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Guidelines

French guidelines from the GTE, AFCE and ENDOCAN-RENATEN (Groupe d'étude des Tumeurs Endocrines/Association Francophone de Chirurgie Endocrinienne/Reseau national de prise en charge des tumeurs endocrines) for the screening, diagnosis and management of Multiple Endocrine Neoplasia Type 1

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1. Introduction

Multiple Endocrine Neoplasia type 1 (MEN1) or Wermer syndrome (OMIM#131100) is a rare genetic disease, characterized by co-occurrence of several lesions of the endocrine system [1]. The 3 major lesions are primary hyperparathyroidism (pHPT), pancreaticoduodenal neuroendocrine tumor (pdNET) and pituitary adenoma, now called pituitary NET [2]. Less frequent or minor lesions may also be associated, including adrenal NET, bronchopulmonary NETs (bpNET) and thymic NET (thNET). Other non-neuroendocrine tissues may be affected: skin, adipose tissue, central nervous system and uterine smooth muscle. An increased risk of breast cancer has been observed [3]. Diagnostic criteria were established by a group of international experts in 2012 [4]. However, technical advances in molecular genetics and a number of studies now call some of these diagnostic criteria into question.

Prevalence of MEN1 is 3–10/100,000. In order of frequency, MEN1 NETs affect the parathyroid, duodenum-pancreas, pituitary, adrenals, lungs and thymus. Thymic involvement shows male predominance. Penetrance varies with age, starting at around 10 years of age and progressively reaching 100% of all cases by the age of 60. Penetrance varies according to the organ involved, with parathyroid involvement being the most marked, almost complete, and most often the earliest (Table 1a).

Transmission is autosomal dominant, linked to heterozygous inactivating mutations of the MEN1 gene, located at 11q13 [5]. The *MEN1* gene has 10 exons for 9 kilobases; it codes for *menin,* a virtually ubiquitous protein of 610 amino acids, which is involved in numerous cellular processes with multiple partners [6]. The *MEN1* gene is a tumor-suppressor gene, with NETs developing according to the "double hit" mechanism described by Knudson.

Patients presenting with clinical MEN1 or suspected MEN1 according to the criteria explained below should undergo genetic analysis to screen for *MEN1* gene abnormality. Relatives should undergo pre-symptomatic screening, if possible before adolescence, enabling lesion screening and monitoring for carriers of the familial genetic variant and non-carriers to be reassured and excluded from surveillance.

Because of the many different types of disease, patients with MEN1 experience a progressive deterioration in quality of life. Life expectancy is reduced [7]. In some studies, the impairment of quality of life was equivalent to that in severe cancer. Clinically, NET may or may not be secreting. Some become malignant: mainly pdNET and thNET, or much more rarely adrenal tumor and bpNET. These malignant NETs contribute to the poor prognosis of the disease [8,9]. The present document deals with the diagnosis of the disease and the detection and follow-up of lesions, but does not address the question of the nature and frequency of investigations to be carried out once a lesion has been detected and possibly treated (Tables 2 and 3). In the case of poorly studied situations that do not allow for "evidence-based" recommendations, consensual expert recommendations have been made following a 2022 Delphi survey of French experts from the RENATEN centers, the GTE and the AFCE. The text mentions these positions in brackets: (Delphi-GTE-AFCE-2022).

Table 1a
Probability of occurrence of different MEN1 disorders according to age. Data from the GTE/AFCE cohort (1450 patients).

Age (years)	Probability of occurrence (%)		95% confidence interval
10	0.6	0.2	1.4
20	13.9	11.8	16.3
30	33.2	30.2	36.4
40	57.2	53.9	60.5
50	76.8	73.8	79.6
60	89.0	86.6	91.1
70	95.5	93.6	97.0
80	98.0	96.1	99.1

Table 1b
Probability of occurrence of different MEN1 disorders according to age. Data from the GTE/AFCE cohort (1450 patients).

Duodeno-pancreas		
Age(years)	Probability of occurrence (%)	95% confidence interval
10	0.7	[0.4–1.4]
20	6.2	[5.0–7.6]
30	18.9	[16.9–21.2]
40	37.9	[35.3–40.7]
50	58.1	[55.3–61.0]
60	74.0	[71.4–76.7]
70	84.7	[82.2–87.0]
80	90.6	[88.1–92.9]

Table 1c
Probability of occurrence of different MEN1 disorders according to age. Data from the GTE/AFCE cohort (1450 patients).

Zollinger-Ellison Syndrome (gastrinoma)		
Age(years)	Probability of occurrence (%)	95% confidence interval
10		
20	0.3	[0.1–0.7]
30	2.4	[1.7–3.3]
40	10.1	[8.6–12.0]
50	22.2	[19.8–24.8]
60	30.5	[27.6–33.7]
70	38.4	[34.7–42.3]
80	43.5	[39.0–52.5]

2. Diagnosis of MEN1

2.1. Diagnostic criteria for MEN1 and clinical-genetic decision tree

According to the diagnostic criteria established in 2012, MEN1 can be diagnosed [4]: i) on clinical criteria, by presence of at least 2 major MEN1 lesions; ii) on familial criteria, by presence of a MEN1 lesion in a first-degree relative of an individual presenting clinical MEN1; or iii) on genetic criteria, in an individual presenting a pathogenic or probably pathogenic variant of the *MEN1* gene, whether symptomatic or not. Patients diagnosed with MEN1 on clinical, familial or genetic grounds should undergo a management and lesion-screening protocol tailored to the disease. Fig. 1 shows a decision-making algorithm for endocrine lesions, from first suspicion of MEN1 to diagnosis.

2.1.1. Situation 1

In a known MEN1 family, the appearance of a clinical, biological and/or morphological abnormality typical of the MEN1 spectrum is sufficient for diagnosis of MEN1 in an individual (Fig. 1, situation 1). Nevertheless, it is recommended that all relatives, whether symptomatic or not, should be investigated for familial abnormalities.

2.1.2. Situation 2

In a patient presenting two major MEN1 lesions or one major and one minor lesion, MEN1 should be suspected and genetic examination should be conducted (Fig. 1, situation 2).

2.1.3. Situation 3

Diagnosing MEN1 also means systematic suspicion in the presence of any lesion which appears to be part of the MEN1 spectrum, even apparently sporadic, especially if the patient is young and there are several lesions in the same organ (Fig. 1, situation 3).

In the case of isolated endocrine involvement, genetic testing should be proposed in the following cases: primary hyperparathyroidism before the age of 50; multiple parathyroid hyperplasia or adenoma; recurrence of operated primary hyperparathyroidism; gastrinoma-type pdNET (Zollinger-Ellison syndrome (ZES)) regardless of age; multiple pancreatic NET regardless of age; pdNET before the age of 50; and/or secretory or undiagnosed pituitary NET before the age of 30 [10].

At present, there are no established guidelines for systematic genetic screening for pulmonary, thymic or adrenal NETs at a young age, outside contexts of familial involvement. Phosphate-calcium work-up (serum calcium, serum phosphorus, parathyroid hormone) to screen for primary hyperparathyroidism and a skin examination to screen for multiple MEN1 lesions can support diagnosis. In general, as pHPT is the most common condition (penetrance of almost 90% at the age of 60) and screening for it is simple and inexpensive, it is useful to look for it whenever MEN1 is suspected. Dermatological examination is also easy and helpful (skin lesions suggestive of MEN1 genodermatosis: in particular lipoma, angiofibroma and collagenoma, the latter two being frequent on the face and anterosuperior part of the thorax) [11]. In all cases, the indication for genetic analysis may be discussed by the RENATEN multidisciplinary expert review panel.

However, there is no need to screen for MEN1 in patients with NET in the esophagus, appendix, ileum, rectum, colon or stomach (except in case of ZES).

2.1.4. Situation 4

A final situation leading to suspicion of MEN1 is the presence of a single lesion on the disease spectrum in several first- or second-degree relatives (Fig. 1, situation 4). In these cases, analysis of the *MEN1* gene is recommended, bearing in mind that other genes may also be involved and should be analyzed for differential diagnosis depending on the familial presentation (see Section 2.3).

2.2. Genetic diagnosis of MEN1

Genetic diagnosis of MEN1 is based on examination of genetic characteristics in accordance with the French law of May 27th, 2013, defining the rules of good practice applicable to examination of genetic characteristics for medical purposes. The prescribing doctor may be a geneticist or a non-geneticist familiar with the clinical situation (illness, therapeutic management) and the potential consequences of the results for both patient and family (Decree 2013-527 of 20 June 2013 on the conditions for informing relatives in the context of an examination of genetic characteristics for medical purposes), and who is capable of interpreting the results. Prescription forms, decision trees and consent forms are available on the https://www.reseau-gte.org/tengen/ network website.

The first step is to sequence all coding sequences of the *MEN1* gene and the intron/exon junctions. Variations may comprise substitution or micro-rearrangement and are found throughout the gene sequence, mainly in the coding sequences. In 2.2% of index cases, a deletion of one or more exons, or even of the entire gene, is identified; it is therefore important, if screening for a point anomaly is negative, to look for variation in the number of copies at the *MEN1* gene locus [12]. It is advisable to carry out high-throughput sequencing analysis screening for point and copy number variations, or, if this is not possible, to complete *MEN1* gene sequencing using the Sanger technique with analysis using MLPA (multiplex ligation probe amplification) to screen for copy number variation (CNV).

Any pathogenic or probably pathogenic variant of the *MEN1* gene thus identified must be checked on a second sample. This is followed by genetic counselling, which consists of information on the possibilities of prenatal and preimplantation diagnosis, after presenting the file to a multidisciplinary prenatal and preimplantation diagnosis center, and gives relatives access to presymptomatic genetic diagnosis. To date, no clear genotype–phenotype correlation has been demonstrated, preventing follow-up being stratified according to type of mutation.

2.3. Negative results for the MEN1 gene

Patients diagnosed with MEN1 on the basis of clinical, familial or genetic criteria may undergo a management and lesion-screening protocol tailored to the disease. This is not the case when the genetic analysis is negative. Genetic tests may come back negative in an individual with clinical or familial diagnosis of MEN1. There are clinical situations, known as *phenocopies*, in which the patient's phenotype mimics MEN1. These are mainly patients with two major typical lesions, most often a combination of primary hyperparathyroidism and pituitary adenoma, in whom no mutation of the *MEN1* gene has been identified. Consistent with sporadic disease, these patients develop lesions at a later age than MEN1 patients and, above all, never develop a third lesion, making the MEN1 follow-up unnecessary [13,14]. In these patients, if no genetic anomaly is identified on two independent samples, the MEN1 diagnosis should be reassessed for additional arguments (careful personal and family history-taking, multiple lesions within the same organ, presence of multiple skin lesions, biological investigations, etc.) in order to adapt the management of the patient and family, and should be the occasion for a discussion with the referring laboratory.

There may also be rare intra-familial phenocopies (patient belonging to a MEN1 family developing an isolated sporadic endocrine lesion belonging to the disease spectrum) [15]. If the result of the genetic examination is negative in a symptomatic indi-

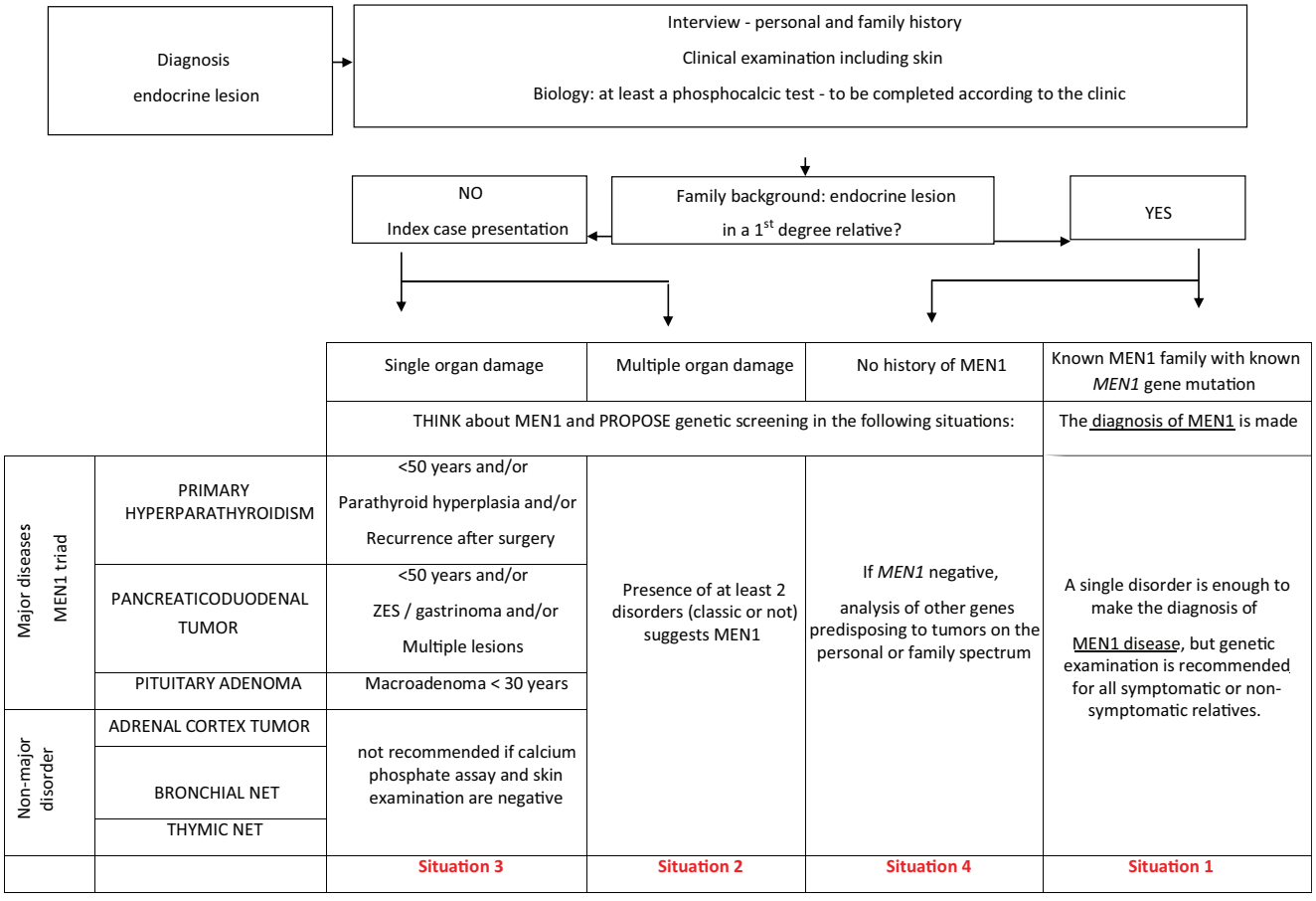

Fig. 1. Decision tree–Diagnostic strategy in MEN1.

vidual from a MEN1 family with a known *MEN1* gene mutation, the genetic examination must be repeated. If the result is again negative, the diagnosis should be reassessed and the case submitted for clinical and biological discussion.

Firstly, a negative result should prompt screening for an anomaly in the *CDKN1B* gene, responsible for MEN4, a syndrome with a "MEN1-like" presentation. However, this is a very rare entity (3 cases identified in 5 years out of more than 4,000 analyses within the TENGEN network).

Depending on the clinical presentation, a negative result should prompt screening for an anomaly in other genes predisposing to neuroendocrine tumors: familial primary hyperparathyroidism (e.g., *CDC73* (HRPT2) gene, *CASR* gene), familial pituitary adenoma (e.g., *AIP* gene), or isolated NET (e.g., *VHL* gene). Decision trees are available on the TENGEN network website (https://www.reseau-gte.org/tengen/) and from the French National Association of Molecular Genetics Practitioners (ANPGM). The development of sequencing techniques and the possibility of sequencing several genes simultaneously are making genetic analyses more efficient. It may therefore be worthwhile, in discussion with the referring laboratory, to re-analyze unresolved cases of MEN1 which were analyzed several years ago. CNVs are sometimes found in families with no known point variation, and mosaic mutations in the *MEN1* gene may be identified in index cases with negative first-line sequencing [16].

Finally, in the event of a negative result in a patient with a typical phenotype, whole genome analysis should be discussed (FIRENDO multidisciplinary board meeting).

2.4. Presymptomatic genetic diagnosis in a MEN1 family

Identification of a pathogenic or probably pathogenic variant of the *MEN1* gene in an individual enables asymptomatic relatives to receive presymptomatic genetic diagnosis. The aim is to be able to make the genetic diagnosis of MEN1 in carriers of the familial variant, to reassure and avoid surveillance for those who are not carriers of the variant, and to initiate early diagnosis, ideally leading to better-quality treatment and improved prognosis in patients with the variant.

Patients themselves must inform their family of the existence of a pathogenic or probably pathogenic variation in the *MEN1* gene (Decree 2013-527 of 20 June 2013 on the conditions for informing relatives in the context of an examination of genetic characteristics for medical purposes). During the initial prescription consultation or the consultation in which the genetic analysis result is communicated, the physician helps the patient to draw up a list of relatives to contact (adults and minors of first and second degree). If the patient refuses to inform relatives, the doctor may suggest sending an information letter them, without mentioning the patient's name, inviting them to consult a geneticist of their choice to receive genetic information if they so wish. The doctor must record any refusal in the patient's medical file. The law does not provide for any derogation from medical confidentiality. Patients should preferably be referred to the endocrine oncogenetic consultation closest to their home.

The prescription of a genetic test in an asymptomatic subject must be within the setting of an individual consultation by a

physician involved in a multidisciplinary team comprising clinical and genetic skills. The procedure follows the same steps as for an index case. In the case of minors, screening can only be carried out with the agreement of the parents or guardians, who sign an informed consent form. The procedure is identical, with the child or adolescent always accompanied by an appropriate adult.

Genetic screening of relatives consists in targeted screening for the familial variant, using a blood sample taken on an EDTA tube, and preferably sent to the laboratory which diagnosed the index case. Analysis of saliva or jugal swabs is possible in certain laboratories. The test result is communicated and explained to the patient by the prescribing doctor during a second consultation. A copy of the genetic analysis result must be given to the patient. Once the first test has been carried out, a second test must be performed on a new sample. This is particularly important if the result is negative.

If the patient has the *MEN1* variant responsible for the familial syndrome, he or she will be referred to a medical team for monitoring and treatment. If the patient does not have the *MEN1* familial variant, they are not at risk of developing the familial genetic syndrome and monitoring is unnecessary.

In children, screening can be proposed from the age of 5 in families in which an early lesion has occurred in a family member between the ages of 5 and 10. In other cases, screening is recommended as the child approaches 10 years of age. This delay allows parents to be informed of the monitoring protocols generally proposed from the age of 10, and to organize management of the genetic anomaly by and expert pediatric endocrinology team.

3. Primary hyperparathyroidism (pHPT)

3.1. Clinical manifestations

Primary hyperparathyroidism is the most common manifestation of MEN1 disease. The clinical manifestations are identical to those of sporadic pHPT.

3.2. Diagnostic criteria

The diagnostic criteria are identical to those for sporadic pHPT. The frequency of inappropriate PTH concentrations (i.e., within the laboratory limits of normal, but not increased) appears to be greater than in sporadic pHPT [17].

3.3. Penetrance kinetics (Table 1a)

Increase is progressive from the age of 10, and penetrance is almost complete by the age of 80. It is 57.2% [95% CI: 53.9–60.5] at the age of 40.

3.4. Outcome

Unlike the other conditions (duodenum-pancreas and thymus), the prognosis is rarely life-threatening, but morbidity is significant in the absence of treatment: osteoporosis, renal lithiasis, renal failure, hypertension, etc. These complications were reported to be more frequent in MEN1 than in sporadic pHPT, probably because of the longer time to diagnosis and treatment [17–19]. However, these were studies of old retrospective cohorts, with possible late diagnosis. Recurrence is 50% at 12 years after subtotal parathyroidectomy [20]. The rate of hypoparathyroidism is then 23% at 6 months and 19% at 1 year (GTE/AFCE data).

3.5. Monitoring

Detection of pHPT begins at the age of 10 in asymptomatic relatives and at the age of the patient's diagnosis of MEN1 in others [21,22]. Detection and monitoring tools are based on measuring blood calcium levels, corrected blood calcium levels, blood phosphorus levels, circulating parathyroid hormone levels and 24 h-urinary calcium levels. Once diagnosis has been made and treatment carried out, vitamin D concentration (with possible supplementation) and bone mineral density (BMD) need to be monitored. Biological follow-up is annual. The frequency of BMD monitoring is adapted to the initial findings.

3.6. Surgical treatment

Several strategies exist. The gold-standard is subtotal parathyroidectomy (SPTX) by cervicotomy, removing 3 or 3.5 parathyroid glands. This leaves a parathyroid gland or parathyroid stump with the size of a normal parathyroid, which is marked with non-absorbable sutures and clips to facilitate any repeat surgery. It is preferable to leave a parathyroid gland that is easily accessible for redo surgery (away from the recurrent nerve: i.e., usually an inferior parathyroid).

There are also other options.

3.6.1. First option

Total parathyroidectomy (TPTX) with reimplantation of parathyroid fragments in the non-dominant forearm. Studies comparing the two techniques (TPTX vs SPTX) showed comparable results but, above all, greater risk of permanent hypoparathyroidism after TPTX and therefore of impaired quality of life, increased bone damage and renal failure [23–27]. The risk of parathyroidosis is also increased in the case of forearm transplants [28]. This method has been virtually abandoned in France (GTE/AFCE cohort).

3.6.2. Second option

Unilateral clearance (i.e., complete unilateral parathyroid resection), in patients with parathyroid gland abnormalities on one side only, seen by various morphological and morpho-functional approaches (ultrasound, MIBI scintigraphy and/or PET-choline). Results were comparable to SPTX but at 4 years' follow-up only and without hypoparathyroidism. Re-operation is easy on the previously unoperated side [29].

3.6.3. Third option

Resection of one or more glands if they have been identified as being responsible for PTH hypersecretion on several morphological and functional imaging examinations with at least 50% fall in PTH levels on intraoperative measurement 20 minutes after resection. The operation is simple, with no hypoparathyroidism, but the recurrence rate is higher and time to recurrence shorter than with TPTX or SPTX [30]. This approach, along with unilateral clearance, is more readily recommended in younger subjects, in whom multiglandular involvement is statistically less likely. Thymic resection is still recommended, mainly to resect a fifth intrathymic gland (22% in the GTE/AFCE cohort).

Preoperative examinations are based on ultrasound of the parathyroids and thyroid (to examine the thyroid) and parathyroid scintigraphy with a fusion CT image including the thorax (to detect an intrathoracic gland and check the thymus) (Sesta-MIBI). Choline PET has proven its value in situations where other imaging is inconclusive or discordant, or if limited surgery is considered an option, but its place in MEN1 remains to be defined due to the small number of studies [31,32]. It is, however, probably necessary if limited surgery is considered.

Indications in adults are identical to those for sporadic pHPT. SPTX surgery is usually the first-line treatment, reinforced by the need for preventive cervical thymectomy. It is also indicated in case of ZES, to reduce gastric acid secretion [33]. The therapeutic

options in the event of recurrence depend on how resection was performed. The choice between repeat surgery and medical treatment is decided in a multidisciplinary board meeting. In children and adolescents, the question is still a matter of controversy (see Controversies, below).

3.7. Medical treatment

Cinacalcet, a calcimimetic, can be used to reduce PTH concentration, and to normalize blood calcium level, the latter being used to titrate the dose of the drug. Indications comprise surgical failure, and particularly recurrence of hyperparathyroidism after SPTX, and inoperable patient. Its use may be limited by poor digestive tolerance (nausea, abdominal pain). Cinacalcet has not been widely evaluated in PTH in MEN1, but its efficacy appears to be comparable to that seen in sporadic forms. Unlike surgery, no data are available on the bone and urinary impact during long-term treatment [34,35].

3.8. Controversies

The role of pre-operative imaging, which is widely used, and the place of PET-choline in the choice of surgical techniques have not been established and are open to debate.

No surgical technique is perfect, with TPTX and SPTX trading hypoparathyroidism and recurrence/persistence of PTH [36]. In the long term, recurrence of hyperparathyroidism is very likely as long as parathyroid tissue persists, but TPTX has been almost abandoned in France; one team would opt for TPTX with reimplantation if all 4 glands are enlarged, and the others for SPTX in first line [37].

The timing of surgery in children and adolescents is debated. The regulation of phosphocalcic metabolism, the sensitivity of bone tissue to PTH and the interactions between PTH and growth factors differ between children and adults [38]. These differences could explain the greater impact on bone than in adults. An additional issue in young subjects is to jeopardize peak bone mass, which has already been reached in young adults [39]. In the absence of validating studies, it is recommended that parathyroid surgery be performed in children/adolescents in the event of an identified complication of primary hyperparathyroidism or, in asymptomatic forms, when blood calcium levels exceed the upper limit of normal by 10% (Delphi-GTE-AFCE-2022). In view of the low gland involvement at the start of the disease and the therapeutic difficulties of hypoparathyroidism, targeted parathyroidectomy or unilateral clearance directed by imaging, and in particular PET-choline (Delphi-GTE-AFCE-2022), is preferred in young subjects [40].

4. Pancreaticoduodenal and gastric neuroendocrine tumor

4.1. General data

Pancreaticoduodenal and less frequently gastric neuroendocrine tumors associated with MEN1 are generally small (< 2 cm) and multiple. The prevalence of pdNETs in MEN1 is high and age-dependent (Table 1b) [41]. It seems to have increased in younger subjects over the last decade, probably due to the **wider** use of high echo-endoscopy (HEE), the most accurate method, but also to the constant improvement in the quality of cross-sectional imaging and diagnostic imaging of somatostatin receptors, particularly for the detection of < 1 cm lesions [42,43]. pdNET is the first clinical manifestation of MEN1 in around 20% of patients. It is exceptional before the age of 8–10 years, except for insulinoma, which very rarely occurs after the age of 5 [22,41,44,45]. pdNET is said to be functional when it presents clinical signs related to secretion or if it permanently secretes a hormone at a level greater than twice the upper limit of normal. Immunostaining alone cannot identify functional pdNET: it can be negative because of poor specificity of the antibodies used for immunostaining, or positive in case of hormone synthesis without the hormone being secreted. pdNET may be associated with symptoms related to the hypersecretion of a hormone (mainly gastrin and insulin, very rarely glucagon, exceptionally vasointestinal peptide (VIP), somatostatin or others). Sometimes, pdNETs with different functional profiles may coexist in the same patient. pdNET (other than insulinoma) is currently the main cause of death in MEN1, due to potential malignancy [8,46]. Systematic screening, improved diagnosis and early treatment (if indicated) have improved survival for patients with MEN1 over the past two decades. Oncological prognosis depends mainly on two independent factors: size (> 2 cm), irrespective of secretion, and the existence of gastrinoma [47]. The management of metastatic pdNET does not differ from that of sporadic forms. Details are given in the National Digestive Oncology Thesaurus [48]. The role of ^{68}Ga-DOTATOC positron emission tomography (PET) in screening and monitoring patients with metastatic triple-negative breast cancer (TNBC) has not been defined in terms of number and location of metastases [41,48–51].

Table 1d
Probability of occurrence of different MEN1 disorders according to age. Data from the GTE/AFCE cohort (1450 patients).

Insulinoma		
Age(years)	Probability of occurrence (%)	95% confidence interval
10	0.6	[0.2–1.2]
20	2.2	[1.5–3.4]
30	4.0	[2.9–5.5]
40	6.9	[5.3–8.8]
50	9.5	[7.6–12.0]
60	10.3	[8.2–12.8]
70	11.8	[9.3–14.9]
80	11.8	[9.3–14.9]

4.2. Non-functional pancreatic NET (pNET)

Non-functional pNET has become the most common pNET since the widespread use of HEE in pancreatic screening of patients with MEN1 [41,51,52]. It is always multiple and rarely occurs before the age of 15; cumulative frequency by the age of 20 is around 20% [21,22,45]. In the majority of cases, non-functioning pNETs associated with MEN1 are discovered incidentally during screening. Very rarely, they may cause symptoms related to their size or to metastases: compression of neighboring organs, pancreatitis, food intolerance, epigastric and/or hypochondrial pain, jaundice. Non-functional pNET is the main cause of excess mortality in MEN1 [8,41]. The main prognostic factor is tumor size, with a generally accepted threshold of 2 to 3 cm [47,53–55]. Other aggressive factors should be taken into account in management: rapid growth (whereas the average growth of pNET is only 0.1–1.3 mm per year), tumor grade and high Ki-67 proliferation index (aspiration by HEE), SUV < 12.3 on ^{68}Ga-DOTATATE PET/CT, high SUV on ^{18}F-FDG PET/CT [56–59].

4.3. Duodenal/pancreatic gastrinoma, gastric neuroendocrine tumor

4.3.1. Gastrinoma

Gastrinomas are pdNETs associated with hypersecretion of gastrin, responsible for ZES. This is the functional syndrome most frequently associated with GEP-NETs in MEN1 (21–70% of cases, approximately 40% on average) but is rarely the inaugural manifestation (8% of cases) [33,41]. Conversely, around 25% of all gastrinomas develop in a context of MEN1, justifying MEN1 screen-

Table 1e
Probability of occurrence of different MEN1 disorders according to age. Data from the GTE/AFCE cohort (1450 patients).

Pituitary gland		
Age(years)	Probability of occurrence (%)	95%confidence interval
10		
20	5.4	[4.1–7.1]
30	15.3	[13.1–18.0]
40	25.9	[23.0–29.1]
50	35.7	[32.3–39.2]
60	42.5	[38.7–46.4]
70	48.7	[44.4–53.2]
80	53.7	[48.0–59.5]

ing in any patient presenting with ZES. Gastrinomas are located in the duodenum (95–100%) or much more rarely in the pancreas [60–62]. They are always multiple. Despite their generally small size (< 2 cm), gastrinomas are associated with lymph node metastases in 34% to 85% of cases [62].

4.3.1.1. Clinical manifestations. ZES is suspected clinically and during gastroscopy. Typical symptoms include peptic manifestations: esophagitis, which may be severe or complicated (hemorrhage, stricture), abdominal pain, duodenal ulcer, very often multiple, extending into the second duodenum (D2) and sometimes beyond, and sometimes complicated (hemorrhage, perforation) and associated with volumogenic manifestations: vomiting of clear acidic liquid, diarrhea. Weight loss may also occur. These symptoms, and particularly diarrhea, improve rapidly with proton pump inhibitors (PPIs). In the specific case of known and monitored MEN1, diagnosis is often made in the absence of the classic overt clinical picture of ZES. In this case, ZES is diagnosed at an early stage linked to early secretion of gastrin by the tumor, at a low level with minimal symptoms: epigastric burning/pain, pyrosis, and/or small progressive changes in transit. It is important to be aware of this mild presentation and to perform gastroscopy and fasting gastrinemia assay before prescribing PPIs. Gastroscopy may show moderate peptic lesions, mild esophagitis, and small limited erosions of the bulb or D2.

4.3.1.2. Diagnostic criteria. Diagnosis of ZES is based on several arguments. It is difficult, because the initial presentation is often incomplete, and because the diagnosis is delayed by the easy use of PPIs, which are effective in the presence of trivial epigastralgia or signs of gastroesophageal reflux disease [46]. ZES can almost certainly be diagnosed in case of gastric pH < 2, associated with inappropriate fasting hypergastrinemia (> 10 N) [51,63]. The rise in gastrinemia is in fact often less significant in forms diagnosed early, and is not specific when moderate, due to false positives (PPI intake, any cause of gastritis, particularly autoimmune or *Helicobacter pylori*) [64]. There may also be false negatives in MEN1 (see previous paragraph). Gastrin stimulation test by secretin (reserved to expert centers) is theoretically necessary to confirm incomplete forms of ZES [33]. However, difficulties in obtaining secretin make it difficult to carry out biological tests. In constituted ZES, gastroscopy reveals enlarged fundus folds and a clear abundant gastric mucosal lake. Diagnostic criteria have recently been published taking account of context (MEN1), symptoms, endoscopic peptic lesions (essential), gastrinemia, gastric biopsies and tumor location [63].

4.3.1.3. Penetrance kinetics. Mean age at diagnosis of gastrinoma associated with MEN1 is 34–39 years, with slight male predominance [65,66]. The penetrance is 10.1% [95% CI: 8.6–12.0] at the age of 40 (Table 1c).

4.3.1.4. Outcome. The main prognostic factors adversely affecting survival in patients with ZES in the setting of MEN1 comprise young age at diagnosis (≤ 33 years), elevated fasting gastrinemia (>20 N), tumor size ≥ 2 cm, presence of liver and/or bone metastases, and presence of associated gastric NETs [33,67].

4.3.2. Gastric NETs

4.3.2.1. Clinical manifestations, diagnostic criteria and screening. Type II fundusNET (i.e., occurring in the context of ZES and MEN1) is well differentiated and develops essentially in enterochromaffin-like cells present in the gastric fundus. It occurs in 23% of these patients and is generally polypoid, multiple and < 1 cm in size [68,69]. It should be distinguished from type I and type III fundus-NETs, which do not occur in the context of MEN1 and are detailed in the French TNCD thesaurus [48]. Most often asymptomatic, gastric NETs are screened by upper gastrointestinal endoscopy performed during ZES follow-up [41,69]. Care should be taken to look for gastric NETs during any EEH whatever the indication.

4.3.2.2. Outcome. Type II gastric NET is associated with lymph node metastases in 10–30% of cases. Nevertheless, it is not easy to be sure whether the primary tumor is in the duodenum or the pancreas. The risk increases with tumor size (probably >10 mm), Ki-67 index and invasion of the muscular layer of the gastric wall. Assessment of these factors is based on HEE and anatomopathological analysis [48,70].

4.4. Insulinoma

4.4.1. General information

Insulinoma is present in 2–24% of MEN1 patients [66,71,72]. After gastrinoma, it is the most frequent functional pNET in MEN1 patients. It is the first manifestation of MEN1 in 10% of patients. It accounts for 10–30% of all pNETs in MEN1 patients. It usually measures > 5 mm, is multiple in more than 30% of patients and malignant in 8% [73]. Insulinomas may be distributed throughout the pancreas, although caudal predominance has been reported (78%) [44].

4.4.2. Clinical manifestations

No studies specifically focused on clinical signs of insulinoma in MEN1. These are dominated by symptoms related to neuroglycopenia (visual disorder, speech disorder, mood disorder, loss of consciousness, convulsions, etc.) associated with symptoms related to the adrenergic response (sweating, pallor, tachycardia, anxiety, etc.). Weight gain is observed in 25% of patients with frank and frequent hypoglycemia leading to repeated glucose intake. Symptoms usually regress rapidly once blood glucose levels have returned to normal. In the vast majority of cases, these symptoms occur between meals, on an empty stomach or during physical exertion, or more rarely postprandially. Exclusively postprandial symptomatology is exceptional but does not rule out diagnosis of insulinoma [74]. In the latter case, it is important to consider the nature of the clinical symptoms, as inappropriate tumoral insulin secretion is more likely in the presence of neuroglycopenic symptoms.

4.4.3. Diagnostic criteria

No studies specifically focused on biological diagnostic criteria for inappropriate insulin secretion in MEN1 insulinoma. The criteria used are therefore those for sporadic insulinoma. Evidence of inappropriate insulin secretion during spontaneous hypoglycemia or induced hypoglycemia during fasting test confirms diagnosis of insulinoma in the context of MEN1. The usual standards for insulin, C-peptide and proinsulin are proposed. Venous blood glucose levels < 0.45 g/L or even < 0.55 g/L, insulin levels > 3 mIU/L, plasma C-peptide levels > 0.6 ng/ml and proinsulin levels > 5 pmol/L are

Table 1f
Probability of occurrence of different MEN1 disorders according to age. Data from the GTE/AFCE cohort (1450 patients).

Adrenal glands		
Age(years)	Probability of occurrence (%)	95%confidence interval
10	0.2	[0.0–0.8]
20	6.4	[0.3–1.4]
30	3.6	[2.5–5.1]
40	9.2	[7.3–11.4]
50	23.2	[20.1–26.7]
60	35.4	[31.4–39.7]
70	44.8	[39.9–50.0]
80	48.0	[42.3–54.2]

indicative of inappropriate insulin secretion [75,76]. A few studies reported that hypoglycemia in patients with insulinoma-MEN1 occurs late during the fasting test (between 48 and 72 hours), probably because investigations were carried out at an early stage [77]. The criteria for premature cessation of the fasting test and the biological criteria for inappropriate insulin secretion are the same as for patients without MEN1.

4.4.4. Penetrance kinetics

Like other neuroendocrine tumors of the pancreas, MEN1-insulinoma is most often diagnosed in the fourth decade, although insulinoma has also been reported in childhood, as early as 5 years of age [22,78]. Prevalence increases throughout the life of MEN1 patients, and is 6.9% [95% CI: 5.3–8.8] at the age of 40 (Table 1d).

4.4.5. Topographical assessment

Precise localization of insulinomas among the other endocrine tumors of the pancreas is essential in order to preserve as much pancreatic tissue as possible in these often young patients. All morphological examinations for localization are useful: MRI, CT scan and pancreatic echo-endoscopy, biopsy sometimes also being useful. Regional pancreatic venous catheterization with selective arterial stimulation by calcium is no longer performed [79]. The 68-Ga-exendin-4 PET/CT image of pancreatic β-receptors to incretins demonstrated good sensitivity in sporadic insulinoma, particularly when not easily visible on cross-sectional imaging [80]. It is of interest in the surgical strategy for patients presenting inappropriate insulin secretion and in whom several neuroendocrine tumors have been identified on imaging. Unfortunately, at present and in the context of MEN1, only a single retrospective study has been published, including 6 patients with 11 insulinomas, in which 68-Ga-exendin-4 PET/CT showed 84.6% sensitivity and 100% specificity for identifying insulinoma in MEN1 patients [81,82]. This procedure appears particularly promising in combination with MRI [81]. However, false positives were reported in patients with gastrinoma or VIPoma [83]. It therefore needs to be validated in a larger cohort of MEN1 insulinomas.

4.4.6. Outcome

Malignant insulinoma is uncommon, but tumor prognosis is similar to that of other pancreatic neuroendocrine tumors. However, there is an increased risk of death from hypoglycemia, although no epidemiological data are yet available to assess the frequency of this.

4.4.7. Screening

In case of discomfort compatible with hypoglycemia, even moderate or atypical, MEN1 patients must be screened for inappropriate tumor secretion of insulin. Careful questioning and education of the patient (and family for young subjects) is therefore essential, and is the main tool for screening for insulinoma. The diagnostic performance of biological screening has not been studied, but is probably minimal. As described so far, in all asymptomatic MEN1 patients, it is based on the systematic annual measurement of venous glycemia and an insulin test if glycemia is low [4]. The diagnostic value of insulinemia or C peptide in diagnosing inappropriate secretion is only valid if blood glucose levels are < 0.45 gr/L, which is hardly compatible with the absence of clinical symptoms [76]. In the case of moderately low blood glucose levels, assay of circulating proinsulin is the most sensitive diagnostic test. For example, 90% of insulinomas have proinsulin levels > 22 pmol/L on a morning sample taken on an empty stomach [77]. However, the value of this assay in the context of MEN1 has not yet been studied. Therefore, if there is the slightest clinical or anamnestic doubt suggesting hypoglycemia, a fasting test should be performed.

4.5. Other secreting tumors

Glucagonoma and VIPoma account for respectively 3.4% and 1.1% of pdNETs associated with MEN1 [41,84]. Functional somatostatinoma is quite exceptional. The symptoms of these tumors do not differ from sporadic forms [85]. Diagnosis of glucagonoma is confirmed by hyper-glucagonemia greater than twice the upper level of normal on the one hand, and clinical signs on the other hand. Anti-secretory treatment is based on somatostatin analogues and surgical resection. Glucagonomas are always found in the pancreas; they may induce diabetes and skin manifestations. Cases have been described of asymptomatic pNET associated with persistently high levels of glucagon, the prognostic significance and therapeutic consequences of which are poorly understood. Diagnosis of VIPoma (diarrhea and hypokalemia) is confirmed by VIP greater than twice the upper level of normal, diagnosis being all the more likely the higher the elevation. Anti-secretory treatment is based on somatostatin analogues, which are used as a matter of urgency once diagnosis has been confirmed, and on surgical resection. VIPomas are always found in the pancreas. These rare functional pNETs are often (> 50%) associated with lymph node or even distant metastases, particularly in case of tumor size > 3 cm [47,51,84,85]. Ten-year survival for these rare functional pNETs is around 50–60%.

4.6. Detection and follow-up of duodenal-pancreatic disorder

4.6.1. Age at detection

In a patient with MEN1, screening for pdNET can begin at the age of 12 or if symptoms are present [41,51]. Insulinomas can occur before the age of 12, but they are small and diagnosis can be made clinically without running the risk of delayed diagnosis [22].

4.6.1.1. Detection and monitoring tools. Screening and diagnosis of pdNET is based primarily on morphological imaging [41,52,56]. Pancreatic MRI is recommended in first line in this indication. It performs well in diagnosing pNET (better than CT), especially when the pNET measures > 1 cm [42]. MRI correlates well with tumor size and is not irradiating [86]. HEE is the most sensitive imaging modality (sensitivity, 90–95%), particularly for pNET <2 cm [43]. However, it can be misleading, particularly for large tumors in the tail of the pancreas [42]. HEE can also be used to perform biopsies and establish a grade. It requires general anesthesia and is operator-dependent. Finally, screening of sub-centimetric lesions is controversial, given their excellent oncological prognosis. Systematic HEE is therefore no longer recommended (Delphi-GTE-AFCE-2022). In the case of duodenal NET (dNET), which is usually sub-centimetric gastrinoma, imaging is not efficient, but has been little studied. For this reason, in cases of ZES, duodenoscopy may be indicated to screen for duodenal gastrinoma, but is of little value in the absence of clinical or biological suspicion. Finally, only fasting blood glucose is recommended as a biological test, despite its very

low sensitivity in asymptomatic patients. The various PET scans are used in second line, to characterize but not detect NETs.

Of note, MRI is the non-irradiating morphological examination of choice and can be used repeatedly. Assays of specific hormones in plasma (e.g., insulin, gastrin, glucagon, pancreatic polypeptide, chromogranin A, VIP) have poor diagnostic performance in the absence of specific symptoms [4,22,87,88] and cannot be systematically recommended for the detection of secreting or non-secreting GEP-NET associated with MEN1. These assays are mainly useful for confirming the existence of a functional syndrome.

4.6.1.2. Frequency of follow-up examinations for the duodenum-pancreas. The recommended frequency of MRI imaging is once every 3 years for asymptomatic pancreatic tumors < 10 mm and stable on 2 successive examinations over more than 1 year (Delphi-GTE-AFCE-2022), and once every 2 years when 10–20 mm in size (Delphi-GTE-AFCE-2022). CT scans should be avoided, being irradiating. Fasting blood glucose levels should be measured annually.

Of note, tumor size is a prognostic factor in itself, independently of secretion [47]. Rapid progression of GEP-NET is extremely rare. The frequency with which MRI is performed can therefore be modulated according to size [42,52,71,89,90]. Annual fasting blood glucose testing is easy and inexpensive, and can sometimes, albeit rarely, detect asymptomatic hypoglycemia,

4.6.1.3. Controversies. HEE can sometimes be discussed from the age of 16–18 years during follow-up on a non-routine basis, in addition to MRI and nuclear imaging, and in cases of diagnostic doubt or to perform a biopsy.

4.7. Treatment of duodenal-pancreatic disorder

4.7.1. Medical treatment

Medical treatment aims primarily at controlling hormone secretion, with or without subsequent surgery. In the case of ZES, PPIs, which should be prescribed as soon as diagnosis is suspected, should never be stopped, given the risk of potentially fatal complications. PPI doses (generally starting at 60 mg omeprazole-equivalent per day) are not standardized and must be adapted to the degree of control of clinical and endoscopic symptoms [42,85]. In case of insulinoma, medical treatment with hyperglycemic targets may be proposed to patients awaiting surgery or when surgery is contraindicated. It may consist in dietary fractionation and treatment with diazoxide or somatostatin analogues. For the rare glucagonomas, VIPomas and somatostatinomas, somatostatin analogues should be used as first-line treatment, or as systemic treatment in metastatic forms.

4.7.2. Surgical treatment

The aim of surgical treatment may be to suppress hormonal secretion, prevent metastatic spread or resect a malignant NET. The choice of resection technique is always a trade-off between risk of malignancy or life-threatening secretion and the operative mortality of pancreatic surgery (especially cephalic duodenopancreatectomy). Ultimately, it is also a question of weighing "satisfactory" wide resection against the functional consequences of large pancreatic amputation.

4.7.3. Surgery for Zollinger-Ellison syndrome

Gastrinomas in MEN1 are almost exclusively located in the duodenum and not the pancreas [60,61]. Surgery is very rarely indicated for functional symptoms in ZES, as these are almost always controlled by PPIs. The main aim of surgery is to reduce the risk of metastatic progression. There is evidence that surgery can prevent metastatic disease and improve survival [91–94]. It can be justified when there is an associated pNET (non-gastrinoma) requiring resection, when the technique used is of low vital risk, and when there is aggressive disease (associated pNET > 2 cm or progressive, peri-duodenal adenopathies).

There are two options.

4.7.3.1. First option. Duodenotomy with resection of duodenal gastrinomas (DUODX) supported by intraoperative endoscopic duodenal transillumination, with regional lymphadenectomy associated or not to left pancreatectomy depending on the need [95,96].

4.7.3.2. Second option. Pancreaticoduodenectomy (PD) with lymphadenectomy. This is the most logical operation, as it removes the duodenum [91–94,97]. However, operative mortality is high: 3.9% in MEN1 according to all the data pooled from the literature [86,91,92,97,98]. PD involves major parenchymal amputation and may lead to impaired quality of life and diabetes. It exposes the patient to a risk of major reduction of the pancreatic parenchyma in the event of recurrence in the remaining parenchyma. The choice is should be discussed within expert teams if the pNET of the associated head measures > 2 cm [47]. It should be noted that there is a major risk of anastomotic ulcer, which makes the continuation of PPIs essential for life after surgery in MEN1 with ZES. The chances of curing ZES by surgery are very low. There is no more indication for total gastrectomy (TG) in order to control gastric secretion. Only one case of TG was published after PPIs withdrawal due to severe hypomagnesemia [99].

Given the complexity of the situations (other pNETs, previous duodenopancreatic surgery, other threatening MEN1 lesions), decisions must be taken in RENATEN multidisciplinary board meetings, between continuing PPIs, DUODX and PD. Decisions should take account of the patient's age, general condition, informed opinion, previous duodenopancreatic surgery, the presence of other pNETs and their metastatic risk, and the expected consequences of parenchymal amputation. Hyperparathyroidism must be treated beforehand to control hypercalcemia and reduce acid secretion. Total pancreatectomy is rarely indicated, as short- and long-term morbidity is high.

4.7.4. Surgery for non-functional pNET

Indications are consensual for non-functioning pNET from 3 cm but debated from 2 cm because of the metastatic risk [47,52–55]. There are no recommendations for 1 cm resection in France [100]. Other associated aggressive factors may help in the decision: high Ki67 (following analysis of biopsies by HEE), 68Ga-DOTATATE PET/CT with SUV < 12.3, 18F-FDG PET/CT with detectable SUV, high growth rate (mean pNET growth of 0.1–1.3 mm per year), presence of metastatic lymph nodes, ductal dilatation and anatomical location (tail versus head), and obstructive symptoms [56,57,59,101,102].

The techniques used are not specific to MEN1, and involve controlled pancreatectomy adapted to the location. If the aim is to resect an a-priori benign NET, priority should be given to parenchyma sparing (enucleation, caudal or central pancreatectomy if possible) and lymph node dissection should be discussed. On the other hand, if the aim is to resect an NET with metastatic potential, lymph node dissection is indicated. On the left, spleen conservation is preferable if possible.

In cases where the risk–benefit ratio is against surgery, making the decision to operate particularly difficult (e.g., non-progressive tumors measuring 20–30 mm located in the head of the pancreas), FDG PET is recommended in the therapeutic discussion (Delphi-GTE-AFCE-2022) [102].

The destruction of non-functioning pNETs by radiofrequency with echo-endoscopy is not currently recommended, but may be discussed in the multidisciplinary board meeting in special cases. It is very likely that future indications for radiofrequency will differ

from those for surgery, and will be more frequent, in the interests of pancreas sparing [103,104].

4.7.5. Insulinoma surgery

Surgery is indicated in the absence of completely satisfactory medical treatment. The strategy is difficult because insulinoma can be multiple and diffuse, although it tends to be located on the left (78%) [44,73]. The performance of current localization tools (MRI, echo-endoscopy, CT scan) has improved surgical results (91% 10-year hypoglycemia-free survival) [73]. Further improvement is expected with the use of exendin PET combined with MRI [81,82,105,106]. The current trend for targeted surgery using minimally invasive techniques does not allow the entire pancreas to be explored manually, and therefore requires rigorous preoperative work-up [94,107]. The surgical technique is adapted to the characteristics of the tumor (single or multiple, size and location) and to the other NETs present: enucleation(s), caudal resection, left pancreatectomy, PD [44,73]. Parenchyma sparing is all the more justified in that these are usually benign NETs in young patients [22,82]; on the left, the spleen should be conserved if possible. If surgery is not possible, or to limit the risk of surgical morbidity and mortality, radiofrequency ablation of MEN1 insulinomas can restore euglycemia, as in patients with sporadic insulinoma [103]. However, few MEN1 insulinomas have been treated using this technique, and follow-up was short. Even so, the technique appears promising for patients not eligible for surgery [103,104,108]. Strict criteria must be met: definite location, at a distance from the main pancreatic duct, not associated with other pdNETs requiring synchronous resection, and more frequently when the insulinoma is cephalic in order to avoid PD.

4.7.6. Surgery for glucagonoma, VIPoma and somatostatinoma

Pancreatic oncological resection is adapted to these rare tumors, which are frequently malignant and larger in size [84].

5. Pituitary neuroendocrine tumor

5.1. Clinical manifestations

In MEN1, pituitary tumors are non-secreting in 20–48% of cases, and may be diagnosed either in routine monitoring on pituitary MRI or, much more rarely, as a result of compressive symptoms or pituitary deficiency, as suggested by the most recent studies evaluating large cohorts of patients [109–112]. Secreting pituitary tumors are observed in 52–80% of cases [109–114]; the most common type is prolactinoma (53–73% of cases of secreting tumor), either isolated or associated with GH secretion. Other secretions are possible but are rare and particularly in Cushing's disease [110–113]. In subjects under 21 years of age at diagnosis, secretion data are fairly contradictory: the youngest patient reported had a macroadenoma with symptomatic secretion of GH and prolactin at the age of 5 [115]. Goudet et al. reported 70% pituitary prolactin tumors and 25% non-secreting tumors between the ages of 10 and 21: the first symptoms were reported at an average age of 16 ± 3 years. The youngest patient with a macroadenoma was 12 years old [22]. In contrast, De Laat et al. reported only 4 secreting tumors in 11 pediatric cases in a series of 123 MEN1 patients with pituitary tumor [13].

5.2. Diagnostic criteria

Clinical manifestations are identical to those of sporadic pituitary tumor, and depend on size (micro- or macro-adenoma) and secretion profile. Classically, a pituitary image suggestive of adenoma is observed on pituitary MRI (performed either in a symptomatic patient or as part of monitoring), and/or hormonal hypersecretion (prolactin, IGF-1, ACTH and cortisoluria, TSH and T4) with the clinical signs associated with this secretion, and/or an anterior pituitary deficit affecting one or more anterior pituitary lineages (in the case of a macroadenoma) [4,41].

Table 1g
Probability of occurrence of different MEN1 disorders according to age. Data from the GTE/AFCE cohort (1450 patients).

Thymus		
Age(years)	Probability of occurrence (%)	95% confidence interval
10		
20		
30	0.2	[0.1–0.9]
40	1.8	[1.0–3.0]
50	4.3	[2.9–6.2]
60	5.8	[4.1–8.2]
70	7.3	[5.1–10.4]
80	7.3	[5.1–10.4]

5.3. Penetrance kinetics

The prevalence of pituitary tumors is estimated at 15–50% [4]. The 2 most recent large studies of MEN1 reported prevalence of 37% and 41% respectively in large cohorts of 551 and 475 patients with MEN1 [110,112]. In the largest study of menin gene variants, the prevalence of pituitary tumors reached 49% at the age of 80 [12]. It was 25.9% [95% CI: 23.0–29.1] at the age of 40 in the GTE cohort (Table 1e). Conversely, while the youngest patient with MEN1 was 5 years old when diagnosed with a pituitary tumor, the most recent studies did not identify any pituitary tumors before the age of 10. It is therefore likely that around 50% of patients with MEN1 will develop pituitary involvement during follow-up, between the ages of 10 and 80. Interestingly, Van Den Broek et al. recently showed that genetic anticipation is present in large families with MEN1: age at diagnosis of pituitary tumor is lower in the 3rd than in the 2nd generation (median, 18 versus 33 years); however, the earliest age is no different (18 years in both 2nd and 3rd generations) [116]. Pituitary involvement classically occurs after primary hyperparathyroidism. However, pituitary tumors may be the first obvious clinical manifestation of MEN1 [66]. Thus, 57% of the 123 patients with pituitary tumor were diagnosed with MEN1 at a later stage in De Laat's study [109]. This does not mean that all these patients had a normal phosphocalcium balance at the time of diagnosis of the pituitary tumor. In the GTE study of a large cohort of patients with MEN1 before the age of 21, pituitary tumors were the first manifestation in 21% of cases, and without other involvement in 15% of cases [22]. Finally, a French series identified pathogenic MEN1 variants in 3.4% of 173 patients diagnosed with isolated macroadenoma before the age of 30 [10].

5.4. Outcome

While earlier studies of MEN1 pituitary tumors reported a higher rate of macroadenoma and/or invasive/proliferative tumor, recent data did not confirm these findings [112,113,114,117]. In 123 MEN1 patients with pituitary tumor, De Laat et al. found a majority ($n = 83$; 67%) of microadenomas; only 3 showed growth at 6 years' follow-up, and growth was limited, with none reaching the macroadenoma stage, and less than 10% requiring specific treatment. Of the macroadenomas operated on, only 1 had a Ki-67 index greater than 3% suggesting aggressive outcome [109]. Four other recent studies did not suggest that MEN1 pituitary tumors are particularly aggressive: Giusti et al. found 63% microadenoma in a cohort of 178 MEN1 patients with pituitary tumor [110]; Wu et al. reported only 3 patients with invasive macroadenoma (Knosp 3 or 4) in a cohort of 54 patients with MEN1 pituitary tumor [111];

Goudet et al. reported that 76% of pituitary tumors diagnosed before the age of 21 were classified as Hardy 1 or 2 [22]. The most recent publication, on 202 MEN1 patients with pituitary adenoma, found 58% microadenoma [112]. Only 4 of the 137 patients with enclosed (i.e., purely intrasellar) microadenoma or macroadenoma showed progression in adenoma size at a median follow-up of 3 years. MEN1 pituitary carcinoma is very rare, with 4 cases reported to date (2 prolactin tumors, 1 TSH tumor and 1 non-secreting tumor) [118–121].

5.5. Screening and monitoring

5.5.1. Age at detection

A first assessment is recommended at the age of 10. This may be brought forward if there are symptoms suggestive of pituitary tumor. Of note, only 1 case of pituitary tumor was described at the age of 5 years, with hypersecretion of GH and prolactin, clinically identifiable. No cases were reported in the most recent series before the age of 10. Between the ages of 5 and 10, clinical monitoring (headache, visual disorder, break in the growth curve, rapid growth, weight gain, etc.) is guided by clinical findings. These data are consistent with penetrance kinetics (Table 1e).

5.5.2. Detection and monitoring tools

Hormonal evaluation (prolactin, IGF-1) combined with pituitary MRI is recommended at the first check-up after positive screening from the age of 10. Approximately 20–48% of pituitary tumors associated with MEN1 are non-secreting, and should therefore be investigated by MRI. The most common secretion profile is hyperprolactinemia, which may be associated with hypersecretion of growth hormone. Other secretion profiles are rare and associated with clinical symptoms.

5.5.3. Frequency of follow-up examinations

It is recommended that a systematic annual biological work-up (prolactin, IGF-1) be carried out. Additional hormonal work-up may be carried out if there are clinical signs suggestive of another hypersecretion or an anterior pituitary deficit. The MRI surveillance schedule for non-secreting pituitary tumors is as follows (Delphi-GTE-AFCE-2022):

- if the 1st MRI is negative, we recommend that pituitary MRI be performed every 3 years;
- if the 1st MRI reveals a non-secreting microadenoma, we suggest that a new MRI be performed after 6 months to assess whether the tumor has progressed, and that the standard monitoring schedule (every 3 years) be repeated if the tumor has not progressed;
- if the 1st MRI reveals a non-secreting macroadenoma, we suggest that a new MRI be performed at 6 months, then at 1 year, then annually for 5 years (following the recommendations of the French Endocrine Society on sporadic non-functioning pituitary tumors);
- if there is no progression, standard monitoring should be repeated every 3 years. If a macroadenoma is found, and if it is close to the optic chiasm, full ophthalmological assessment should be carried out, including visual field and visual acuity (and, depending on availability, optical coherence tomography).

5.5.4. Treatment

There is no evidence that MEN1 pituitary tumors are more aggressive than sporadic tumors. Similarly, and contrary to previous studies (58% resistance to dopaminergics in the study by Verges et al.) [113], the secretion of pituitary tumors does not appear to be particularly resistant to conventional medical treatment, as illustrated by the anti-secretory efficacy in 90% of prolactinomas reported by De Laat et al. [109,113]. In the case of a pituitary tumor, the modalities of therapeutic management should be discussed in an expert center, with various options: anti-secretion treatment (somatostatinergic, dopaminergic or steroidogenesis inhibitors) in the case of hormonal hypersecretion; transsphenoidal surgery in the case of local compression, particularly chiasmatic, or in the case of hormonal hypersecretion; or radiotherapy, most often in the case of a residue that increases in volume or becomes secreting after surgery has failed. Some pituitary tumors may be monitored on a long-term basis, without treatment, after discussion at an expert multidisciplinary board meeting, particularly in the case of small/moderate lesions with no visual field impact and no associated hormonal abnormality. In conclusion, the therapeutic management of MEN1 pituitary tumor should not differ from that of sporadic pituitary tumor.

Table 1h
Probability of occurrence of different MEN1 disorders according to age. Data from the GTE/AFCE cohort (1450 patients).

Thymus according to gender				
Age(years)	Women Probability of occurrence (%)		Men Probability of occurrence (%)	
10				
20				
30			0.5	[0.1–2.0]
40	0.5	[0.2–2.0]	3.2	[1.8–5.8]
50	0.5	[0.2–2.0]	8.7	[5.9–12.7]
60	0.5	[0.2–2.0]	12.2	[8.6–17.0]
70	0.5	[0.2–2.0]	15.4	[10.8–21.8]
80	0.5	[0.2–2.0]	15.4	[10.8–21.8]

6. Adrenal disorder

6.1. Clinical manifestations

There are usually no clinical manifestations. Pheochromocytoma is a tumor of the adrenal medulla and does not normally belong to the MEN1 spectrum. Abnormal hormone secretion is only seen in around 15% of patients with adrenal tumor on imaging. This may be primary hyperaldosteronism or Cushing's syndrome (to be differentiated from pituitary origin or ectopic ACTH secretion). Mixed and/or androgenic secretion (virilization in children and women) should raise concerns about malignant adrenocortical disease [122,123].

6.2. Diagnostic criteria

Adrenal lesions are almost always discovered on MRI or CT imaging of the abdomen. On cross-sectional imaging, they usually appear as global hypertrophy or micronodules, with >1 cm tumors present in only around 10% of patients [122]. In the absence of specific studies in MEN1, the proposed characterization corresponds to that of non-MEN1 cortical tumors on non-enhanced CT or MRI. A homogeneous size of < 4 cm and a spontaneous density of < 20 HU on CT or fatty content on MRI (opposite phase sequences) are in favor of benign adenoma [124,125]. In the case of > 4 cm tumor, heterogeneous tumor on non-enhanced CT or MRI, or density > 20 HU, additional characterization imaging, in particular 18FDG PET, and surgical resection should be discussed.

6.3. Penetrance kinetics

The probability of occurrence at the age of 40 was 9.16% (95% CI: 7.32–11.44) in the AFCE/GTE cohort (Table 1f). Adrenal lesions are bilateral in more than a third of cases [122,123].

6.4. Prognosis

Prognosis is usually excellent due to the benign, non-secreting nature of the vast majority of lesions. However, the prevalence of malignant adrenocortical carcinomas, although very low, is higher than in the population of adrenal incidentalomas and may concern up to 7% of MEN1 patients with morphological adrenal involvement [122]. These are always tumors measuring > 25 mm, not typical of adenoma according to conventional CT or MRI criteria, or growing relatively rapidly in volume [122,126].

6.5. Age at detection

Detection is from the age of 12, during cross-sectional imaging examinations for pancreatic involvement and in the absence of earlier clinical signs. This is consistent with penetrance kinetics and benefits from duodenal-pancreatic monitoring [122].

6.6. Detection and monitoring tools

MRI is preferred. If a > 10 mm lesion is found, blood pressure should be measured, clinical signs of hyperandrogenism or hypercortisolism should be screened for, and the following tests should be carried out (as a minimum): plasma aldosterone + renin in sitting position in case of hypertension or hypokalemia, plasma testosterone in children and women with signs of virilization or > 3 mm tumor, and 1 mg overnight dexamethasone suppression test (expert recommendation). It is not recommended to repeat the biological hormonal tests after normal initial hormonal work-up without onset suggestive clinical signs or significant progression in adrenal lesion size.

6.7. Frequency of follow-up examinations

For tumors that are typically benign on imaging, abdominal MRI every 3 years is suggested in adults, and may be included when imaging is requested for pancreatic controls (expert recommendation). A clear progression in size (arbitrarily, > 20% in 6–12 months) associated with absolute size > 5 mm without the above-mentioned benign adenoma criteria on imaging should raise fears of malignancy and lead to the discussion of surgery by a surgeon with expertise in adrenal carcinology and/or to a complementary imaging work-up including 18FDG PET and hormonal work-up in a specialist center.

6.8. Treatment

Medical treatment is initiated in rare cases of excessive hormone secretion (spironolactone/hyperaldosteronism, cortisol-lowering drugs/Cushing's syndrome). Surgical treatment, in addition to the tumor-based criteria for the above-mentioned intervention, is also indicated in case of hormonal hypersecretion. A laparoscopic/robotic approach, by a surgeon with expertise in adrenal carcinology, is considered only in the absence of malignancy criteria and for < 6 cm tumors [127].

6.9. Controversies

The actual prevalence of morphological damage detectable by modern imaging tools is probably higher than that published in retrospective reference studies, as suggested by echo-endoscopic studies, but probably concerns small lesions that are often of no pathological significance [123], whereas the prevalence of lesions of concern because of their size, secreting nature or suspected malignancy (7% of adrenocortical carcinomas) is unlikely to change [122]. The question of whether adrenocortical carcinoma associated with MEN1 has better prognosis than sporadic cases has been raised but remains unanswered [122].

Table 1i
Probability of occurrence of different MEN1 disorders according to age. Data from the GTE/AFCE cohort (1450 patients).

Bronchial and pulmonary disorders (if histological diagnosis)		
Age (years)	Probability of occurrence (%)	95% confidence interval
10		
20		
30	0.5	[0.2–1.2]
40	1.3	[0.7–2.4]
50	3.5	[2.3–5.3]
60	7.7	[5.6–10.6]
70	13.2	[9.8–17.7]
80	17.6	[12.4–24.6]

7. Thymic (th) disorders

7.1. Clinical manifestations

Thymic tumors in MEN1 are predominantly ThNETs and very rarely functional [128,129]. Thymoma is rarer, and is associated with MEN1 on the basis of evidence of loss of heterozygosity in thymic tissue [130]. ThNET occurs almost exclusively in men in Western countries, and there are families with predisposition to ThNET (clusters) with no phenotype–genotype correlation [131,132]. One in 5 cases of ThNET occur in a context of MEN1 [128]. It is rare for it to be indicative of MEN1, although it may be present at the time of diagnosis of the disease [133,134]. Thymic tumor is either asymptomatic and detected on imaging work-ups, or symptomatic in the presence of a tumor syndrome (pain, cough, superior venous syndrome, etc.) or metastatic manifestations (pericardial, pleuropulmonary or bone involvement) [135,136]. Smoking may be a risk factor, but results are contradictory [127,130,134,136,137].

7.2. Diagnostic criteria

An abnormal mass in the anterosuperior mediastinum on imaging indicates a thymic tumor in MEN1. Preoperative histology is not necessary if surgical resection is possible. ThNET is usually a well-differentiated neuroendocrine lesion (typical or atypical carcinoids), but large-cell lesions or even high-malignancy small-cell neuroendocrine carcinoma may be observed [131,138].

7.3. Penetrance kinetics

ThNET has total prevalence of 5%, and is extremely rare before the age of 20. A few male cases were observed after the age of 25 (4 cases between the ages of 26 and 30 out of 59 thNETs in the GTE/AFCE/2023 cohort: i.e., 7%). ThNET occurs almost exclusively in men in Western countries [72,127]. The probability of occurrence is 3.2% [95%CI: 1.8–5.8] at the age of 40 in men, and virtually nil in women (Tables 1g–1h).

7.4. Outcome

Although not common, ThNET is the most aggressive MEN1-related NET, requiring specific and rigorous surveillance [8]. Median survival was 9 years and 7 months in the GTE/AFCE cohort [131]. The only clear prognostic factor is tumor size (> 6 cm) at diagnosis [134].

Table 2
GTE/AFCE recommendations for lesion screening in MEN1 patients. Biological and morphological tests.

Organ	Biological tests	Age at onset and frequency of biological tests	Morphological examinations	Age at onset and frequency of morphological examinations
Parathyroid	Blood calcium Corrected blood calcium Phosphoremia ± Parathyroid hormone	To 10 years Then annually (or MEN1 diagnosis if later)	Ultrasound. MIBI scintigraphy or even PET-choline if surgery is planned	Before parathyroid surgery Screening for ectopic gland
Duodeno-pancreas	Fasting blood glucose	To 10 years then annually	Abdominal MRI	At the age of 12 – every 3 years if stable and diameter ≤ 10 mm – every 2 years if stable and diameter 10-20 mm
Gastric fundus			Duodeno gastroscopy	During follow-up of ZES And at each EEH
Pituitary gland	Prolactin. IGF-1	To 10 years then annually	Brain MRI	To 10 years – If negative, every 3 years – If micro-adenoma, at 6 months then every 3 years if stable -If non-secreting macroadenoma, at 6 and 12 months then every year for 5 years. Then every 3 years if stable
Adrenal			Abdominal MRI	At age 12 then every 3 years
Lung and Bronchi			Thoracic MRI or low-dose CT	At 30 then Every 3 years if diameter <10 mm and stable
Thymus		Chest MRI or low-dose CT)	At age 30 for women, then every 3 years At age 25 for men, then every 3 years At age 20, then every 3 years if family history of thymic NET	
Breast			Mammography	At age 40 and every 2 years thereafter

7.5. Age, detection tool and frequency of follow-up examinations

These data argue for detection in men from the age of 25, and unquestionably from the age of 30, by imaging repeated every 3 years (Delphi-GTE-AFCE-2022) (Tables 1g–1h) [131]. We suggest that ThNET should be detected from the age of 30 in women, from the age of 25 in men with no family history of ThNET, and from the age of 20, regardless of gender, in a MEN1 family in which at least one case of thymic tumor has already been identified. Thoracic MRI is the preferred non-irradiating tool (Delphi-GTE-AFCE-2022) [126]. If CT is used, it should be low-dose.

7.6. Surgical treatment

As a preventive measure, and in the absence of any family history of ThNET, we suggest performing preventive thymectomy, as total as possible, via the neck, in men and in women only at the time of parathyroid surgery. Its efficacy is relative [127,131,139,140]. This also makes it possible to remove any 5th intrathymic parathyroid gland. On the other hand, in a family in which at least 1 case of thymic tumor has been identified, we suggest that preventive total thymectomy, preferably minimally invasive, should be performed systematically in men from the age of 30 (Delphi-GTE-AFCE-2022) [141]. In a curative situation and in the presence of proven thNET, thymectomy for oncological purposes should be performed. The aim is complete R0 resection. It is performed by sternotomy, or by minimally invasive means in the case of < 3 mm tumor with no signs of invasion on video-thoracoscopy or robotic thoracoscopy (Delphi-GTE-AFCE-2022) [142,143].

7.7. Preoperative examinations

In preventive surgery prior to parathyroidectomy, parathyroid scintigraphy (to look for a 5th intra-thymic gland) and follow-up thoracic imaging data (lungs + thymus) should be used, noting that PET-choline, which is increasingly used in the assessment of hyperparathyroidism (with CT fusion image), can mark ThNET [32]. If curative surgery is performed for thymic carcinoma, extension assessment is based on thoracic CT and gallium PET/CT (^{68}Ga-somatostatin receptor PET/CT) [140].

7.8. Medical treatment

Indications for chemoradiotherapy for poorly differentiated unresectable lesions or systemic treatment by chemotherapy, internal vectorized radiotherapy (IVRT) or targeted therapy (everolimus) in metastatic situations should be discussed in the multidisciplinary board meetings (RENATEN).

8. Bronchial and pulmonary disorders (bpNET)

8.1. Clinical manifestations

BpNET is usually asymptomatic and discovered by imaging during follow-up work-up for thymic monitoring, but also sometimes in the presence of hemoptysis, cough or dyspnea.

8.2. Diagnostic criteria

Diagnosis is preferably histological by bronchial endoscopy after detection on imaging (4.6–6.6% of patients), but may be based on radiological criteria without systematic histological confirmation (23% of patients), particularly in small bpNETs in patients who may have several bpNETs simultaneously [144,145]. PET-DOTATOC has recently demonstrated efficacy in the detection and confirmation of bpNET [146]. Histologically, these are typical or atypical carcinoids which progress slowly, but exceptional cases of small- and large-cell neuroendocrine carcinoma are possible [142]. These poorly

Table 3
Age at first screening for each MEN1 disorder.

Starting age	Examination	Detection
10 years	Blood calcium, corrected blood calcium, with or without parathyroid hormone	Hyperparathyroidism
10 years	Prolactin, IGF-1 Pituitary MRI	Pituitary NET
12 years	Blood glucose Abdominal MRI	Insulinoma Pancreaticoduodenal NET Adrenal tumor
20 years	Chest MRI	Thymic tumor If family history
25 years (men)	Chest MRI	Thymic tumor
30 years (women)	Chest MRI	Thymic tumor
30 years	Chest MRI	Bronchial and pulmonary tumor
40 years	Mammography	Breast cancer

differentiated forms are associated with smoking in patients with sporadic bpNET [147].

8.3. Penetrance kinetics

Penetrance is 1.3% [95% CI: 0.7–2.4] at the age of 40 (AFCE/GTE) (Table 1i).

8.4. Outcome

The probability of survival was 87.8% [95% CI: 80.1–96.3] at 10 years in the GTE/AFCE cohort. Seven of the 15 deaths were directly related to bpNET. They were diagnosed after 35 years of age [144]. The probability of survival was 78.0% [95% CI: 64.6–94.2] at 15 years in the Dutch cohort, without any bpNET-related deaths [145]. Progression was slow in terms of diameter, at 6% per year, with a doubling time of 11.8 years. Median diameter at diagnosis was 5 mm (IQR: 3.0–6.3 mm). In the 29 patients operated on, those with lymph node involvement were never less than 35 years of age [145]. In spite of this slow natural history, bpNET can, in very rare cases, change its course abruptly or lead to death [144,145]. These unfavorable cases may not be due to the MEN1 context. However, it is essential to detect them. The link with smoking is an open question.

8.5. Age at detection, detection tool and frequency of examinations

Detection is recommended from the age of 30; surveillance is performed every 3 years if the previous examination was negative, or for < 10 mm bpNET remaining stable on 2 successive examinations (Delphi-GTE-AFCE-2022). Thoracic MRI is recommended, with low-dose CT as an alternative.

8.6. Treatment

If surgery is indicated, extension is assessed by thoracic CT and somatostatin receptor PET-CT imaging (DOTA-TOC/DOTA-NOC [142]). Given the excellent prognosis, frequency of small (< 10 mm) stable tumors, multiplicity of possible lesions, risk of successive new lesions and the need for parenchyma sparing, surgical indications are assessed and discussed in multidisciplinary board meetings (RENATEN). Smoking cessation is recommended.

8.7. Controversies

Small cell lung carcinoma (SCLC) and large-cell neuroendocrine carcinoma (LCNEC) are more frequent in smokers, and there is some debate as to whether they can be attributed to MEN1 [144,147].

9. Other associated diseases

9.1. Skin lesions

Skin lesions comprise multiple facial angiofibroma (22–88%), collagenoma (0–72%), and histiocytofibroma and lipoma (3–34%) [148]. They can be very useful in suggesting MEN1 in the presence of a suspicious NET picture. Lipomas are ubiquitous, can be painful and require surgical resection. Numerous other lesions, and in particular melanoma, have been described, that are less clearly imputable [149]. Full dermatological examination is an essential part of work-up.

9.2. Central nervous system

In order of frequency, meningioma (0.85%), ependymoma (0.60%), astrocytoma (0.35%) and schwannoma (0.30%) (together known as MESA) are detected on MRI monitoring of pituitary adenomas.

9.3. Breast cancer

The risk of breast cancer is multipliers by 2.01 [95% CI : 1.33–2.88] i.e., a slight increase. Age at onset is 10 years earlier than in the general population. Annual clinical examination is recommended from the age of 20. Additionnal screening every 2 years should begin at the age of 40 for women who have been diagnosed with MEN1.

9.4. Other tumor associations

Other associations are possibly linked to MEN1: leiomyoma, sarcoma (several cases in the MEN1 AFCE/GTE cohort), B lymphoma and mesothelioma [150–153].

10. Quality of life, patient associations and RENATEN multidisciplinary board

The various quality of life (QoL) indicators in MEN1 patients are impaired on average compared with the general population [26,153,154]. However, QoL is linked above all to the extent of damage, which varies from patient to patient and increases over time, from a completely normal QoL to significant impact with the risk of cumulative damage [155–157]. Many factors that can affect QoL, including unnecessary additional invasive examinations and surgery, with their possible side-effects (the probability of undergoing surgery at least once in a lifetime is over 80% after the age of 70), fear of risks incurred by family and friends, and greater financial difficulties [7,153,158,159]. Independently of QoL, it should be borne in mind that life expectancy is significantly lower than in the general population [7,160]. Consequently, the choice of relevant complementary examinations and therapeutic decisions must be made at an individual level in groups with expertise in MEN1 disease, with the constant concern of not worsening QoL. This is the role of the RENATEN multidisciplinary board meetings. Patient associations play a major role in supporting patients to combat isolation. In France, the "*Association Française des NEM*", MEN association (AFNEM) and the "*Association des Patients porteurs de Tumeur EnDocrine*", association of endocrine tumor carriers (APTED) can

be reached via the following links: https://www.afnem.fr and https://www.apted.

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