{67,68}. Cross sectional imaging studies, such as MRI and CT of the Chest/ Abdomen/Pelvis, are typically performed. Additionally, functional imaging such as ⁶⁸Ga or ⁶⁴Cu-DOTATATE PET/CT can be used to rule out any evidence of a neuroendocrine tumor that is not visible on anatomical imaging^{69,70} (see 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 six to twelve months is recommended⁷¹. In cases of metastatic disease, somatostatin agonists (SSAs) may be considered. Insulinoma should be managed by initiating treatment with diazoxide at a dose of 3 to 8 mg/kg per day, divided into three or four daily doses. Additionally, somatostatin agonists can be used as part of the treatment plan (Table 2)⁵².

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 dpNETs and case reports demonstrating efficiency of SSAs, targeted therapies, chemotherapy, and radiological therapy⁵. Additionally, FDA approved PRRT (Peptide Receptor Radionuclide Therapy) with ¹⁷⁷Lu-DOTATATE for dpNETs is an important therapy for SSTR (somatostatin receptors)-expressing NETs. Although the aforementioned therapeutic modalities have proven to be 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 as compared to sporadic NETs due to presence of multifocal tumors within multiple concurrent organs and metastatic disease which may be challenging to definitively trace back to a single primary tumor⁷³.

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 is 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).

Healthcare providers need both short-term and long-term risk assessments information to accurately assess when choosing initial and follow-up treatments for advanced neuroendocrine tumors. 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^{58,73–78}. 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 (EUS) is recognized for its high sensitivity in identifying neuroendocrine tumors of the pancreas (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, magnetic resonance imaging (MRI) was found to be more sensitive than computed tomography (CT) and offers the added benefit of no exposure to ionizing radiation, which is particularly important for a condition requiring lifelong monitoring⁶⁹. Studies have shown that small NF-pNETs (< 2 cm) typically grow at a rate of 0.1 to 1.32 mm per year⁶⁹. Therefore, it is generally considered safe to wait 2–3 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^{69,70,79}. Thus, personalized imaging intervals should be established based on individual tumor growth rates. Current evidence supports the use of somatostatin receptor positron emission tomography (PET)-CT (⁶⁸Ga or ⁶⁴Cu-DOTATATE PET/CT) in cases where it can impact treatment decisions, such as in detecting occult metastases in pNETs larger than 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 duodenal and pancreatic associated neuroendocrine neoplasms (dpNETs) in MEN1 is not well defined. pNETs are thought to affect anywhere between 30–80% of MEN1 patients. Surgery is the gold standard to prevent the malignant progression of dpNETs in MEN1 patients, and to prevent or resolve hormone-derived endocrine syndromes. Functioning tumors, regardless of size, should be resected. Nonfunctioning tumors can be observed if they are under 20 mm, but if they are >20 mm or have significant growth while under surveillance, surgical resection should be strongly considered. Given the fact 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 MEN1 patients, in contrast to that of 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 the MEN1 syndrome, the residual pancreas and duodenum are at high risk of development of new dpNENs. Some studies have evaluated the risk of relapse in the residual pancreas after a partial pancreatectomy in MEN1 patients, but the characteristics of the studies were heterogeneous, and the post-operative follow-up was generally shorter than 10 years^{80–83}. 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 patients overall health. Studies show that MEN1 patients who have been treated with surgery have good long-term survival. Five-year overall survival (OS) rates can range from 90–100% for patients with functional PNETs and 65% to 100% for NF-pNETs post-resection. Disease specific survival is also favorable with outcomes in the >80% range⁶⁷.) As previously mentioned, local recurrence (intrapancreatic and not margin related) of pNETs after surgical resection is common in MEN1 patients due to the multifocal nature of the disease. In the literature, recurrence rates vary widely but are reported to be as high as 50%^{78,84}. 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, risks of surgery which can include pancreatic leak, exocrine insufficiency, diabetes, must be discussed with the patient. In short, most studies support the proactive surgical management of pNETs in MEN1 patients, as they can control symptoms and improve outcomes, but given high rates of recurrence, surgical approach must be tailored based on the patient's 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 MEN1 patient cohorts. 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.⁸⁵

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, and meningiomas and others. Thymic NETs have been reported to be almost exclusively in male patients with MEN1⁸⁶, frequently associated with smoking, representing a prevalence of 3.7% and a 10-year survival rate of 30%⁸⁷. While commonly a disease found in males, Sakurai et. al found a prevalence of thymic NETs in men of 7.6% compared to 3.2% in women, majority of whom were non-smokers⁸⁸; suggested 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 male patients compared to female patients⁸⁹.

For adrenal tumors, the incidence of asymptomatic adrenocortical tumors in patients with MEN1 is reported to be 20–73%⁹⁰. Adrenal tumors are more often small, non-functional and arise later in the course of the disease⁹¹. 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 exceeding 1 cm in size on imaging studies, should undergo biochemical evaluation for hormone excess. Notably, the incidence of ACC in tumors larger than 4 cm increases to 31% (ACC is rarely diagnosed with reported incidence rates varying from 1.1% to 7%).^{92,93} Additionally, patients diagnosed with MEN1 and adrenal tumors should receive annual imaging assessments, with careful consideration for surgical intervention if tumors exceed 4 centimeters in diameter, present 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.^{91,93,94}

Central nervous system tumors, including ependymomas, schwannomas, and meningiomas, have been reported. Meningiomas are found in less than 10% of MEN1 patients. Subcutaneous lipomas may occur in more than 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.^{95,96}

Screening

While MEN1 associated thymic tumors are usually asymptomatic, they are a significant determinant of survival due to their high malignant potential and accompanying recurrence and distant metastases⁸⁸. Screening should begin at 8–15 years of age and should be repeated every 1–3 years with low dose CT or MRI⁵. CT or MRI of the chest every 1–3 years is recommended for the screening of thymic and bronchopulmonary tumors^{5,97}. For screening of MEN1 patients for abdominal tumors, such as adrenal nodules, cross-sectional abdominal imaging by CT or MRI should be considered every 1–3 years⁹⁷.

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 non-contrast CT indicates a benign adrenal mass. In such scenarios, no further imaging is necessary. For masses exhibiting HU values between 11 and 20 and measuring less than 4 cm, 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 non-contrast CT or MRI should be considered at a 12-month follow-up interval^{98–101}.

Masses that are ≥ 4 cm or demonstrate heterogeneous features or HU values exceeding 20 present 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 FDG-PET/CT, should be ensured prior to surgical intervention. If surgery is deemed unnecessary, follow-up imaging should be scheduled within 6 to 12 months^{101–105}. Adrenal biopsy is discouraged unless there is a known extra-adrenal malignancy that necessitates further examination. In cases where adrenocortical carcinoma is suspected based on imaging or clinical presentation, measurement of sex steroids and steroidogenesis precursors is advisable^{106,107}. The use of multiteroid profiling via tandem mass spectrometry is preferred for this purpose^{108–110}.

For masses that do not conform to established criteria (e.g., size ≥ 4 cm with HU between 11 and 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 months¹⁰¹.

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 age 40 to detect any potential breast tumors at an early and more treatable stage^{111–113} (see 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's syndrome, hyperaldosteronism, or pheochromocytoma¹¹⁴. 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 reconsidered¹¹⁵. The outcomes of the DST should be interpreted as a continuum rather than in binary terms. Specifically, a serum cortisol level measured post-dexamethasone ≤ 50 nmol/L (≤ 1.8 $\mu\text{g/dL}$) serves as a threshold for excluding autonomous cortisol secretion^{116,117}. 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^{114,116,118,119}. In patients presenting with concomitant hypertension or unexplained hypokalemia, determining the aldosterone/renin ratio is advisable to evaluate for primary aldosteronism^{116,119}. 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 strategy¹⁰¹.

Treatment and Related Clinical Considerations

Whether prophylactic thymectomy reduces the risk of thymic NET development or improves survival for MEN1 patients remains unclear, and cases of thymic carcinoid arising despite prior prophylactic resection have been reported¹²¹. Surveillance for metastatic disease to the lungs, liver, and bone should be performed¹²². 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, mTOR inhibitors, chemotherapy, and PRRT are possible therapies for unresectable or metastatic thymic NETs and the treatment plan should be coordinated by a multidisciplinary tumor board¹²². Whereas some studies have suggested surveillance for small MEN1-associated lung NETs, the tumor size, location, and growth rate should prompt determination for surgery¹²³.

Treatment of MEN1-associated adrenal tumors is similar to that for non-MEN1 adrenal tumors. Surgery is indicated for functioning tumors (e.g. primary hyperaldosteronism or hypercortisolism) and nonfunctioning tumors with atypical features, a size greater than 4 cm, or significant growth over a 6-month interval. Some studies suggest consideration for surgery when adrenal lesions reach a size greater than 3 cm^{91,101,120}.

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^{124–126} (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 pattern 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 MEN1 patients 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, non-functional adrenal nodules may be surveilled with cross-sectional imaging⁹¹. It is recommended abdominal MRI 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 greater than 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 discussed¹²⁷.

Nonsurgical Management

Lipomas are the most common non-endocrine MEN1 associated cutaneous tumor and many cases do not require surgery¹²⁸

MEN1 Genetic Testing

Who should be evaluated for MEN1 genetic testing

Guidelines recommend genetic testing if an individual (i) is diagnosed with clinical or familial MEN1, (ii) has a first-degree relative with a germline MEN1 PV/LPV, or (iii) has manifestations suspicious for MEN1, including PHPT before 30 years of age, multiglandular PHPT, gastrinoma or multiple pNETs at any age, or at least two MEN1-associated tumors that are insufficient for clinical MEN1 diagnosis⁵. 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.^{111,112} 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 disease¹²⁹. These data substantiate performing genetic testing and initiating tumor surveillance between the ages of 5 and 10 years, (per guidelines at age 5 years)⁵.

The likelihood of identifying an MEN1 PV/LPV depends upon the number of manifestations and the presence of an affected family member; 91–93%, 56–69% and 29–57% with family history *versus* 31–69%, 2–23% and 0–4% without family history, for individuals with three, two or one cardinal MEN1 tumor, respectively^{130,131}. 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 criteria⁵. Hence, germline MEN1 testing may be considered under clinical circumstances anticipated to have a PV/LPV diagnostic yield $\geq 5\%$: (i) NET of the bronchus, thymus or stomach (age < 40), (ii) pNET and (iii) identification of an MEN1 LPV/PV by somatic tumor sequencing^{129,132,133} (Table 6).

Benefits and harms of genetic testing

Prior to genetic testing, all individuals should be provided genetic counseling to discuss potential benefits and harms of testing⁵. 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 off-spring, 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 pre-symptomatic) disease detection, and earlier intervention (prior to metastasis)^{134–136}; anticipated to reduce MEN1-related morbidity and mortality¹³⁷. Additionally, 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 progression¹³⁸. 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?

The 2012 guidelines recommend a sequential genetic testing approach: MEN1 coding sequence analysis, then MEN1 deletion analysis, followed by consideration of additional gene testing⁵. 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^{54,139}. Approximately 16% of individuals with clinical/familial MEN1 have negative MEN1 testing, reflecting phenotypically overlapping genetic conditions and sporadic co-occurrence of MEN1-related tumors⁸¹. Gene panel testing for patients presenting with endocrine tumors/cancers is practical and relatively high yield (~15%)¹³³. Among patients presenting with early onset, multi-glandular or familial pHPT, comprehensive testing includes AP2S1, CASR, CDC73, CDKN1B (MEN4), GCM2, GNA11, MAX (MEN5), MEN1 and RET^{140–143}. Among patients presenting with PitNET comprehensive testing includes AIP, CDKN1B (MEN4), MAX (MEN5) and MEN1. Among patients presenting with neuroendocrine tumor, comprehensive (not exhaustive) genetic testing includes BRCA2, CDKN1B (MEN4), MAX (MEN5), MEN1 and VHL^{132,144,145}. Importantly, a broader testing approach increases clinically significant PV/LPV identification as well as variants of uncertain significance (VUS). Although clinical benefit and cost effectiveness of panel testing has not been demonstrated, this approach is preferred 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^{79,129,131,146–148}. Missense and in-frame insertion/deletion variants are variably associated with an attenuated phenotype and may be over-represented in familial isolated primary hyperparathyroidism (FIPA) pedigrees^{149,150}. However, many FIPA-associated variants have been associated with the full disease spectrum^{54,149}. Notably, familial clustering has been observed for thymic NETs, pituitary tumors and adrenal tumors¹⁵¹. 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 MEN1 patients 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 *versus* 33–35 years), absent-rare development of a third cardinal MEN1 tumor (compared to 48% of mutation-positive MEN1 individuals) and life-expectancy comparable to the general population^{53,152}. Most GN-MEN1 patients 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 VUS misclassification^{152,153}. Current guidelines recommend uniform surveillance for all MEN1 diagnostic categories and, annual clinical and biochemical screening for asymptomatic GN-MEN1 first-degree relatives⁵. Although, most evidence suggests that reduced surveillance may be appropriate for GN-MEN1 patients 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 familial 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^{80–83,122}.

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 at least three cardinal MEN1 tumors¹⁵⁴. Additionally,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 testing¹⁵⁵. Additionally, it is anticipated that surveillance guidelines for GN-MEN1 patients, 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 collaborate prospective research consortiums.

Conclusions

The consensus statement provides a comprehensive framework for managing patients with multiple endocrine neoplasia type 1 (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 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*. Note: Pending.

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AACE reviews and updates or retires its guidance documents five years following publication or sooner if significant scientific developments or changes in public policy occur.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AACE	American Association of Clinical Endocrinology
AVP-D	arginine vasopressin deficiency
BMD	bone mineral density
BNE	bilateral neck exploration
COI	Conflicts of Interest
dpNETs	duodenopancreatic neuroendocrine tumors
EETS	Endoscopic endonasal transsphenoidal resection
eGFR	estimated glomerular filtration rate
GN-MEN1	genotype-negative multiple endocrine neoplasia, type 1
MEN1	Multiple Endocrine Neoplasia, Type 1
NETs	neuroendocrine tumors
NF-pNETs	non-functioning pancreatic neuroendocrine tumors
PEA	Percutaneous ethanol ablation
PHPT	primary hyperparathyroidism
pitNETs	pituitary neuroendocrine tumors
pNETs	pancreatic neuroendocrine tumors
PRRT	Peptide Receptor Radionuclide Therapy

PTH parathyroid hormone

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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 MEN1 and associated tumors.

Scope

This consensus statement presents key questions to address aspects of diagnosis, management, and surveillance of patients with multiple endocrine neoplasia, type 1 (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 (RCTs) to support the use of safe and effective therapies and FDA-approved drugs 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, breast, cutaneous, meningioma, leiomyoma, 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 to the remaining members of the Task Force with attention to career level, expertise, 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 interests form, which requires disclosure of all activities and relationships (e.g. speaker's bureaus, consulting, stock ownership, company ownership, research funding, etc.) within the prior 24 months. The Clinical Practice Guidelines Oversight Committee's Conflict of Interest (COI) Subcommittee reviewed all disclosures. Per the AACE Conflict of Interest 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, 40% or less, may have conflicts of interests 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 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:

An individual with a diagnostic genetic test OR a parathyroid adenoma, pituitary neuroendocrine tumor, or duodenal and pancreatic neuroendocrine tumors (dpNETs) and a first-degree relative with MEN1, OR 2 or more endocrine gland tumors (parathyroid, pituitary or dpNET) and negative genetic testing and no MEN1 family history.

Table 1.

Screening Frequency of MEN1-related Tumors

Tumor	Age of screening	Screening modality-biochemistry	Screening modality-imaging modalities	Frequency
MEN1-related parathyroid tumors	Early childhood (5–8 years of age)	PTH, calcium, phosphorus	Imaging may be considered if surgery is indicated but no role in diagnosis	Yearly
MEN1-related pituitary tumors	≥16 years	Prolactin and IGF-1 levels	Contrast-enhanced dynamic MRI	1–3 years
MEN1-related duodenal and pancreatic neuroendocrine tumors	≥16 years of age	Hormonal evaluation indicated only if symptoms	Cross-sectional imaging study (CT or MRI abdomen and pelvis) ⁶⁸ Ga or ⁶⁴ Cu DOTATATE PET CT	1–3 years
MEN1-related bronchopulmonary/thymic tumors	8–15 years of age	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
MEN1-related adrenal tumors	≥16 years of age	Hormonal evaluation indicated if symptoms	Cross-sectional imaging study (CT or MRI abdomen) ^a	1–3 years
MEN1-related breast cancer	≥40 years of age	Breast examination	Mammogram	Yearly

Abbreviations: PTH, parathyroid hormone; IGF-1, insulin-like growth factor; MRI, magnetic resonance imaging; CT- compute tomography

Note: This table 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.

^aFor masses exhibiting HU values between 11 and 20 and measuring less than 4 cm, 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 non-contrast CT or MRI should be considered at a 12-month follow-up interval

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 Hypertension, type 2 diabetes or prediabetes, obstructive sleep apnea, colon polyps, thyroid nodules, carpal tunnel	1st Generation SRLs Octreotide LAR Lanreotide depot Oral Octreotide (patients controlled on injectable) 2nd Generation SRL Pasireotide LAR Dopamine Agonists Cabergoline GH Receptor Antagonist Pegvisomant	Nausea, diarrhea, abdominal pain or distention, cholelithiasis, bradycardia, hyperglycemia, injection site reactions Same as for octreotide LAR but no injection site reaction Hyperglycemia more frequent than 1 st generation SRLs; other side effects similar Same as for prolactinoma Transaminitis, injection site reaction, nausea, diarrhea, flu-like symptoms
Corticotroph (Cushing disease)	Elevated 24 UFC Elevated LNSC 8am cortisol > 1.8 mcg/dL after 1mg dexamethasone 11pm	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 & SC) Cabergoline Steroidogenesis Inhibitors Ketoconazole	Same as for acromegaly Same as for prolactinoma GI disturbance, transaminitis, gynecomastia, skin rash, AI

Adenoma Type	Biochemical Diagnosis	Signs/symptoms	Medical Treatment Options	Side Effects
			Levoketoconazole Metyrapone Osilodrostat Etomidate (only parenteral agent) Glucocorticoid receptor antagonist Mifepristone	Similar to ketoconazole HTN, hypokalemia, hirsutism, GI disturbance, AI Similar to metyrapone Nausea, vomiting, shock, apnea, AI GI disturbance, headache, hypokalemia, HTN, arthralgia, vaginal bleeding, AI

Abbreviations: IGF, insulin like growth factor; GH, growth hormone; OGTT, oral glucose tolerance test; SRL, somatostatin receptor ligand; LAR, long-acting release; UFC, urine free cortisol; LNSC, late night salivary cortisol; SC subcutaneous; GI, gastrointestinal; AI, adrenal insufficiency.

^aTranssphenoidal surgery is the treatment of choice when indicated for all pituitary tumors, with the exception of prolactinomas and treatment-resistant prolactinomas

^b30 % of patients with acromegaly have nadir GH < 0.4 ng/mL during OGTT and healthy, lean individuals and female patients on oral estrogen may not suppress^{35–37}

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 non-surgical 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 Diabetes	Management of diabetes 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	Diabetes Mellitus Cholelithiasis Diarrhea/steatorrhea	Management of DM Loperamide	Octreotide/Lanreotide Liver directed therapies Surgery, ablation, embolization Other systemic therapeutic approaches listed in Table 4
Adrenocorticotrophic hormone (ACTH) dependent- Cushing's	ACTH	Cushing's syndrome	Bilateral adrenalectomy Metyrapone, ketoconazole	Octreotide/Lanreotide Liver directed therapies Surgery, ablation, embolization Other systemic therapeutic approaches listed in Table 4

^a Surgery is the treatment of choice when indicated^b Everolimus decrease insulin secretion**Abbreviations:** IV, intravenous; VIP, vasoactive intestinal polypeptide; ACTH, adrenocorticotrophic hormone

Table 4. Tolerability, safety, and monitoring issues of therapeutics for advanced NETs⁷⁴
 (Adapted from Chauhan et al. Treatment Sequencing Strategies in Advanced Neuroendocrine Tumors: A Review. Cancers 2022, 14, 5248.)

Agent	Common AEs	Safety Concerns
Octreotide LAR	Incidence >20% • Back pain, fatigue, headache, abdominal pain, nausea, dizziness	Cholelithiasis and complications of cholelithiasis, hypoglycemia or hyperglycemia, hypothyroidism, cardiac dysfunction
Lanreotide	Incidence >10% • Abdominal pain, musculoskeletal pain, vomiting, headache, injection site reaction, hyperglycemia, hypertension, cholelithiasis	Cholelithiasis and complications of cholelithiasis, hypoglycemia or hyperglycemia, hypothyroidism, bradycardia
Sunitinib	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, and thrombocytopenia	Hepatotoxicity, cardiovascular events, QT interval prolongation and torsade de pointes, hypertension, hemorrhagic events, tumor lysis syndrome, thrombotic microangiopathy, proteinuria, dermatologic toxicities, reversible posterior leukoencephalopathy syndrome, thyroid dysfunction, hypoglycemia, osteonecrosis of the jaw, impaired wound healing, embryo-fetal toxicity
Everolimus	Incidence ≥30% ^a • Stomatitis, infections, rash, fatigue, diarrhea, edema, abdominal pain, nausea, fever, asthenia, cough, headache, decreased appetite	Non-infectious 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, embryo-fetal toxicity
¹⁷⁷ Lu-DOTATATE	Grade 3–4 AEs (≥4% with a higher incidence in ¹⁷⁷ Lu-DOTATATE arm) • Lymphopenia, increased GGT, vomiting, nausea, increased AST, increased ALT, hyperglycemia, hypokalemia	Risk from radiation exposure, myelosuppression: secondary myelodysplastic syndrome and leukemia, renal toxicity, hepatotoxicity, neuroendocrine hormonal crisis, embryo-fetal toxicity, risk of infertility
CAPTEM	Grade 3 to 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%), and transaminase elevation (0.1%)	Cardiotoxicity, myelosuppression, coagulopathy, opportunistic infections, diarrhea, dehydration and renal failure, myopathy, severe toxicity due to dihydropyrimidine dehydrogenase deficiency, mucocutaneous and dermatologic toxicity, hyperbilirubinemia

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

Please be advised that in certain cases involving these tumors, active surveillance may be warranted unless there is evidence of hormonal activity or progressive growth.

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 age 30 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) 10. Identified MEN1 PV/LPV on somatic testing
Timing of genetic testing	1. Genetic testing of at-risk individuals is recommended between 5 and 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). <i>PHPT</i>: AP2S1, CASR, CDC73, CDKN1B (MEN4), GCM2, GNA11, MAX (MEN5), MEN1 and RET <i>dpNET</i>: BRCA2, CDKN1B (MEN4), MAX (MEN5), MEN1 and VHL <i>PA</i>: AIP, CDKN1B (MEN4), MAX (MEN5) and MEN1

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