

Multiple Endocrine Neoplasia type 1 (MEN1) : Recommendations and Guidelines for Best Practice

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Summary

Multiple endocrine neoplasia type 1 (MEN1) is characterised by combined occurrence of parathyroid tumours, duodenopancreatic neuroendocrine tumours (NETs) and anterior pituitary adenomas. Some patients may also develop thymic and bronchopulmonary NETs, and adrenal tumours. MEN1 is an autosomal dominant disorder caused by mutations in the tumour-suppressor gene *MEN1*, which encodes a scaffold protein, menin. Without treatment, MEN1 patients have higher morbidity and premature mortality, which can be mitigated by earlier tumour detection and intervention. Identification of such individuals at high risk for MEN1 can be facilitated by genetic testing of patients and their first degree-relatives, and undertaking periodic clinical, biochemical and radiological screening in patients and *MEN1* mutation carriers. However, no consensus exists regarding the optimal assessment and management of MEN1. To provide such recommendations, a multidisciplinary group was convened to undertake systematic reviews and meta-analysis of the literature, and to use a Delphi approach for the development of consensus statements. Fifty-five clinical recommendations were developed to guide clinicians, patients and stakeholders about approaches for MEN1 in adults and children.

Introduction

Multiple endocrine neoplasia (MEN) syndromes are autosomal dominant disorders characterised by the occurrence of tumours involving two or more endocrine glands within a single patient. Five major forms of MEN, referred to as MEN types 1 to 5 (MEN1 to MEN5) are recognised, and each form is characterised by the development of tumours within specific endocrine glands (table 1). Parathyroid tumours, neuroendocrine tumours (NETs) of the pancreas (PanNET) and duodenum, and pituitary adenomas (PAs) are the main manifestations of MEN1.^{1,2} Patients with MEN1 may also develop other endocrine tumours, including adrenal cortical tumours as well as thymic, bronchopulmonary and gastric NETs. Non-endocrine tumours associated with MEN1 include facial angiofibromas, collagenomas, and lipomas, and possibly also meningiomas, breast cancer and melanoma. Thus, MEN1 patients may have tumours and clinical features that overlap with those of the other MEN syndromes, especially MEN4 and MEN5 (table 1). Patients with MEN1 have a decreased life expectancy, with metastatic NETs representing the most important disease-related cause of death.^{3,4}

The first case reports describing the co-occurrence of multiple endocrine neoplasms were in the early 1900s, and this led to the recognition of a unifying disorder in which individual patients developed the triad of parathyroid, pancreatic islet cell and anterior pituitary tumours, which are the hallmarks of MEN1. In 1954, a familial basis for MEN1 was established by documenting its occurrence in a father and daughter of one family,⁵ and in a father and four daughters of another family.⁶ In 1997, the identification of the *MEN1* gene^{7,8} facilitated DNA testing to reveal those individuals in an MEN1 family who have a mutation, which is defined in this article as a change in the DNA sequence of a gene that causes a person to have or be at risk of developing the disease,

and is equivalent to the “pathogenic” or “likely pathogenic” variant classification of the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) standards and guidelines (appendix p3).⁹ Importantly this development of genetic testing identified pre-symptomatic individuals, i.e. those who had the mutation but as yet had not developed clinical symptoms or manifestations of MEN1. Such pre-symptomatic individuals were therefore considered to have *genetic* MEN1. In 2001,¹ clinical practice guidelines, based on expert opinions, were developed and updated in 2012² to advise on the diagnosis and management of patients with MEN1. These guidelines advocated uniform screening and surveillance methods that would also help to gather information, which in the future could better inform clinicians to address the complex management decisions in MEN1.

The use of presymptomatic genetic testing and subsequent prospective screening advocated in existing guidelines, has resulted in patients being diagnosed at earlier stages of the different manifestations. This frequently poses challenges in clinical management as smaller, mostly indolent, non-functioning (i.e. not secreting hormones) PanNETs (NF-PanNETs), thoracic NETs, pituitary microadenomas and adrenal adenomas are identified in asymptomatic patients, alongside hormone-secreting neoplasms (e.g. parathyroid tumours, gastrinomas and insulinomas) at very early stages. Furthermore, during the past few decades large multicentre (population-based) and single-centre cohort studies^{3,10-15} have provided valuable insights into many aspects of the natural course of MEN1-related tumours. However, owing to a lack of evidence-based guidelines, clinical applications of screening and surveillance protocols for MEN1-related tumours vary, even among different centres of excellence.¹⁶

As a first step to provide evidence-based recommendations, we performed three systematic reviews and a meta-analysis regarding key therapeutic topics in each of the main MEN1-related tumours (figure 1).¹⁷ This process identified over 3,000 articles published since 2001, although most (~90%) were retrospective series with sparse data that were insufficient for providing high or moderate certainty for the evidence using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach.^{18,19} Despite these limitations, we were able to ascertain 37 publications, including 27 retrospective and 1 prospective cohort study, and 9 case series. From these studies, we extracted and analysed data from 1814 patients, allowing us to establish that in MEN1 patients: 1) subtotal parathyroidectomy (SPTX), when compared to than less than SPTX (<SPTX), for treatment of parathyroid tumours causing primary hyperparathyroidism (PHPT), was associated with a significantly lower risk of PHPT persistence and recurrence, but a significantly higher risk of post-operative chronic hypoparathyroidism; 2) for NF-PanNETs ≤ 2 cm, metastatic disease and mortality rates, based on a limited number of studies, were not different between the surgery versus active surveillance groups; and 3) dopamine agonist (DA) responses for prolactinomas in MEN1 and non-MEN1 patients were similar.¹⁷ It is important to note that the GRADE levels (scores) for all were low or very low. Moreover, due to the complexity of MEN1 and the varying methodological quality of available information, many other questions remained unanswered, and for these we used the Delphi method (figure 1, appendix p4), a technique for structured quantification of expert opinion,²⁰ to re-examine the literature and develop practical clinical recommendations that would help to provide guidance for patients and families affected by MEN1, patient advocacy groups, other stakeholders and health care professionals. In addition, we aimed to identify knowledge gaps and suggest research priorities that would promote impactful, patient-centred research on MEN1.

Methods

An international writing committee (appendix pp5-6) was assembled and tasked with developing evidence-based and consensus-based clinical practice recommendations for MEN1. The Delphi proceedings, which were coordinated by the Delphi core-group from the international writing committee (appendix pp5-7), aimed to address controversies in screening and surveillance practices, as well as in the timing and extent of initial parathyroidectomy. The Delphi Expert Panel comprised international experts, who were selected on the basis of their recognised clinical experience, academic excellence, and contributions to professional organisations with remits for endocrine tumours and/or MEN1, represented 22 countries from 5 continents (Asia, Australia and Europe, North America and South America) (appendix pp8-13). Delphi consensus meetings were held for each of the main MEN1-related manifestations (PHPT, NETs, and PAs) as well as for paediatric-specific considerations (appendix p4 and pp14-27). Initial statements were developed by the Delphi Core group (appendix pp6-7). Experts could be part of one or more of the topic-specific panels. Each Delphi consensus process consisted of three rounds, two individual questionnaire rounds and a final online meeting. Statements were finalised through voting and discussions in the online meetings. The wording of the final statements (table 2) was chosen to reflect the level of consensus (appendix pp14-27). “**Recommend**” was used for statements that reached consensus in the first two rounds (agreement $\geq 80\%$), “**suggest**” for statements with near consensus (agreement 70-79%) and “**consider**” for statements where opinions among experts are more varied (agreement 51-69%, appendix p14).

Recommendations

The outcomes of the Delphi proceedings comprised 52 consensus statements (table 2) which included those pertaining to: the screening, surveillance, sequelae and treatments of parathyroid

tumours (n=16); screening and surveillance of duodenopancreatic (n=14) and thoracic (n=5) NETs; screening, surveillance and management of PAs (n=9); genetic testing (n=4); and general comments (n=4). These statements are detailed with remarks, nuances and caveats from the discussions of the final online Delphi expert meeting (appendix pp14-35). These Delphi consensus statements together with the outcomes from the systematic reviews and meta-analysis¹⁷ form the foundations for the current recommendations, which were supplemented by literature-based expert opinion for topics not included in the systematic reviews or Delphi consensus (figure 1).

General recommendation

Due to the complexity and rarity of the disorder, patients and families with MEN1 should be managed in centres of expertise by multidisciplinary teams (#3, table 2) that collaborate nationally and internationally for optimisation of clinical care and research.

Recommendations for Screening for MEN1-related tumours

The aim of screening for MEN1-related tumours is to enable for their earlier detection, thereby allowing for timely intervention and prevention of tumour-related morbidity and mortality. Clinical evaluation with careful assessment of symptoms and education of patients and family members is an integral part of screening in patients with MEN1. This is because an important goal of screening is to identify clinically relevant disease, and not necessarily to detect the earliest onset of disease. In addition, cumulative costs, adverse effects and ease of undertaking the investigations should also be taken into consideration in a lifelong screening program.

Screening for MEN1-related tumours is challenging because clinical and biochemical manifestations in members of any one family are not uniformly similar, and there is no genotype-phenotype correlation.^{21,22} Age-related penetrance (i.e., the proportion of gene carriers manifesting symptoms or signs of the disease by a given age) has been ascertained, and penetrance below the age of 10 years is low, and near zero below age 5 years.^{1,23-25} Thereafter, penetrance steadily rises to reach > 95% by age 70 years.^{1,24-26} Screening recommendations are intended for: patients with MEN1, which may be genetically confirmed, or obligate carriers (#1, table 2; figure 2); patients developing endocrine tumours at an early age and hence there is suspicion of MEN1 (#49, #50, #51 and #52, table 2; figure 3); asymptomatic children of a parent with MEN1 (#4, table 2; figure 4), and other first-degree relatives of patients with MEN1; and in certain cases for patients with clinical MEN1 who do not have *MEN1* mutations (i.e. are mutation-negative).²⁷

Screening should commence in childhood (#4, #6, #7, #22, #23, #25, #43-#47 table 2, table 3 and figure 4) and clinical evaluation including routine auxologic evaluation and assessment of pubertal status is an essential part of this screening (#43, table 2). Parents with MEN1 should have an initial consultation (with or without the child present) with a paediatric endocrinologist when the child is around the age of five years (#4, table 2). Symptoms of clinical manifestations of MEN1 (with specific emphasis on symptoms of hypoglycaemia and deviation from normal patterns of growth and puberty) should be discussed and shared decision-making undertaken regarding screening and surveillance plans (#4, table 2 and figure 4). In asymptomatic children, biochemical screening should consist of serum albumin-adjusted calcium measurements, although some centres may prefer to use ionised calcium, at 1-3 year intervals (#6, table 2). Additionally, we suggest measuring serum prolactin and insulin-like growth factor 1 (IGF-1) to screen for hormone-

secreting (i.e. functioning) PAs (#44, tables 2 and 3). There is no consensus regarding the need for fasting serum gastrin measurement in childhood (#25, table 2). Initiating biochemical screening from the age of 10 years can be considered (#7 and #45, table 2). We recommend screening for PanNETs with MRI, starting with an initial scan between ages 10 and 15 years (#22, tables 2 and 3), repeating this at 2-3 year intervals if negative (#27, tables 2 and 3). There was no consensus on the benefit of MRI pituitary screening in asymptomatic children with normal growth and development (#46, table 2), but if screening with MRI pituitary is preferred then it is suggested that this commences from 15 years of age (#47, tables 2 and 3).

It is recommended that adults have a clinical consultation and undergo biochemical screening (figures 2 and 3) at least once per annum and also have regular abdominal, pituitary and thoracic imaging (tables 2 and 3). Screening history and physical examination should be directed toward eliciting symptoms and signs of hypercalcaemia, nephrolithiasis, peptic ulcer disease, hypoglycaemia, hypopituitarism, galactorrhoea and amenorrhoea in women, acromegaly, Cushing disease, and visual field loss and the presence of subcutaneous lipomas, angiofibromas, and collagenomas. Recommendations for biochemical screening include serum albumin-adjusted calcium, fasting gastrin, prolactin, and IGF-1 in all individuals (#5, #24 and #44, tables 2 and 3), with more specific endocrine-function tests being undertaken in individuals who have symptoms or signs of a clinical syndrome. Recommendations for radiologic screening include an MRI abdomen, encompassing the pancreas and adrenal glands, every 2-3 years (#21 and #27, table 2), and MRI of the pituitary every 3-5 years (# 40 and #41, tables 2 and 3). Screening for thoracic NETs, including bronchial and thymic NETs (also referred to as carcinoids) should begin in adulthood, between ages 20-25 years (#36, table 2). We suggest imaging for these NETs using

CT every 3-5 years (#35-#37, tables 2 and 3), as MRI of the chest is reported to be not the optimal imaging modality for screening due to increased risk of false positives as a result of: motion artefacts from the cardiac and respiratory cycles; lower signal-to-noise ratio due to the high air content of the lungs; and reduced sensitivity for detecting small pulmonary nodules.^{28,29} Screening for thymic NETs is likely to require cross-sectional imaging with ‘low-dose’ CT, thereby resulting in cumulative doses of ionising radiation, and the risks of this need to be assessed and discussed with patients, as only a minority will develop thymic NETs with a potentially rapid and aggressive course. MRI screening for PAs can be stopped at the age of 75 years in asymptomatic patients with negative pituitary imaging and normal biochemistry (#42, table 2). Screening for breast cancer in women with MEN1 from age 40 years has also been proposed,³⁰ although it should be noted that this is undertaken for all women aged 50-71 years in some countries.

Recommendations for management of MEN1-related tumours and MEN1 patients

Recommendations will focus on MEN1-specific aspects of the management of tumours, and when there is insufficient evidence for MEN1-related tumours, then reference to appropriate clinical practice endocrine, neuroendocrine and oncology guidelines will be provided.

Parathyroid Tumours

Clinical manifestations and diagnosis

Parathyroid tumours, which are the most common and typically earliest manifestation of MEN1, are associated with elevated (or inappropriately normal) circulating parathyroid hormone (PTH) concentrations and hypercalcaemia, that are the hallmarks of PHPT.^{4,12,24,31-34} PHPT is frequently

detected in individuals who commence prospective screening in childhood, and is found in 45-92% of children who have developed a MEN1-related tumour.²¹ PHPT is usually asymptomatic in children with MEN1, but may become symptomatic by the third decade. Clinical manifestations include hypercalcaemia-related symptoms such as polyuria, polydipsia, anorexia, nausea and constipation, as well as end-organ effects of PTH excess, including reduced bone mineral density (BMD) and nephrolithiasis. In contrast to non-MEN1 (sporadic) PHPT, parathyroid disease in MEN1 is multiglandular, with glands often affected asynchronously.³⁵ The occurrence of parathyroid carcinoma is rare (<1%) in MEN1 and similar to that in sporadic PHPT patients.³⁶ However, the female preponderance seen in sporadic PHPT is absent in MEN1, and PHPT in MEN1 is associated with more severe bone mineral loss and kidney complications.³⁷⁻⁴⁰ However, in a recent publication of a contemporary cohort, BMD was within the normal range a decade after initial parathyroidectomy, although BMD was still reduced compared to population controls.⁴¹ Thus, it is important to screen MEN1 patients for PHPT and, once diagnosed, to evaluate for its potential sequelae.

Assessment of target organ involvement

There is limited evidence available regarding assessment and monitoring of target organ involvement in MEN1-related PHPT. Therefore, we recommend following the guidelines from the Fifth International Workshop on Primary Hyperparathyroidism⁴² to assess and monitor target organ involvement in adult MEN1 patients with PHPT (#8 and #11, table 2). However, in young, prospectively screened MEN1 patients with recent-onset PHPT, assessment of renal and skeletal involvement constitutes more of a baseline measurement than a test to inform/dictate management decisions. In this setting, the timing of the initial assessment of target organ involvement can be

left to the discretion of the managing clinician, to prevent over-screening and premature interventions. This particularly applies to BMD assessment with dual-energy X-ray absorptiometry (DXA) in young adults. For patients with PHPT under surveillance, the guidelines from the Fifth International Workshop on Primary Hyperparathyroidism recommend annual assessment of kidney function using creatinine clearance (preferred over estimated glomerular filtration rate), with 24-hour urinary calcium excretion and abdominal imaging only if clinically needed.⁴² For evaluation of skeletal involvement, three-site (i.e., lumbar spine, proximal femur and distal radius) DXA is recommended every 1-2 years and if BMD is normal then less frequent DXA measurements are reasonable.⁴² As MEN1 patients with PHPT are often much younger than those with sporadic disease, the frequency of DXA monitoring in this group should be reduced to minimise radiation exposure. For children and adolescents with PHPT, assessment of renal function is recommended (#9 table 2), but routine DXA assessment is not recommended (#10, table 2).

Treatment: Timing and type of index surgery, risks of recurrence and hypoparathyroidism as a complication

In patients diagnosed by predictive genetic testing who are subsequently prospectively screened, PHPT can often be observed from the outset and it is not necessary to operate immediately at the initial diagnosis of PHPT in these patients (#12, table 2). Ideally, the timing of the initial operation is planned after shared decision-making with the patient, parents/guardians if applicable, the (paediatric) endocrinologist, and the surgeon, taking into account serum albumin-adjusted calcium concentrations, symptoms and well-being, the presence of target organ involvement, and the patient's personal circumstances, including access to an expert parathyroid surgeon, who performs

>40-50 parathyroidectomies/year (i.e. high-volume), and has experience in the challenging procedures required for hereditary forms of PHPT, paediatric patients, PHPT without unequivocal pre-operative localisation, and reoperations.^{43,44} Parathyroidectomy is usually indicated if total serum albumin-adjusted calcium concentrations are consistently 0.25 mmol/l (1 mg/dl) above the upper limit of the reference range, or if there are symptoms of PHPT and/or evidence of target organ involvement (#13-#15, table 2). Additionally, the presence of a symptomatic gastrinoma should be taken into account as successful parathyroidectomy with restoration of normocalcaemia has been reported to ameliorate the clinical symptoms and hypergastrinaemia in 20% of patients (#16, table 2).

Planning for beyond the initial operation also needs to be considered when managing patients with MEN1-related PHPT, which is a multi-gland disease, although glands may be affected asynchronously. The majority of patients will experience recurrence and consequently require additional surgery at some point during their lives, and operations after the index procedure inevitably have a higher risk of complications. The goals of management are to maintain a (near) normal serum calcium concentration for as long as possible with as few operations as possible, and preventing or limiting target organ damage while avoiding permanent post-operative hypoparathyroidism. Therefore, the initial operation also needs to facilitate future safe reoperation. To achieve these goals, a SPTX with concomitant transcervical thymectomy to remove supernumerary parathyroid glands, performed by an MEN1-experienced, high-volume parathyroid surgeon, is the recommended initial operation (#17, table 2).¹⁷ This entails a bilateral cervical exploration with visualisation of all four parathyroid glands, typically involving resection of three glands and a portion of the fourth, or if the fourth gland is normal-size then removing three glands alone and leaving a tagged and viable normal-sized remnant. For pre-operative imaging, a

consensus was not reached on the need or type of studies (#19, table 2) prior to SPTX with transcervical thymectomy in MEN1 patients, although most expert centres would undertake an ultrasound to rule out concomitant disease and to inform about benign lymphadenopathy. However, pre-operative imaging studies may be indicated in specific circumstances, such as when a unilateral clearance procedure is being considered (#19 and #20, table 2).

A unilateral clearance (unilateral exploration removing both parathyroids and the cervical thymus from only one side of the neck) has been considered as the initial operation in children, adolescents and young adults when disease is grossly limited to one side of the neck.⁴⁵⁻⁴⁷ This staged procedure allows for the avoidance of post-operative hypoparathyroidism in the young patient's early life, but with the understanding that inevitable reoperation will be required on the contralateral unoperated side of the neck. However, this comes at the expense of higher rates of persistent disease and shorter time to recurrence.^{33,46,48} Unilateral clearance additionally limits the options for generating a viable remnant during subsequent operations, which may impact the long-term risk of hypoparathyroidism.³³ Therefore, in general, we recommend that a SPTX should be considered the standard-of-care initial operation in MEN1 patients (#17 and #18, table 2). If a unilateral clearance is considered, then pre-operative imaging is essential.

In MEN1 patients, any residual parathyroid tissue remaining *in situ* after surgery has the potential to contribute to disease recurrence, and recurrence rates of ~40-60% and ~65-70% have been reported following SPTX and <SPTX, respectively.^{46,49} The highest PHPT recurrence rates are reported in studies with follow-up durations exceeding 10 years, thereby suggesting that PHPT will eventually recur in the majority of patients if monitored for long enough.^{33,48} Recurrences may also be caused by: supernumerary glands, which have been reported in ~10% of individuals with

MEN1;^{48,50} and failure to identify and resect multiple affected glands, which often occurs in patients in whom the diagnosis of MEN1 was not recognised prior to surgery.

The indications for re-intervention for persistent or recurrent MEN1-related PHPT are generally the same as for index surgery,⁴² although there are important caveats. Re-operative neck surgeries are inherently complex, and working within a scarred field carries an increased risk of complications, such as persistent hypoparathyroidism and recurrent laryngeal nerve injury. Therefore, the procedure should be performed by an experienced parathyroid surgeon with expertise in managing MEN1-related PHPT. In contrast to index surgery, multimodal non-invasive imaging is essential in the re-operative setting to localise the hyperfunctioning remnant or identify additional parathyroid tissue. Evaluation of vocal cord function should be undertaken in patients with a history of prior cervical exploration, particularly if the index procedure was performed by a different surgeon, as the results of this may influence the decision on proceeding with further surgery. Immediate autotransplantation is performed in some centres if there is uncertainty about sufficient functional parathyroid tissue remaining *in situ* post-operatively. However, total parathyroidectomy as an index operation with parathyroid autotransplantation, which was described as a surgical option in previous guidelines,^{1,2} is no longer recommended because of the associated high risks of prolonged hypoparathyroidism.³³ Further surgical considerations are described in the Fifth International Workshop on Primary Hyperparathyroidism.⁵¹

The calcimimetic drug cinacalcet, which is a positive allosteric modulator of the calcium-sensing receptor, may be used to reduce or normalise serum calcium and PTH concentrations in patients who are not candidates for (re-operative) surgery or are awaiting surgery.^{52,53} However, the effects

of long-term cinacalcet treatment on BMD, hypercalciuria and prevention of nephrolithiasis in MEN1 patients are not known, although in non-MEN1 patients with PHPT cinacalcet has been reported to not affect BMD, and also to not increase urinary calcium excretion or occurrence of nephrolithiasis.^{54,55} The side-effects (e.g. nausea, arthralgia, diarrhoea, and paraesthesia) associated with cinacalcet, which occur in ~33% of patients, limit its long-term use.⁵⁶

Persistent hypoparathyroidism may have a deleterious impact on quality of life with a substantial financial burden.⁵⁷ The incidence of long-term hypoparathyroidism, defined as persisting beyond 12 months after surgery for MEN1-related PHPT, varies from 6-30% and depends on the procedure performed and duration of follow-up.^{33,48,50,58} The management of hypoparathyroidism in MEN1 follows the same principles outlined in recent international guidelines for sporadic disease, and includes treatment with calcium and an active vitamin D analogue, with the goal of raising serum calcium to the lower half of the normal reference range or just below the normal reference range, and alleviating symptomatic hypocalcaemia, while avoiding hypercalciuria.⁵⁹ PTH therapy can also be considered in patients whose hypoparathyroidism is inadequately controlled with conventional therapy.⁵⁹ It is important to recognise that in MEN1 patients, recovery due to PTH secretion from a remaining parathyroid gland or remnant has been reported to occur after prolonged periods ranging from 6 months to several years.⁵⁰

Duodenopancreatic Neuroendocrine Tumours (NETs)

Duodenopancreatic NETs (DP-NETs) are common in individuals with MEN1 and may be the presenting feature in 10–20% of cases.^{31,32,34,60} Non-functioning pancreatic NETs (NF-PanNETs), which are either non-hormone secreting or secrete pancreatic polypeptide (PP) which is not

associated with any hormonal syndrome or sequelae, are the most frequently diagnosed DP-NET,^{4,24} followed by duodenal gastrinomas and insulinomas, while other functioning PanNETs (such as glucagonomas, VIP-omas, somatostatinomas, and tumours secreting ectopic calcitonin, growth-hormone releasing hormone (GHRH), or adrenocorticotrophic hormone (ACTH)) are rare.^{21,22,61,62} Such, ectopic hormone secretion from PanNETs may result in manifestations of pituitary hormone hypersecretion (e.g., acromegaly/gigantism and Cushing syndrome), and this should be especially considered in children in whom occurrence of PAs is rare, as recently illustrated by GHRH secretion from a PanNET causing gigantism in a patient with MEN1.^{63,64} Finally, MEN1 patients may have synchronous or metachronous occurrence of different PanNETs, e.g. NF-PanNETs, gastrinomas, and insulinomas.²²

Clinical manifestations, diagnosis and management of NF-PanNETs

The cumulative probability of NF-PanNETs increases steadily, rising from >8% at 15 years to 80% by age 80 years.⁶⁵ These tumours are mostly detected by surveillance imaging and are only rarely associated with symptoms secondary to local mass effects. However, they represent the leading cause of premature mortality in MEN1 due to distant (i.e. hepatic) metastases that can develop in 15-20% of patients.^{11,66,67} The outcomes of the systematic review would suggest that active surveillance could be pursued for stable MEN1-associated NF-PanNETs ≤ 2 cm, as the combined metastatic disease and mortality rates were comparable between surgery and active surveillance, although the precision of this estimate was low due to small sample sizes and a limited number of events¹⁷. Moreover, confounding factors may have arisen because of the indication for surgery for NF-PanNETs ≤ 2 cm that showed growth on serial imaging, and hence

there may have been an underestimation of the effects of surgery. Therefore, given the possible implications of active surveillance for patient morbidity, metastasis and mortality, which are important and irreversible, a more cautious approach may be prudent. We therefore suggest that for PanNETs ≤ 2 cm under surveillance, imaging intervals should be individualised and based on observed growth rate and absolute size. In newly diagnosed NF-PanNETs ≤ 2 cm, imaging should be repeated after 6-12 months and, if stable, again after 12 months. If the tumour remains stable with a growth rate < 1 mm/year, the surveillance interval can be lengthened to every 1-2 years (#28, table 2). MRI remains the basis for surveillance of NF-PanNETs, with somatostatin receptor (SSTR) scintigraphy-PET/imaging and endoscopic ultrasound (EUS) being reserved for use in circumstances in which they will affect management (#30 and #31 table 2). Thus, it is recommended that SSTR-PET/CT or SSTR-PET/MRI should be performed for staging in patients scheduled for duodenopancreatic surgery, as the outcomes may alter the surgical strategy (#29, table 2). At present, there is no role for routine EUS-guided biopsy (#32 table 2). Surgery should be considered for growing NF-PanNETs and those > 2 cm in size, with the indications having been determined by a multidisciplinary team discussion that involved shared decision-making with the patient.

Clinical manifestations, diagnosis and management of gastrinoma

Gastrinomas in patients with MEN1 are invariably located in the duodenum and are multiple,^{68,69} with a median age of onset in the third to fifth decade of life.⁷⁰⁻⁷² Despite their small size, local lymph node metastases are reported in $\sim 80\%$ of patients, but these do not appear to have an adverse impact on survival.^{66,73} However, distant metastases occur in $\sim 25\%$ and are an important cause of MEN1-related mortality.⁷³ Hypersecretion of gastrin leads to excessive gastric acid secretion with

subsequent peptic ulceration and gastrointestinal bleeding (the Zollinger-Ellison syndrome (ZES)). Traditionally, a diagnosis of gastrinoma is established by a raised fasting gastrin concentration that is ≥ 10 -fold elevated above upper limit of normal, in the absence of proton pump inhibitors (PPIs), and in association with increased basal gastric acid secretion (gastric pH ≤ 2).⁷⁴⁻⁷⁶ However, the widespread use of PPIs, the diminished availability of functional tests (e.g. secretin stimulation) and assessment of basal acid output, and the high risk of PPI cessation, make it challenging to establish a diagnosis.⁷⁶ Therefore, alternative diagnostic criteria have been proposed and these are: characteristic symptoms, combined with elevated fasting serum gastrin and the presence of a DP-NET with positive SSTR imaging (or positive gastrin staining on biopsy), as described in the European Neuroendocrine Tumor Society (ENETS) guidelines.⁷⁶ Diagnosis can be even more challenging in prospectively screened MEN1 patients as they may be asymptomatic but have mild elevations in fasting serum gastrin, which become more prominent with symptoms over time. Localisation of gastrinomas in MEN1 can also be challenging as the primary duodenal tumours are often very small (several millimetres in size) and may occur with larger and more readily visible NF-PanNETs. In this setting SSTR-PET/CT, MRI and/or oesophagogastroduodenoscopy with EUS may be particularly useful (#30 and #31, table 2). Patients who are symptomatic should undergo oesophagogastroduodenoscopy, and this is also suggested in all patients with elevated fasting serum gastrin levels to look for signs of ZES, a duodenal primary and gastric NETs (#33 and #34, table 2).

Five-year, 10-year and 20-year survival rates for MEN1 patients with gastrinoma are reported to be 80-90%, 65-95% and 60-90%, respectively.⁷⁶ The goals of treatment are to control symptoms and/or sequelae associated with hypergastrinaemia and to reduce the mortality associated with the development of distant metastatic disease. The first step is to control acid-related symptoms and

sequalae with adequate doses of PPIs, and this is often highly successful. Thus, the primary goal of surgery for gastrinomas, unlike other functioning PanNETs associated with MEN1, is to reduce the risk of metastatic disease. However, extensive surgery which includes duodenal surgery is required for MEN1-related gastrinomas, and there is a clinical dilemma in deciding on its timing, as often patients are young and may also have concomitant PanNETs.⁷⁶ Apart from a severely elevated fasting serum gastrin, there are no accurate prognostic factors to predict risk of gastrinoma-related distant metastases.²¹ Based on current retrospective studies, no definitive recommendation can be made on decisions regarding the timing and extent of surgery, and therefore these decisions should be made by multidisciplinary teams in centres of expertise, together with a discussion of the risks and benefits with the patient, as part of a shared decision-making process. A role for local endoscopic resection of MEN1-related gastrinoma is not established.

Clinical manifestations, diagnosis and management of insulinoma

The median age for insulinomas in MEN1 patients is 30 years,⁷⁷ although insulinomas have been reported in children with MEN1 as young as 5-6 years.^{31,32} Insulinomas typically present with Whipple's triad: hypoglycaemic symptoms, a plasma glucose concentration <3.1 mmol/L (<55 mg/dL) and resolution of symptoms after glucose administration. In prospectively screened MEN1 patients, initial signs and symptoms may be subtle and establishing the diagnosis may take a prolonged time. Most MEN1-related insulinomas are benign and solitary, although up to one third of MEN1 patients may have multiple insulinomas that are distributed throughout the pancreas.⁷⁷ The diagnosis is established with a 72-hour fast, similar to that in non-MEN1 patients with insulinomas.^{76,78} Pre-operative localisation may be challenging due to the presence of other

concomitant functioning and non-functioning DP-NETs and it is important to note that the largest tumour identified by imaging may not correspond to the PanNET responsible for insulin over-production. Functional imaging techniques for differentiating insulinomas from other contemporaneous DP-NETs are currently under investigation. For example, 68Ga-Exendin-4 PET/CT utilises the high expression of glucagon-like peptide 1 (GLP-1) receptors on the surface of insulinoma cells, although its widespread use is currently limited as it is available only in a small number of European centres.^{16,79} In some cases, selective intra-arterial calcium stimulation and hepatic venous sampling may help to regionalise the insulin-secreting NET.⁷⁶ Surgery is the mainstay of treatment of insulinomas and is associated with excellent long-term hypoglycaemia-free outcomes.⁷⁷ If technically feasible, enucleation can be performed for suspected solitary insulinomas with high rates of symptom resolution and minimal risk of pancreatic endocrine and exocrine insufficiency.^{77,80}

Management of metastatic duodenopancreatic NETs

In the absence of MEN1-specific evidence regarding the management of advanced/metastatic DP-NETs, we recommend following the current clinical practice guidelines for metastatic DP-NETs that are appropriate for non-MEN1 and MEN1 patients.^{76,81-85}

Gastric NETs

Type II gastric NETs (also referred to as enterochromaffin-like cell carcinoids (ECLomas)) are observed in 15-70% of MEN1 patients with co-existent hypergastrinemia and are frequently detected incidentally at the time of upper gastrointestinal endoscopy.^{86,87} The tumours are usually small (e.g. <1.5cm) and multiple,⁸⁸ and SSTR scintigraphy may demonstrate increased uptake in

the stomach. Usually, these gastric NETs are indolent and may be followed by regular endoscopy. Larger or growing gastric NETs may be treated by endoscopic resection, although treatment with somatostatin analogues (octreotide or lanreotide), has also been reported to result in regression of these tumors.⁸⁹ Gastric surgery may be considered for more extensive tumours or those with spread to locoregional lymph nodes, as the risk of metastases has been reported to be between 10 and 30%.⁸⁷

Thoracic NETs

MEN1-related thoracic NETs, which comprise bronchopulmonary NETs and thymic NETs, are usually non-hormone secreting (i.e. non-functioning), although rarely they may secrete hormones.

Thoracic NETs and Hormonal syndromes

Thoracic NETs may present with carcinoid syndrome or a syndrome due to ectopic hormone secretion, e.g. Cushing syndrome from ACTH and/or corticotropin-releasing hormone (CRH) production, acromegaly from GHRH secretion, hypercalcaemia from PTH-related peptide (PTHrP) secretion, or flushing and diarrhoea from hypercalcitoninaemia. The management of these NETs and syndromes in MEN1 patients is the same as that reported in clinical practice guidelines for non-MEN1 patients.⁹⁰⁻⁹⁴

Clinical manifestations, diagnosis and management of bronchopulmonary NETs

Bronchopulmonary NETs in MEN1 generally have an indolent course, with a tumour doubling time of ~12 years and are associated with favourable long-term survival rates.^{95,96} Histologically confirmed bronchopulmonary NETs are observed in approximately 5% of MEN1 patients,

although radiologically suspected lesions have a much higher prevalence, ranging from 20-30%.^{13,97-99} Earlier reports suggested a female predominance, although this has not been supported by recent studies.^{95,96,99} Bronchopulmonary NETs are primarily seen in adults, with only two documented cases in adolescents.^{12,100}

Small bronchopulmonary NETs in MEN1 patients may be followed with active surveillance instead of surgery (#38, table 2). However, this decision will depend on the tumour size, location, multiplicity and other patient characteristics such as other MEN1-related tumours, co-morbidities and patient preference. If an active surveillance approach is taken, follow-up intervals should be tailored to observe growth rate and absolute size. In newly diagnosed lung NETs ≤ 2 cm, imaging should initially be repeated after 6-12 months and when stable, again after 12 months. If the tumour remains stable, subsequent surveillance intervals can be increased to 1-2 years (#39, table 2). Bronchopulmonary NETs under surveillance that show growth should be considered for surgery, which is the treatment of choice for locoregional disease. There is no evidence for benefit from routine adjuvant therapy after resection of bronchopulmonary NETs, although this can be considered in fit patients with a high risk of relapse.^{92,101,102} Distant metastatic disease is seen in 3-16% of MEN1 patients.^{96,103} MEN1-specific evidence regarding the treatment of locoregional disease, advanced unresectable disease, and distant metastatic disease is not available and we recommend referring to the lungNET guidelines.^{85,92,102}

Clinical manifestations, diagnosis and management of thymic NETs

Thymic NETs have been reported in approximately 2-8% of individuals with MEN1,^{95,98,104,105} yet they account for up to 20% of MEN1-related deaths due to their aggressive behaviour.¹¹ Over 50% of patients present with distant metastases, with a 10-year survival rate of 33%.¹⁰⁴ The median age

at diagnosis is in the fifth decade. Thymic NETs predominantly develop in males with MEN1, although this sex predominance is reported to be less pronounced in East Asian cohorts.^{95,98,104,106} Thymic NETs are typically non-functional and therefore, screening is dependent upon imaging. A significant challenge lies in their early detection, as most reported cases have not been identified during routine surveillance.

Screening for thymic NETs may result in their earlier detection and at a smaller size, and surgery, the treatment of choice, for such locoregional disease is associated with more favourable outcomes.¹⁰⁷ There is no evidence for benefit from routine adjuvant therapy after resection, although the European Society for Medical Oncology (ESMO) guidelines recommend case-by-case discussion for additional therapy in patients who have had an R0 resection with stage 3 or 4 disease; or an R1 or R2 resection at any disease stage.⁹² In the absence of MEN1-specific evidence regarding the management of advanced/metastatic thymic NETs, we advise following the treatment guidelines reported for non-MEN1 patients.^{85,92} It is important to note that complete resection of the thymus is not achievable by transcervical thymectomy performed concomitantly with the index subtotal parathyroidectomy. Therefore, while reducing the thymic tissue volume may lower the risk for thymic NET development, these tumours can still occur despite preceding transcervical thymectomy.¹⁰⁸

Pituitary Adenomas (PAs)

Clinical manifestations, diagnosis and management of PAs

The prevalence of PAs ranges from 36-52% and PAs may be the first clinical manifestation of MEN-1 in ~15% of patients.^{14,109-113} The mean age of diagnosis of PAs is in the fourth decade, but with a wide range.^{23,109-112} Most PAs in MEN1 are hormone-secreting (52-85%)^{14,109,110,113} and follow a similar distribution to sporadic PAs, with prolactinomas being the most common subtype (43-79%) closely followed by clinically non-functioning PAs (15-43%),¹⁰⁹⁻¹¹² somatotrophinomas (4-9%; gigantism/acromegaly), corticotrophinomas (1-4%; Cushing disease), and thyrotrophinomas (<1%). Clinical manifestations of PAs in MEN1 patients are similar to those in non-MEN1 patients, and it is recommended that their investigation should be according to the appropriate clinical guidelines (#48, table 2).^{2,114-116} Plurihormonal PAs are more commonly seen in MEN1 patients than non-MEN1 patients.¹¹⁷ These tumours usually co-secrete prolactin and one or more other anterior pituitary hormones, e.g. growth hormone (GH), and sommatolactotrophinomas (GH- and prolactin-secreting PAs) are reported in ~4% of MEN1 patients. Multifocal PAs are infrequent, but still more common than in non-MEN1 patients with PAs.¹¹⁷ PAs in MEN1 patients were previously reported to be larger, more aggressive and less responsive to surgical and medical treatment,^{112,117-119} although this has not been confirmed in independently performed (population-based) studies.^{109,110,113} Nevertheless, several studies of MEN1 families have reported young patients with pituitary macroadenomas, that were invasive and therapeutically challenging,^{112,117-119} and biochemical and radiological screening in asymptomatic individuals with a *MEN1* mutation is therefore advised to commence from 10 years and 15 years of age, respectively (table 3). Interestingly, our systematic review revealed that DA

(cabergoline, bromocriptine or quinagolide) resistance in prolactinomas was not more common in MEN1 patients than in non-MEN1 patients,¹⁷ hence confirming that use of DA for treatment of prolactinomas is appropriate in MEN1 patients, although the GRADE levels (scores) for this were very low. Management and treatment of MEN1-associated PAs is similar to that in non-MEN1 patients, and we recommend following the appropriate clinical practice guidelines for PAs (#48, table 2).^{93,94,114-116,120-123}

Adrenal cortical tumours

Clinical manifestations, diagnosis and management of adrenal cortical tumours

Adrenocortical adenomas (ACAs) have been reported in ~40% of MEN1 patients by age of 80 years,²⁴ compared to 10% in the general population,¹²⁴ and the prevalence of ACAs in MEN1 patients is reported to range from >3 to ~25%,^{3,14,111,125} with a mean age of diagnosis of 40-47 years.^{14,24,111,125} Most patients are asymptomatic, as the majority of these tumours are non-functioning, although manifestations of hormonal hypersecretion occur in <10% of patients, and among these primary hyperaldosteronism (Conn's syndrome) and ACTH-independent Cushing syndrome are the most common.^{125,126} Pheochromocytomas, which are tumours of the adrenal medulla and one of the main manifestations of MEN2 (table 1), are reported to occur rarely in MEN1 patients, and represent <2% of adrenal tumours.^{127,128} Pheochromocytomas occurring in patients with genetically proven MEN1, i.e. presence of a germline *MEN1* mutation, have been shown to have loss of heterozygosity involving the *MEN1* locus with reduced menin expression, consistent with a tumour-suppressor role for the *MEN1* gene in these tumours,^{127,128} although the possibility of other MEN syndromes (table 1) should be considered in such patients who do not

have a *MEN1* mutation. The incidence of ACC is ~1% in MEN1 patients, but it is higher at 10-15% in MEN1 patients with adrenal tumours >1 cm.¹²⁶ If functional, ACCs most commonly secrete cortisol and/or sex steroids. Biochemical investigation (e.g.: plasma renin and aldosterone concentrations; low-dose dexamethasone suppression test; plasma and urinary metanephrines; and serum dehydroepiandrosterone sulfate (DHEAS) in both sexes and testosterone in females) should be undertaken for those with symptoms or signs suggestive of functioning adrenal tumours, ACC, or tumours >1cm.² Since regular pancreatic imaging is indicated in MEN1, both adrenal glands can be assessed simultaneously. If an adrenal lesion is detected, an initial adrenal-protocol CT scan should be performed to evaluate its baseline size and characteristics.

Consensus has not been reached about the management of MEN1-associated non-functioning ACAs as the majority are benign.² However, the risk for malignancy is increased if the tumour has a diameter >4cm, although ACCs have been identified in tumours <4cm in MEN1 patients.^{2,126} Surgery is recommended for adrenal tumours that: are >4cm in diameter; have atypical or suspicious radiologic features (e.g. increased Hounsfield units on unenhanced CT) and are 1 to 4cm in diameter; or show significant measurable growth over a 6-month interval.^{2,126} The treatment of functioning (i.e., secreting) adrenal tumours in MEN1 patients is similar to that for tumours occurring in non-MEN1 patients.^{2,124,129}

Non-endocrine manifestations

Breast cancer

Women with MEN1 may have a 2-3 fold increased risk of breast cancer developing at an earlier age, when compared to the general population.^{30,130} Studies of these breast cancers have reported menin expression to be reduced¹³¹ or increased,¹³² and it seems that at present there is insufficient evidence to consider breast cancer as a component of MEN1. The need for earlier breast cancer screening in women with MEN1 is also debated, although some countries (e.g. The Netherlands and USA), have commenced screening for breast cancer in women with MEN1 from the age of 40 years, which is 10 years before the start of the population-based screening program in other countries.³⁰ The UK Cancer Genetics Group does not currently recommend increased breast surveillance based on *MEN1* status alone, but advises that all women heterozygous for a *MEN1* mutation should have an assessment of their family history for breast cancer and be offered breast surveillance in accordance with their family history, and advice on self-examination and symptom awareness.

Tumours of the skin, adipose tissue and smooth muscle

MEN1 patients may develop angiofibromas and collagenomas of the skin, and lipomas, which occur in ~30% of MEN1 patients.¹³¹ Recognition of these lesions in patients with endocrine tumours can aid the diagnosis of MEN1. Additionally, patients are at risk of developing leiomyomas, mainly of the upper gastrointestinal and genitourinary tract.¹³¹ Leiomyosarcomas or other sarcomas rarely occur, and it is important to note that on [¹⁸F] Fluorodeoxyglucose ([¹⁸F] FDG) PET/CT, hibernomas which are benign rare brown fat tumours, may be mistaken for these

malignant lesions.^{133,134} Melanoma has been reported in some MEN1 patients, but at present there is not sufficient evidence to consider this as part of MEN1¹³¹.

Meningiomas and ependymomas

Meningiomas and ependymomas are reported to have a higher incidence in MEN1 patients, compared to the general population, and biallelic *MEN1* loss has been observed.¹³⁵ However, it is debated whether these tumours are causally linked to MEN1 and currently this has no consequences for screening.¹³¹

Genetic testing in the diagnosis of MEN1

A diagnosis of MEN1 may be established in an individual by one of three criteria: 1) on the basis of the occurrence of two or more main MEN1-associated endocrine tumours (i.e. parathyroid neoplasms, DP-NETs and PAs), referred to as clinical MEN1; 2) the occurrence of one of the main MEN1-associated tumours in a first-degree relative of a patient with a diagnosis of MEN1, referred to as familial MEN1; and 3) identification of a germline *MEN1* mutation in an individual, who may be asymptomatic and has not yet developed serum biochemical or radiological abnormalities indicative of tumour development, referred to as genetic MEN1 (table 4). However, the diagnosis of genetic MEN1 may be challenging to establish if a DNA sequence variant of uncertain (or unknown) significance (VUS) (appendix p3) is identified. This is becoming an increasing problem in the clinical setting because of the rapid advances in DNA sequencing technology and the advent

of high-throughput next-generation DNA sequencing, and the ACMG and the AMP have provided a broad 5 category classification of DNA sequence variants⁹. Thus, variants are described as: “pathogenic” if they are well-documented to have a deleterious effect and to cause disease; “likely pathogenic” if they are more than 90% likely to be disease-causing but lack definitive proof; “benign” if they are not disease-causing; “likely benign” if they are more than 90% certainty that they are not causative for a disease; and of “uncertain (or unknown) significance” if their effects on function or health are unknown or there is conflicting clinical evidence (appendix p3)⁹. A diagnosis of genetic MEN1 may be also be challenging to establish if patients with clinical MEN1 are found to not have a *MEN1* mutation (i.e *MEN1* mutation-negative) (appendix p36); whereas diagnoses of clinical MEN1 and familial MEN1 may be confounded by the occurrence of phenocopies (appendix p37).^{2,16,25,136}

Variants of uncertain significance (VUS)

The majority (~75%) of *MEN1* variants identified in patients are disease-causing mutations, i.e. pathogenic (or likely pathogenic), based on the ACMG and the AMP classification⁹ (appendix p3), as they are nonsense mutations or frameshifting alterations that predict truncations of the menin protein.^{14,24,137} However, the remaining (~25%) are missense and in-frame indels, and a subset of these would be classified as VUS.²⁴ Interpretation of VUS following *MEN1* genetic testing is a major challenge and poses difficulties in making clinical decisions for MEN1 patients.^{24,138} For example, of 122 *MEN1* missense variants identified from the French oncogenetics network of neuroendocrine tumours (TENGEN), ~60 % were classified as (likely)-pathogenic variants using TENGEN criteria but <30% were classified as (likely)-pathogenic variants using the ACMG-AMP guidelines; importantly 20 of the ACMG-AMP VUS were found in patients with clinically authentic MEN1 disease.¹³⁸ Such variances in classification of *MEN1* missense variants can have

major adverse effects on the clinical management of patients and their families. The TENGEN therefore proposed locus-specific adjustments based on assessments of patient's phenotype and family history, to the ACMG-AMP framework, for use in interpreting *MEN1* missense variants.¹³⁸

Other studies have used *in silico* thermodynamic and structural analysis of menin to further evaluate the pathogenicity of a VUS (appendix p3). At present, we recommend using a combination of the ACMG-AMP classification with locus-specific adjustments and consideration of the structural consequences of the *MEN1* missense variants.^{9,138}

***MEN1* Mutation-negative patients and Phenocopies**

Between 10-30% of patients with clinical MEN1 (i.e. having 2 or more MEN1-associated tumours), may not be found to have a germline *MEN1* mutation (i.e. *MEN1* mutation -negative) (appendix p36).²⁷ However, such patients may have: mutations in non-coding regions that are not usually interrogated by current genetic testing methods;¹³⁹ somatic mosaicism;¹⁴⁰⁻¹⁴² coincidental occurrence of two separate tumours;¹⁴³ or represent phenocopies¹⁴⁴ (also sometimes referred to as MEN1-like phenotypes). We recommend that if initial genetic testing has failed to identify a *MEN1* abnormality by methods such as - DNA sequence analysis, multiplex ligation-dependent probe amplification (MLPA), a method that detects abnormal copy numbers of DNA in specific regions of the genome, or next generation sequencing (NGS) multigene (i.e. targeted- or virtual- panel) testing-, then repeat testing should be considered using another bioinformatic pipeline or libraries that could overcome some bias of the first testing, before using whole exome sequencing (WES) or whole genome sequencing (WGS), which may detect *MEN1* mutations in ~50% of such patients¹⁴⁵ and identify *MEN1* mosaic mutations.¹⁴⁰⁻¹⁴² Patients with clinical MEN1 but who are “true-negative” for a *MEN1* mutation, may represent phenocopies, and have a mutation in another

gene that is more typically associated with a different disease (appendix p37).¹⁴⁴ Such genes may include *CDKN1B*, *RET*, and *MAX*, whose mutations are associated with MEN4, MEN2 and MEN5, respectively (table 1), or the *cell division cycle 73 (CDC73)*, *Calcium sensing receptor (CASR)* and *aryl hydrocarbon receptor-interacting protein (AIP)* genes (appendix p37).^{144,146} However, the frequencies of *CDKN1B*, *MAX*, *CDC73*, *CASR*, *RET* and *AIP* mutations in *MEN1* mutation-negative patients are not known, although it was estimated that patients with *CDKN1B* mutations may account for ~3% of MEN1-like individuals,¹⁴⁷ but a recent study of 5600 patients with suspected MEN1 has reported that only 0.07% had *CDKN1B* mutations.¹⁴⁸ At present, we recommend that *MEN1* mutation-negative patients, and depending upon their clinical phenotype, should be tested for mutations of *CDKN1B*, *MAX*, *CDC73*, *CASR*, *RET* and *AIP*, while noting that other as yet unreported genes may be involved.¹⁴³ Moreover, it is important to identify these patients with clinical MEN1 who do not have an identified mutation in the *MEN1* gene or other endocrine neoplasia associated genes, as they are reported to have a more favourable prognosis, in having less aggressive disease, with the median ages of first and second tumour manifestation 13 and 9 years later, respectively, when compared to patients with *MEN1* mutation.^{27,149} Furthermore, third tumour manifestations were not reported to be identified in such *MEN1* mutation-negative patients, in whom the median survival was 14 years greater than those with a *MEN1* mutation (87 versus 73 years of age).^{4,27}

Phenocopies have also been reported in the context of familial MEN1, in which a member of the kindred has a clinical manifestation of MEN1 (e.g. PA, or PHPT), but is subsequently found not to harbour the familial *MEN1* mutation (i.e. likely representing a coincidental sporadic occurrence of the tumour). Thus, analysis of a large MEN1 family comprising 152 members, indicated that

10% of individuals within the family who were diagnosed as having clinical MEN1 did not have the *MEN1* mutation, thereby indicating that phenocopies can be common in patients with a family history of MEN1. The importance of phenocopies lies in their recognition as they can substantially alter the screening strategy, which needs to be targeted to identifying the tumours associated with the specific syndrome that is caused by identified pathogenic variants.

Importance of genetic testing

Genetic testing for *MEN1* mutations is helpful for identification of patients who harbour the *MEN1* mutation and require screening for tumour detection and early/appropriate treatment, and also for identification of the 50% of family members who do not harbour the familial germline *MEN1* mutation and can therefore be reassured and alleviated of the anxiety burden of being at high risk of developing future tumours (table 4). This latter aspect cannot be over-emphasised as it helps to reduce the cost to the individuals and their children, and also to the health services in not having to undertake unnecessary biochemical and radiological investigations (table 4).¹⁵⁰ *MEN1* mutational analysis may also be helpful in facilitating preconception genetic counselling and in some settings pre-implantation genetic diagnosis, and consultation with a clinical geneticist should be offered.

We recommend therefore that *MEN1* mutational analysis should be undertaken (table 4) in: 1) an index case with two or more MEN1-associated endocrine tumours; 2) a first-degree relative of a *MEN1* mutation carrier expressing familial MEN1 (i.e. having symptoms, signs, biochemical or radiological evidence for one or more MEN1-associated tumours); 3) asymptomatic first-degree relatives of a known *MEN1* mutation carrier; and 4) patients with suspicious or atypical MEN1

(#49-52, tables 2 and 4).¹⁵⁰ Once a genetic diagnosis of MEN1 has been established in an index case (the first patient diagnosed in a family), predictive testing should be offered to first-degree relatives, also known as cascade screening (figures 2 and 3). Delays in diagnosis of MEN1 are common, and a median lag-time of ~3.5 years has been reported between index case diagnosis and that of subsequent family members, leading to higher rates of metastatic disease in family members.¹⁵¹ The delay in diagnosis may be due to multiple reasons, which include the relevant information not being available to the patient (or doctors) because they may be unaware of relevant family history due to: medical information not being shared between family members (and/or medical teams); geographical or social separation of family members; relatives dying prematurely of causes unrelated to the disorder; or incomplete or variable penetrance of manifestations.¹⁵¹ Also, MEN1 patients are naturally anxious about disease occurrence for themselves and their relatives, and this may be compounded by the investigations and regular surveillance screening.² There are also potential ethical issues to consider for predictive testing, and therefore individuals should receive appropriate genetic counselling. Presently, a large number of patients are diagnosed with MEN1 by predictive genetic testing because one of their parents has MEN1 (figure 4). Predictive testing in children, which requires parental/guardian consent, is recommended in the first decade of life.

Accredited genetic diagnostic laboratories

We recommend that genetic testing should be undertaken in accredited genetic diagnostic laboratories (table 4) and include DNA sequence analysis using an appropriate method that will detect abnormalities (e.g., variants and insertion-deletions (indels)) involving all exonic and splice site regions of the *MEN1* gene. The identified DNA sequence variants (e.g single nucleotide

variants (SNVs) and indels) should then be assessed for variant pathogenicity using validated methods, and many testing laboratories adopt the ACMG-AMP guidelines.¹⁵²

Conclusions

Our studies provide 55 evidence-based and consensus-based recommendations for best practice in the management of MEN1, a rare hereditary disorder predominantly associated with tumours of the parathyroids, pancreatic islets, anterior pituitary and adrenal glands. However, these recommendations have limitations owing to the varying methodological quality of available data, which is derived primarily from studies of retrospective series studies and is not sufficient for providing high or moderate certainty for evidence using the GRADE approach. This is despite the availability of over 3000 publications during the past decade on the management of tumours of the parathyroids, pancreatic islets and anterior pituitary in patients with MEN1, of which only ~1.2% met the inclusion criteria for systematic reviews.¹⁷ We therefore used the Delphi method to address gaps and controversies in screening and surveillance practices for MEN1 and developed 55 clinical recommendations to guide clinicians and patients about approaches for MEN1 management in adults and children. Moreover, our studies have identified unmet clinical needs and deficiencies in the evidence that underpins our current approaches for the management of MEN1. Thus, further studies are required to validate and optimise the proposed screening protocols and to develop shared decision-making tools. In addition, a similar evidence-based and consensus-based approach is required to provide recommendations for the management of adrenal tumours which are frequently found as “incidentalomas” in MEN1 patients having surveillance abdominal MRIs.

There is also a need for biomarkers that allow for: accurate risk stratification of NETs; prediction of aggressive PanNETs; personalised and risk-based management strategies; and early detection of thymic NETs. To enable such research, prospective well-annotated cohorts of MEN1 patients with clinical biobanks and global collaborations are needed. These will be critical for facilitating clinical trials and to explore the effectiveness of targeted, non-invasive or minimally invasive early interventions. In genetic testing, better VUS prediction tools are required, and the development of high-throughput functional assays will be essential in helping to validate these prediction tools and to determine the likely pathogenicity of *MEN1* variants. In the meantime, our evidence-based and consensus-based recommendations provide important foundations for educating and guiding clinicians, patients, and stakeholders about approaches that aim to improve outcomes and overall health for adults and children with MEN1.

Search strategy and selection criteria

The recommendations outlined in this article were established by a multidisciplinary group that was convened to undertake systematic reviews and meta-analysis of the literature, and used a Delphi approach for the development of consensus statements. Full details of the literature search criteria are included in the accompanying systematic review article.¹⁷ In brief, MEDLINE Ovid, Embase Ovid, The Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials (CENTRAL)), and Web of Science from December 1, 2001, (i.e. after publication of the first MEN1 guidelines) were searched with a combination of free text and MeSH terms without language restriction. In addition, to ensure more recent articles or articles not relating to the systematic review questions were included, PubMed was searched using terms including: ‘Multiple Endocrine Neoplasia Type 1’, ‘Neuroendocrine Neoplasm’; ‘MEN1

mutation'; parathyroid tumours; primary hyperparathyroidism; pancreatic islet tumours; pituitary adenomas; adrenal adenomas; adrenal carcinomas; pheochromocytomas; genetic testing; and genetic counselling, and articles published after December 1, 2001 were selected.

Contributors

M-LB, GV, RVT, CRCP, SGW, FC, NP, ML, and CS were responsible for the conceptualisation of the project and M-LB, GV and RVT provided resources. M-LB, GV and RVT were responsible for project supervision, and RVT also for project administration. M-LB, GV, RVT, CRCP, SGW, FC, OAS, TC, KEL, FM and KAE were members of the systematic review working group. GW was Delphi lead and CRCP was Delphi co-lead, and M-LB, RVT, SGW, FC, OAS, TC, FM, and KAE were members of the Delphi core group. RVT, GV, CRCP were responsible for the methodology. GV, RVT, CRCP, OAS, KEL, and KAE wrote the original Draft, and M-LB, GV, RVT, CRCP, SGW, FC, OAS, TC, KEL, FM, KAE, NP, ML and CS undertook review and editing of the draft. All authors gave final approval of the version to be published.

Declaration of Interests

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Figure Legends

Figure 1: Evidence generation for Recommendations for best practice

There is a lack of evidence-based guidelines for the screening and surveillance for MEN1-related tumours. Therefore, to provide evidence-based recommendations, we initially formulated 2 PICO questions and 1 PECO question for therapeutic topics for each of the main MEN1-related tumours, and performed three systematic reviews and a meta-analysis. However, many other questions remained unanswered because of the complexity of MEN1 and the varying methodological quality of available information, and for these we used the Delphi method to develop practical clinical recommendations. This yielded 52 final recommendations for best practice that will help to provide guidance for health care professionals and patients. Population, intervention/exposure, comparator/control and outcomes (PICO/PECO); primary hyperparathyroidism (PHPT); subtotal parathyroidectomy (SPTX); less than total parathyroidectomy (<SPTX); non-functioning pancreatic neuroendocrine tumour (NF-PanNET); Multiple Endocrine Neoplasia Type 1 (MEN1).

Figure 2: Flow chart for patient with a clinical diagnosis of MEN1 or suspected of having

MEN1. Individuals with a clinical diagnosis of MEN1 should be offered genetic counselling and *MEN1* mutation testing. If a *MEN1* mutation is identified, then cascade genetic counselling and testing of first-degree relatives should be undertaken. No further testing is required for first-degree relatives who do not carry a *MEN1* mutation, as these individuals have the same background risk of developing a MEN1-related tumour as the general population. Individuals who carry a *MEN1* mutation (i.e., index case and first-degree relatives) should undergo initial evaluations, including clinical history, biochemistry for functional MEN1-related tumours and radiological investigations. If an abnormality is detected, then these individuals should undergo further

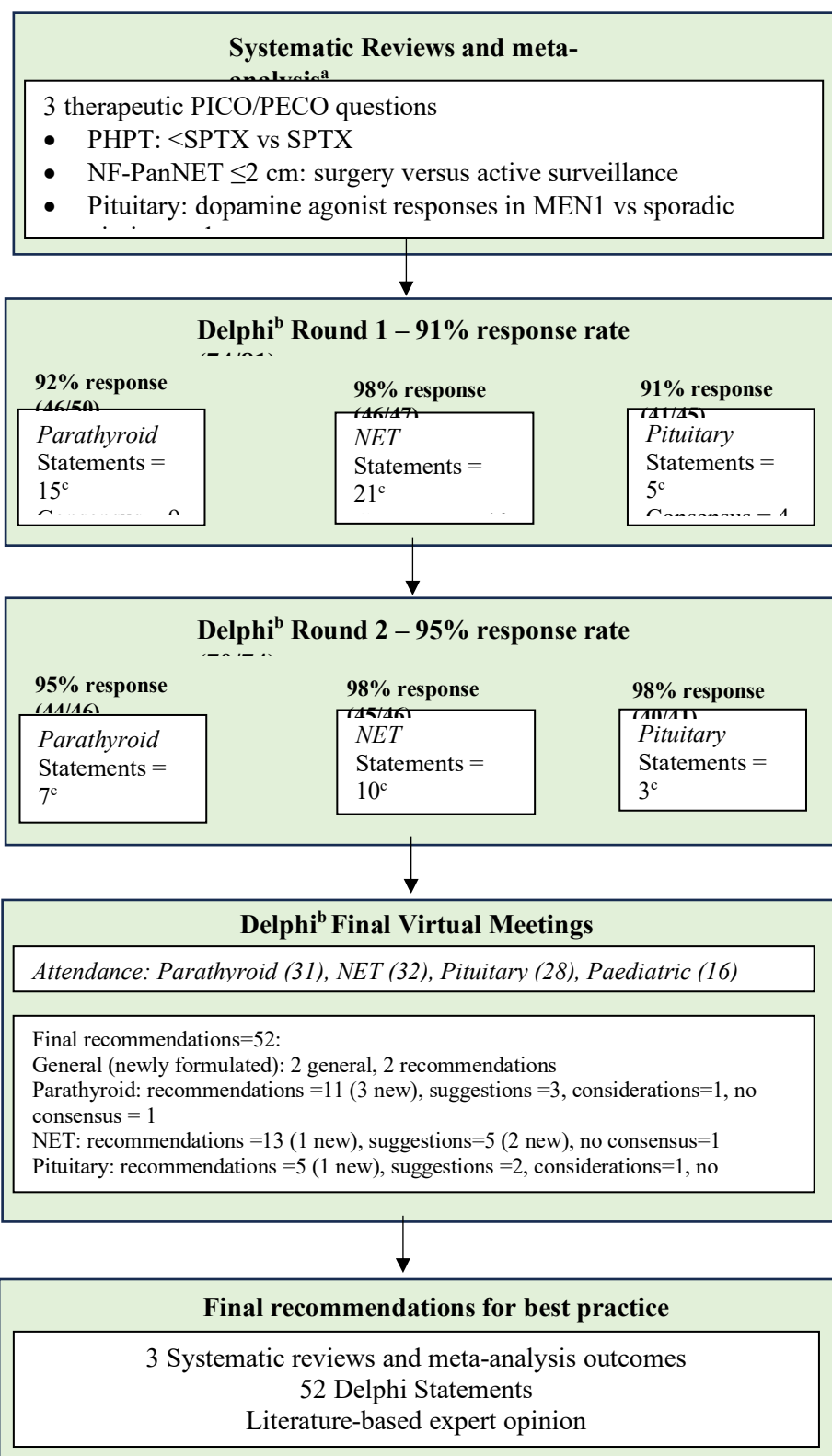
appropriate investigations and treatment. Individuals with a *MEN1* mutation who are clinically asymptomatic with normal clinical evaluations should undergo regular screening for MEN1-associated tumours. Individuals with no evidence of a PA (radiologically) by age 75 years, may continue screening by clinical exam and biochemistry alone. Index cases with clinical MEN1 and no identified *MEN1* mutation (i.e. *MEN1*-mutation negative), should undergo genetic testing for *MEN1* phenocopies due to germline mutations in genes including *CDKN1B*, *CDC73*, *CASR*, *RET*, *MAX*, and *AIP* depending on the phenotype (table 1 and appendix pp36-37). Patients with clinical MEN1 and no mutation should undergo initial evaluations and screening similar to those with a *MEN1* mutation. However, screening in these *MEN1*-mutation negative patients, who tend to have a more indolent clinical course when compared to patients with *MEN1* mutations, should be considered more in the context of the family history and associated clinical phenotypes.²¹

Figure 3: Flow chart for young patient with ≥ 1 MEN1-associated tumour(s). Young individuals with a suspicion of MEN1 based on either the presence of one or more MEN1-associated tumours, but without a known family history should be considered for *MEN1* genetic testing. This will aid in identifying individuals at risk of developing further MEN1-associated tumours and to ensure that they enter into an appropriate screening pathway. If a *MEN1* mutation is identified, then cascade genetic counselling and testing of first-degree relatives should be undertaken. No further testing is required for first-degree relatives who do not carry a *MEN1* mutation, as these individuals will have the same background risk of developing a MEN1-related tumour as the rest of the population. Individuals who carry a *MEN1* mutation (index case and first-degree relatives) should undergo initial evaluations and subsequent screening, which will depend on the individual's age, and risk of tumour development. In adults, initial evaluations include a detailed clinical history, biochemistry for functional (hormone-secreting) MEN1-related

tumours and radiological investigations (refer to figure 2). In children (<19years of age), the initial clinical evaluation should include a detailed history and examination looking for abnormalities in growth (e.g. aberrations of height and weight using standardised, population specific growth charts) and pubertal development. However, there is no consensus on the timing for initial biochemical and radiological screening in asymptomatic children, and this decision should be made between the patient, parents/guardians and clinician. If an abnormality is detected, then these individuals should undergo further appropriate tests and treatment. Children <19 years old with a *MEN1* mutation who are clinically asymptomatic with normal clinical evaluations should undergo regular surveillance for MEN1-associated tumours, with the screening biochemistry and radiological intervals determined by shared decision-making with parents/guardians and clinicians. Individuals with no evidence of a PA (radiologically) by age 75 years, may continue surveillance by clinical exam and biochemistry alone. Index cases with MEN1 and no identified *MEN1* mutation, should undergo genetic testing for *MEN1* phenocopies due to germline mutations in genes including *CDKN1B*, *CDC73*, *CASR*, *RET*, *MAX*, and *AIP* depending on the phenotype (table 1 and appendix pp36-37). Patients with clinical MEN1 and no *MEN1* mutation (i.e. *MEN1*-mutation negative) should undergo initial evaluations and screening similar to those with MEN1 mutations. However, screening in these *MEN1*-mutation negative patients, who tend to have a more indolent clinical course when compared to patients with *MEN1* mutations, should be considered more in the context of the family history and associated clinical phenotypes.²¹

Figure 4: Flow chart for an asymptomatic child of a parent with MEN1. Children of a parent with a known *MEN1* mutation require an individualised approach with input from parents/guardians, clinician and paediatric endocrinologist from the age of approximately 5 years (or earlier), as each child has a 50% chance of carrying the *MEN1* mutation from the affected

parent. There is no consensus on the age at which to undertake genetic testing, although it should preferably be undertaken before biochemical and radiological screening commences to prevent inappropriate tests. Clinical history and examination, including tracking height and weight percentiles (using standardised, population specific growth charts), and pubertal development, are key to monitoring these children. The age at which to undertake genetic testing should be made by shared decision-making by the paediatrician, geneticist and parents/guardians. Children should continue regular clinical follow-up every 12 months (history and examination) until the decision to undertake genetic testing is made or if the child becomes symptomatic. In asymptomatic children who carry a *MEN1* mutation, screening (biochemistry and radiology), should be undertaken at intervals determined by shared decision-making, as there is no consensus on the time or interval to commence. For any symptomatic child, screening should commence if appropriate and further investigation/treatment undertaken depending on the abnormal findings. For a child of a parent with a known *MEN1* mutation, who does not carry that mutation, the risk of developing MEN1-associated tumours is the same as that for the general population, and these individuals do not need to proceed into a specialised screening program for MEN1.

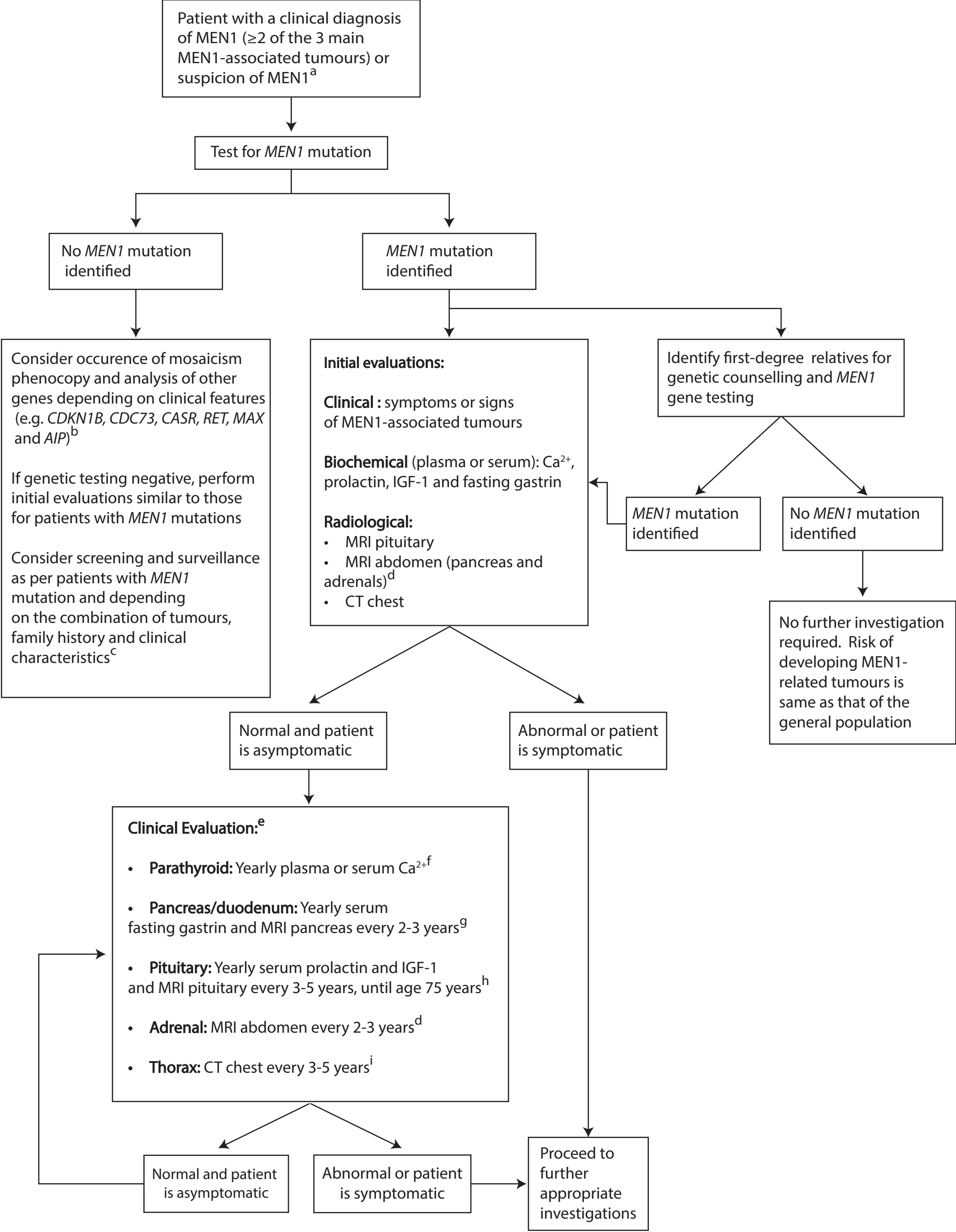


^a Reference¹⁷

^b For detailed methodology regarding the Delphi, see appendix pp4-35

^c Several statements included substatements, see appendix pp28-35

Figure 1



^a Suspicion for MEN1, detailed in table 4.

^b Genes reported to be associated with phenocopies, as detailed in table 1 and appendix p37.

^c Detailed in reference 27 and appendix p36.

^d MRI abdomen can be performed to screen for pancreatic and adrenal nodules. However, if detailed views of the pancreas cannot be obtained, a dedicated MRI pancreas is also recommended.

^e tables 2 and 3 and appendix pp14-35.

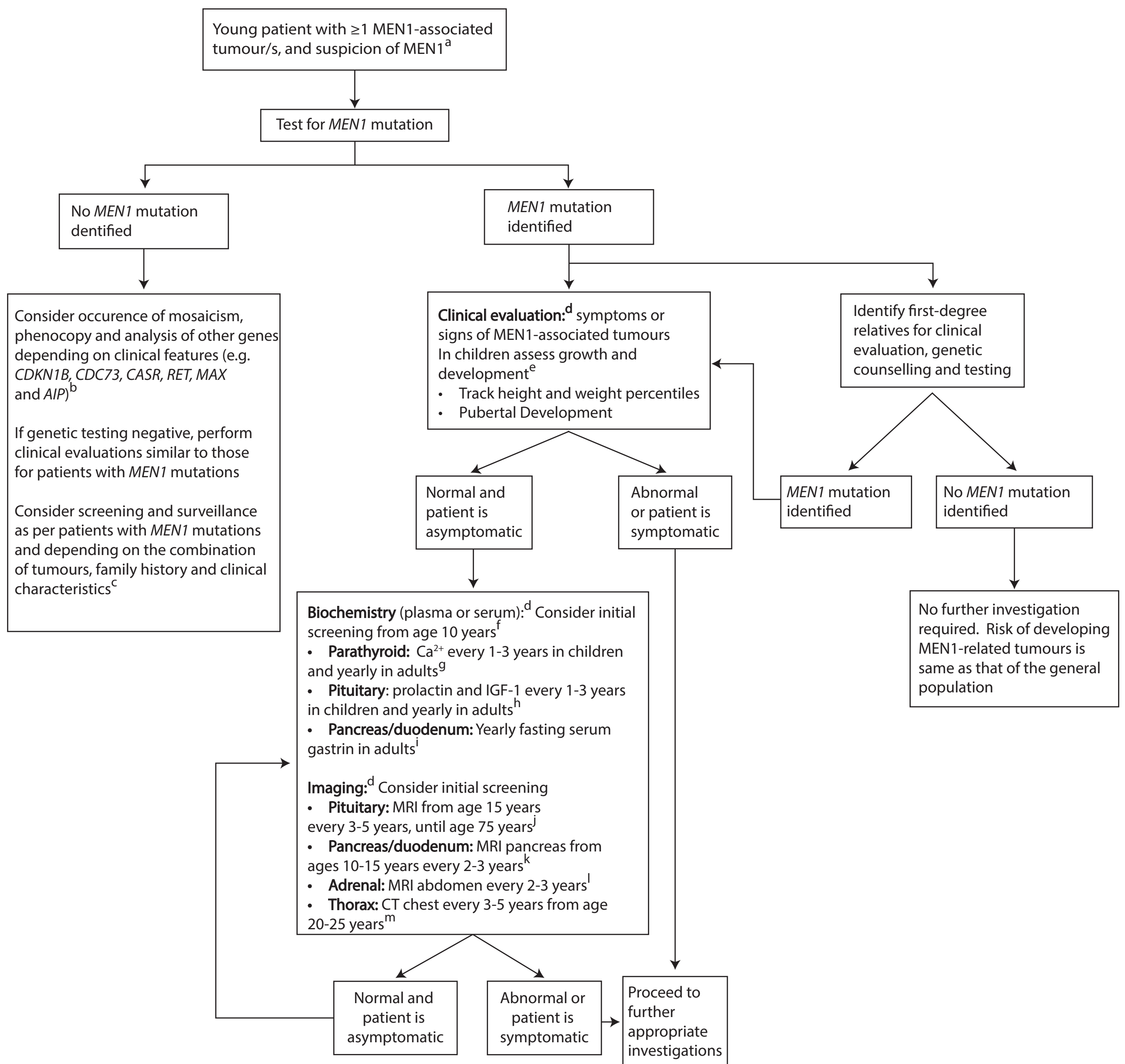
^f #5-#7, table 2.

^g #21-#27, table 2.

^h #41-#47, table 2.

ⁱ #35-#37 , table 2.

Figure 2



^a Young refers to PHPT patient <30 years of age, PanNET patient <40 years of age and PA patient <30 years of age. #49-#52, (tables 2 and 4 and appendix pp14-35) Suspicion for MEN1, detailed in table 4.

^b Genes reported to be associated with phenocopies, as detailed in table 1 and appendix p37.

^c Detailed in reference 27 and appendix p36.

^d tables 2 and 3.

^e #43, table 2.

^f There is no consensus on the exact age to start screening in children (<19 years). #7,#25,#45, table 2.

^g #5-#7, table 2.

^h #44-#45, table 2.

ⁱ There is no consensus regarding screening with fasting serum gastrin in childhood. #23-#26, table 2.

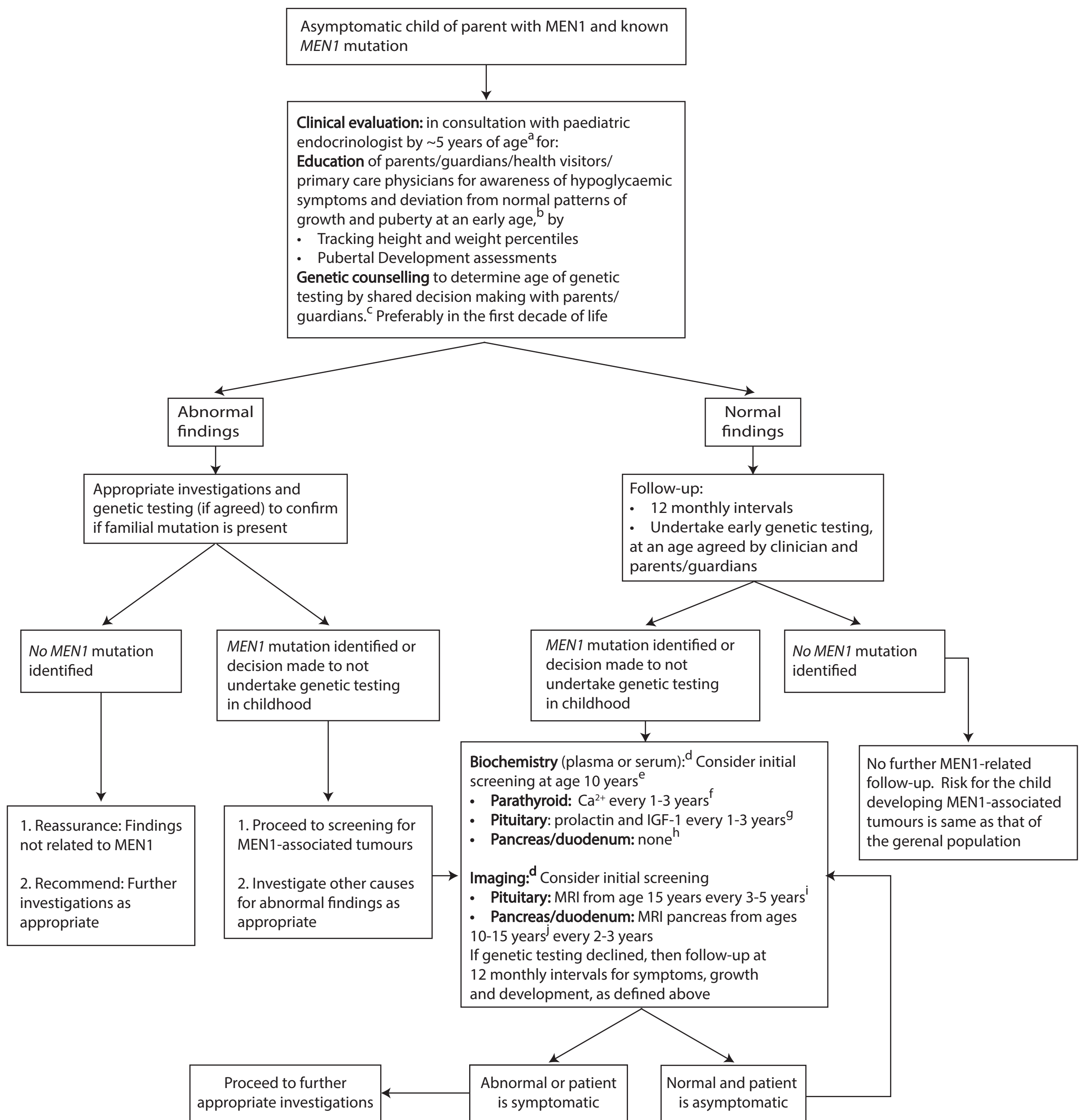
^j There is no consensus on the benefit of MRI screening for a pituitary adenoma in asymptomatic children with normal growth and development. #40-#42, #46 and #47, table 2.

^k #21, #22 and #27, table 2.

^l MRI abdomen can be performed to screen for pancreatic and adrenal nodules. However, if detailed views of the pancreas cannot be obtained, a dedicated MRI pancreas is also recommended.

^m #35-#37, table 2.

Figure 3



^a In some countries consultation with a paediatric endocrinologist may be earlier.

^b #43, table 2 and appendix pp14-35.

^c This can be with or without the child present.

^d Tables 2 and 4

^e There is no consensus on the exact age to start screening in children. #7,#25,#45, table 2.

^f #6-#7, table 2.

^g #43-#45, table 2.

^h There is no consensus regarding screening with fasting serum gastrin in childhood. #25, table 2.

ⁱ There is no consensus on the benefit of MRI screening for a pituitary adenoma in asymptomatic children with normal growth and development. #46 and #47, table 2.

^j #22 and #27, table 2.

Figure 4

TABLE 1. MEN syndromes and their characteristic tumours and associated genetic abnormalities		
Type (chromosome location)	Tumours (estimated penetrance)	Gene, most frequently mutated codons
MEN1 (11q13)	Parathyroid adenoma (90%) Duodenopancreatic tumour (30-80%): gastrinoma (40%), insulinoma (10%), nonfunctioning and PPoma (20-80%), glucagonoma (<1%), VIPoma (<1%) Pituitary adenoma (~35–>50%): prolactinoma (~45–~80%), clinically non-functioning (15–~45%), somatotropinoma (<10%) and corticotropinoma (<5%) Associated tumours: adrenal tumours (~40%) adrenal cortical tumour (>90%), pheochromocytoma (<1%), adrenocortical carcinoma (~1%) ^a ; bronchopulmonary NET (5-30%), thymic NET (<10%), gastric NET (10%), lipomas (30%), angiofibromas (85%), collagenomas (70%), meningiomas (<10%)	<i>MEN1</i> 83/84, 4-bp del (=4%) 119, 3-bp del (=3%) 209–211, 4-bp del (=8%) 418, 3-bp del (=4%) 514–516, del or ins (=7%) Intron 4 ss, (=10%)
MEN2A (10 cen-10q11.2)	MTC (90%) Pheochromocytoma (50%) Parathyroid adenoma (20–30%)	<i>RET</i> missense e.g. Cys634Arg (~85%)
		<i>RET</i> Cys618Arg, missense (>50%)
MEN2B (also known as MEN3)	MTC (>90%) Pheochromocytoma (40–50%) Associated abnormalities (40–50%) Mucosal neuromas Marfanoid habitus Medullated corneal nerve fibers Megacolon	<i>RET</i> Met918Thr (>95%)
MEN4 (12p13)	Parathyroid adenoma ^b Pituitary adenoma ^b Reproduction organ tumours (e.g. testicular cancer, neuroendocrine cervical carcinoma) ^b ?Adrenal + renal tumours ^b	<i>CDKN1B</i> No common mutations identified to date
MEN5 (14q23)	Paraganglioma ^b Pheochromocytoma ^b Parathyroid adenoma ^b Pituitary adenoma ^b Ganglioneuroma ^b Ganglioneuroblastoma ^b	<i>MAX</i> No common mutations identified to date

Autosomal-dominant inheritance of the MEN syndromes has been established. Deletion (del); insertion (ins); Pancreatic polypeptide-secreting tumour (PPoma); Medullary thyroid cancer (MTC); neuroendocrine tumour (NET); Ret Proto-Oncogene (*RET*); Cyclin Dependent Kinase Inhibitor 1B (*CDKN1B*), MYC Associated Factor X (*MAX*); and splice site (ss)

^a Adrenocortical carcinoma risk is reported to be 10-15% in adrenal tumours >1cm.

^b Insufficient numbers reported to provide prevalence information.

Table 2. Final Delphi Statements

GENERAL		
#1	The statements in these Delphi proceedings pertain to patients with genetically confirmed MEN1 or those who are obligate carriers.	
#2	In accordance with the WHO definition, children and adolescents are defined as people age <19 years.	
#3	Patients with MEN1 should be treated in centers of expertise with high-volume, experienced multidisciplinary teams. <i>(unchanged)</i>	R
#4	Parents with MEN1 should have an initial consultation (with or without the child present) with a pediatric endocrinologist when the child is around the age of five years. Symptoms of MEN1 clinical manifestations should be discussed and shared decision-making undertaken regarding screening and surveillance plans. <i>(new)</i>	R (100%) Paed
PRIMARY HYPERPARATHYROIDISM		
Screening		
#5	Adults with MEN1 should be screened for primary hyperparathyroidism with yearly serum calcium measurements. <i>(changed, interval similar, PTH now omitted)</i>	R (91%)
#6	Children and adolescents with MEN1 should be screened for primary hyperparathyroidism with serum calcium measurements at 1-3 year intervals. <i>(changed, enabling longer interval)</i>	R (98%)
#7	In asymptomatic children, there is no consensus regarding the age at which to initiate screening. Screening starting at the age of 10 years can be considered. <i>(changed; 2001 and 2012 initiate age 8 years)</i>	C
Management		
#8	To assess renal and skeletal involvement in adults with MEN1 and newly diagnosed PHPT according to the Guidelines from the Fifth International Workshop on Primary Hyperparathyroidism. <i>(new)</i>	R (97%)
#9	In children/adolescents with MEN1 and newly diagnosed PHPT renal function (creatinine or cystatin C eGFR) should be assessed. <i>(new)</i>	R (92%)
#10	In asymptomatic children/adolescents with PHPT routine DXA assessment is not recommended. For those children undergoing BMD assessment this needs to be interpreted in the context of age and height. <i>(new)</i>	R (92%) Paed
#11	To monitor target organ involvement in adults with MEN1 with PHPT, if surgery is deferred according to the Guidelines from the Fifth International Workshop on Primary Hyperparathyroidism. <i>(new)</i>	R (95%)
#12	In asymptomatic children, adolescents and adults with MEN1, in whom the onset of PHPT is observed but who do not have evidence of target organ involvement, initial active surveillance is acceptable. <i>(new or now explicit)</i>	R(A90%, P88%)
#13	Parathyroidectomy is indicated in children, adolescents and adults diagnosed with MEN1-related PHPT who are symptomatic or have evidence of target organ involvement. <i>(new or now explicit)</i>	R (98%)
#14	Irrespective of symptoms, parathyroidectomy is indicated in adults diagnosed with MEN1-related PHPT, in whom total serum calcium levels are consistently >1 mg/dl (0.25 mmol/L) above the upper limit of the reference range of the specific assay used. <i>(new or now explicit)</i>	R (96%)
#15	We suggest parathyroidectomy in children and adolescents diagnosed with MEN1-related PHPT, whose total serum calcium levels are consistently >1 mg/dl (0,25 mmol/L) above the upper limit of the reference range of the specific assay used. <i>(new or now explicit)</i>	S
#16	In patients with MEN1, the presence of a symptomatic gastrinoma should be taken into account when considering the timing of parathyroidectomy. <i>(unchanged)</i>	R (96%)
#17	In children, adolescents and adults with MEN1-related PHPT, subtotal (3 to 3½ gland) parathyroidectomy with concomitant transcervical thymectomy is the recommended index operation, which should be performed by an experienced MEN1 parathyroid surgeon. <i>(2001, 2012 unchanged)</i>	R (89%)

#18	In selected cases, unilateral clearance can be considered as the index operation for children or adolescents with MEN1-related primary hyperparathyroidism. <i>(new)</i>	S
#19	There is no consensus on the need nor type of pre-operative imaging studies for parathyroid localization before the index operation in adults. <i>(new or now explicit)</i>	
#20	The need and type of pre-operative imaging for parathyroid localization before the index operation in children and adolescents are determined on a case-by-case basis. <i>(new or now explicit)</i>	S
NEUROENDOCRINE TUMORS (NETs)		
Duodenopancreatic NETs - Screening		
#21	To screen asymptomatic patients with MEN1 with magnetic resonance imaging (MRI) for the presence of a pancreatic NET. <i>(changed now stating preference for MRI)</i>	R (80%)
#22	To perform the first MRI in asymptomatic children between ages 10-15 years, the exact age to be at the discretion of the clinician and with shared decision making. <i>(changed 2001 20yr, 2012 <10yr)</i>	R (84%)
#23	Children, adolescents, and adults with MEN1 should be screened for insulinoma by careful assessment for hypoglycemic symptoms. For symptomatic patients we recommend further biochemical evaluation as per established guidelines. <i>(changed, removed screening with glucose and insulin).</i>	R (100%)
#24	In asymptomatic adults with MEN1, we recommend screening for gastrinoma with fasting serum gastrin. <i>(unchanged)</i>	R (95%)
#25	There is no consensus on screening asymptomatic children with fasting serum gastrin for the presence of a gastrinoma.	
#26	In asymptomatic patients with negative abdominal imaging, additional biochemical screening for the presence of a pancreatic NET is generally not useful. <i>(changed, removes biochemical screening with CgA, PPT, glucagon and VIP)</i>	R (86-93%)
#27	To perform pancreatic imaging every 2-3 years in adults with MEN1 who have a negative baseline MRI, normal serum gastrin and no signs or symptoms of a (functioning) duodenopancreatic NET. <i>(changed, 2001 every, 2012 yearly)</i>	R 59% 2y 41% 3y
Duodenopancreatic NETs – Management		
#28	In patients with MEN1 and stable NF PanNETs ≤ 2 cm with growth rates <1 mm/year (for more than 1 year) on active surveillance, we recommend performing imaging every 1-2 years, taking into account tumor size. <i>(new)</i>	R (92%)
#29	To perform SSTR-PET/CT or SSTR-PET/MRI in all patients with MEN1 planned for duodenopancreatic surgery. <i>(new)</i>	R (100%)
#30	SSTR-PET imaging can play a role in the surveillance of patients with MEN1 and gastrinoma or PanNET when the results would affect management. <i>(new)</i>	S NET
#31	EUS can play a role in the surveillance of patients with MEN1 and gastrinoma or PanNET when the results would affect management <i>(changed, more explicit statement about the role)</i>	S NET
#32	Routine EUS-guided biopsy is not recommended. <i>(new)</i>	R (100%) NET
#33	Patients with symptoms suggestive of Zollinger-Ellison Syndrome (ZES) should undergo OGD. <i>(unchanged)</i>	R
#34	To perform an OGD in patients with MEN1 who have consistently elevated fasting serum gastrin levels to look for signs of ZES and gastro-duodenal NETs. <i>(unchanged)</i>	S
Thoracic NETs – Screening		
#35	To screen asymptomatic adults with MEN1 with CT for the presence of a thoracic NET. <i>(changed, now stating preference for CT)</i>	R (82%)
#36	To initiate thoracic imaging screening between ages 20-25 years in asymptomatic patients with MEN1. <i>(changed, 2001 20yr, 2012 15yrs)</i>	R (86%)
#37	To perform thoracic imaging every 3-5 years in adults with MEN1 who have negative baseline imaging and no signs or symptoms of a thoracic neuroendocrine tumor. <i>(changed compared to 2012 every 1-2 yr, similar to 2001 every 3yr in table 3-5 yrs in text)</i>	S
Thoracic NETs – Management		

#38	Active surveillance is an acceptable management strategy for small (<1-2 cm) lung NETs in patients with MEN1. <i>(new)</i>	S
#39	To perform imaging every 1-2 years taking into account tumor size in patients with MEN1 and stable (growth <1 mm/year over >1 year) small (<1-2 cm) lung NETs on active surveillance. <i>(new)</i>	R (97%)
PITUITARY		
Screening - adults		
#40	To screen asymptomatic adults with MEN1 with MRI for the presence of a pituitary adenoma. <i>(unchanged)</i>	R (95%)
#41	In adults with no mass detected by MRI at baseline, persistent absence of features of hypo- or hyperpituitarism and normal hormonal testing, we recommend performing an MRI of the pituitary every 3-5 years. <i>(unchanged, 2001 every 3yr in table 3-5 in text, 2012 every 3 years)</i>	R 54% 3y 43% 5y
#42	In asymptomatic patients with no pituitary adenoma history, who have negative pituitary imaging and normal hormone testing, imaging screening can be stopped at the age of 75 years while continuing clinical and biochemical screening. <i>(new)</i>	R(94%)
Screening in children		
#43	Physical examination in children with MEN1 should include the evaluation of growth and pubertal development. <i>(new)</i>	R (100%) Paed
#44	To screen asymptomatic children with MEN1 with normal growth and development, for pituitary tumors using prolactin (PRL) and Insulin-like Growth Factor 1 (IGF-1). <i>(unchanged)</i>	S
#45	There is no consensus regarding the age to initiate biochemical screening. Initiating biochemical screening from the age of 10 years can be considered. <i>(changed, 2001 and 2012 start age 5)</i>	C
#46	There is no consensus on the benefit of MRI screening in asymptomatic children with normal growth and development for the presence of a pituitary adenoma. <i>(changed)</i>	
#47	To perform the initial MRI from the age of 15 years, if in shared decision making, it is decided to screen asymptomatic children with normal growth and development with pituitary MRI. <i>(changed)</i>	S
Management		
#48	When a pituitary tumor is diagnosed in a patient with MEN1 we recommend management according to sporadic pituitary tumor guidelines. <i>(unchanged)</i>	R (92%)
GENETIC TESTING IN APPARENTLY SPORADIC MEN1-RELATED TUMORS		
#49	Offer genetic testing including MEN1, to patients with apparently sporadic PHPT <30 years of age and/or patients with multi-gland disease. <i>(unchanged)</i>	S
#50	In patients aged <40 years diagnosed with an apparently sporadic solitary PanNET, genetic testing for MEN1 can be considered. <i>(new)</i>	C
#51	MEN1 genetic testing can be considered in adults below 30 years of age with an apparently sporadic, functioning pituitary adenoma (with the exception of a micro-prolactinoma in women) or a non-functioning pituitary adenoma larger than 1 cm. <i>(new)</i>	C
#52	Genetic testing, including MEN1, should be considered in children/adolescents (<19 years) with an apparently sporadic pituitary adenoma. <i>(new)</i>	C

Final Statements from the Delphi consensus. See also appendix pp28-35 which provides a summary of the final discussions for each statement, with details, nuances and caveats.

Statements are followed by the strength: R for recommendation (statements that reached consensus in the first two rounds (agreement $\geq 80\%$)), S for Suggestion (Statements with near consensus in the first two rounds (agreement 70-80%) and C for consideration (Statements where opinions among experts were more varied in the first two rounds (agreement 51-70%)) Recommendations are in white, suggestions and consideration in grey. For recommendations the percentage agreement is provided.

Statements that were not part of the first two questionnaire rounds but have been newly developed in the final meetings are indicated: Paed-formulated in the Paediatric meeting, Para-formulated in the para meeting, NET-formulated in the neuroendocrine tumour meeting, Pituitary-formulated in the pituitary meeting. For each of the statement the changes compared to the previous guideline(s) have been pointed out.

OGD - oesophagogastroduodenoscopy

Table 3. Suggested biochemical and radiological screening in asymptomatic individuals with MEN1, after obtaining a careful history and physical examination.

Tumour	Age to begin biochemical screening (time interval)	Recommended screening biochemical test (plasma or serum)	Age to begin imaging screening (time interval)	Recommended screening imaging modality
Parathyroid	10 years (annual) ^a	Calcium	N/A	None
DP-NET				
NF-PanNET	None	None	10-15 years (every 2-3 years)	MRI pancreas/abdomen
Gastrinoma	>18 years (annual)	Fasting gastrin ^b	None	None
Insulinoma	5 years	None ^c	None	None
Anterior pituitary	10 years (annual) ^d	Prolactin, IGF-1 ^e	15 years (every 3-5 years) ^{e,f}	MRI pituitary ^g
Adrenal	None	None	10-15 years (every 2-3 years) with pancreatic imaging	MRI abdomen
Thoracic NET	None	None	20-25 years (every 3-5 years)	CT chest ^h

Duodenopancreatic neuroendocrine tumour (DP-NET); Neuroendocrine tumour (NET) and non-functioning pancreatic neuroendocrine tumour (NF-PanNET), N/A – not applicable.

^a In children and adolescents, biochemical screening for primary hyperparathyroidism can occur at 1-3 year intervals, while in adults yearly serum calcium measurements should be performed. #5,#6 and #7, table 2 and appendix pp14-35.

^b Annual for adults (#24, table 2), but no consensus reached for childhood screening. #25, table 2.

^c Screening for insulinoma should be performed by careful assessment for hypoglycaemic symptoms, and if present, further biochemical and imaging evaluation is recommended. #23, table 2.

^d Consider initiating biochemical screening at 10 years of age. #45, table 2.

^e In children and adolescents, biochemical screening for pituitary adenoma can occur at 1-3 year intervals, while in adults, yearly measurements should be performed.¹⁵²

^f Imaging screening for pituitary tumours can be stopped at the age of 75 years in asymptomatic patients with normal pituitary imaging and biochemistry. #42, table 2.

^g No consensus on the benefit of MRI screening in asymptomatic children with normal growth and development. #46 and #47, table 2.

^h #35-#37, table 2.

Table 4. Suggested approach for *MEN1* germline mutation analysis in a clinical setting

Value in clinical setting

- Aids in confirming the diagnosis
- Identifies germline mutation carriers in a family for screening and development of tumours, thereby facilitating earlier diagnosis and treatment
- Identifies the 50% of family members who do not harbour the *MEN1* mutation, thereby alleviating the anxiety and burden of disease from them and their progeny

Who should be tested?

- Index case with two or more classical *MEN1*-associated tumours
- First-degree relative of a family member with a known *MEN1* germline mutation, clinical *MEN1*, or family history suggestive of endocrine tumours
- Suspicion of *MEN1*:
 - PHPT: Individuals with apparently sporadic PHPT <30 years of age^a, multigland PHPT^a or family history of PHPT or other *MEN1*-associated disorders
 - PanNETs: Individuals with a gastrinoma^b or multiple PanNETs^b at any age, or apparently sporadic PanNET at <40 years of age^c
 - Pituitary: Adults <30 years of age with apparently sporadic, functioning pituitary tumour (with the exception of micro-prolactinoma in females), or non-functioning pituitary tumour > 1 cm^c; Children/adolescents <19 years of age with an apparently sporadic pituitary tumour^c
 - Individuals with a thymic NET^{b,d} at any age
 - Atypical for *MEN1* (i.e. development of two nonclassical tumours, e.g. parathyroid and adrenal tumours)^b

When should testing be done?

Within the first decade of life or at clinical diagnosis

Where should testing be performed?

In an accredited department/laboratory undertaking DNA testing of the *MEN1* gene

Primary hyperparathyroidism (PHPT); Pancreatic neuroendocrine tumour (PanNET); and Neuroendocrine tumour (NET).

^a Genetic testing suggested. #49, table 2 and appendix pp14-35;⁴²

^b Genetic testing recommended.¹⁵²

^c Genetic testing should be considered. #50 #51,#52, table 2.

^d 25% of reported thymic NETs are *MEN1*-associated.²¹

Appendix for Multiple Endocrine Neoplasia type 1 (MEN1) : Recommendations and Guidelines for Best Practice

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- d Academic Endocrine Unit, Oxford Centre for Diabetes, Endocrinology and Metabolism, Radcliffe Department of Medicine, University of Oxford, Oxford, UK
- e Oxford NIHR Biomedical Research Centre, University of Oxford, Churchill Hospital, Oxford, UK
- f School of Biological and Medical Sciences, Faculty of Health and Life Sciences, Oxford Brookes University, Oxford, UK
- g Division of Endocrine Surgery, Mayo Clinic, Rochester, MN, USA
- h Department of Surgical Oncology, Section of Surgical Endocrinology, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA
- i Aix Marseille University, Department of Endocrinology, Centre d'Investigation Clinique 1409, La Conception hospital, Marseille, France
- j Department of Gastrointestinal oncology, Intermountain Health, Salt Lake City, Utah, USA
- k "EDIMO & Human Genetics and Precision Medicine, Institute for Molecular Biology & Biotechnology (IMBB), Foundation for Research & Technology Hellas (FORTH), Heraklion, Greece, and Medical Genetics, H. Dunant Hospital and ASTREA Health, Athens, Greece
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- m Aix Marseille Univ, INSERM, MMG, Department of endocrinology, La Conception Hospital, Assistance Publique Hopitaux de Marseille, Marseille, France and Endo-European Reference network on rare endocrine conditions – « Genetic endocrine tumor syndromes » Main thematic group.
- n Centre for Endocrinology, Metabolism, William Harvey Research Institute, Barts and The London School of Medicine, Queen Mary University of London, London, UK

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Supplementary table 1. Variant classification criteria*

	Population data	Computational and predictive data	Functional data	Segregation data [§]	De novo data	Allelic data	Other database	Other data
Pathogenic	Prevalence in affected statistically higher than controls	Null variant where LOF is known mechanism OR Same a.a. change as a pathogenic variant	Show deleterious effect	Yes	Yes with confirmation by testing parents			
Likely Pathogenic	Absent in population databases	Novel missense change at a.a. residue of a known pathogenic missense variant OR Protein length changing variant OR Multiple lines of computational evidence show deleterious effect on gene/ product	Mutational hotspot/well studied functional domain without benign variation OR Missense in gene with low rate of benign, and common missense variants	Yes	No	For recessive disorder - in trans with a pathogenic variant	Pathogenic	Phenotype/family history specific for gene
Likely Benign		No impact on gene / product in multiple lines of computational evidence OR Missense in gene where only truncating cause disease OR Silent variant/non predicted splice impact OR In-frame indels in repeat without known function	Not available or equivocal	No	No	Yes, in trans with a dominant variant OR Yes, in cis with a pathogenic variant	Benign in reputable source without shared data	In patient with alternative cause
Benign	MAF too high for disorder OR observation in controls inconsistent with disease penetrance		No deleterious effect	No	No		Benign	

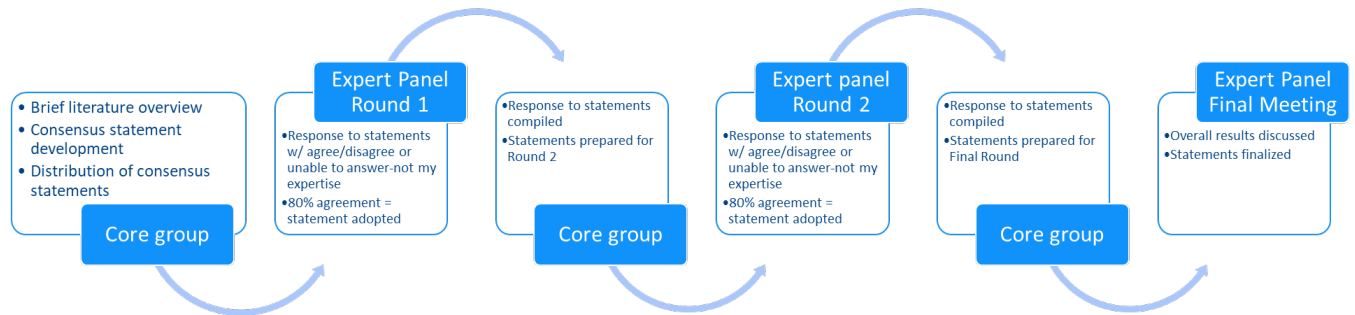
Variant of uncertain (or unknown) significance (VUS) If all above criteria are not met e.g. unknown or conflicting clinical significance. Additional evidence is needed in order to determine whether or not the variant is causative for a particular disease As additional data and research emerges over time, variants of unknown significance may get moved to other categories, frequently towards the benign or likely benign categories.

**Based on American College of Medical Genetics and Genomics (ACMG) and Association for Molecular Pathology (AMP)¹*

§ segregates with multiple affected members

MAF – major allele frequency; *LOF* – loss of function; *a.a.* amino acid

Supplementary figure 1



Supplementary figure 1: Delphi Consensus Methodology

w/ with

Supplementary table 2. International Writing Committee and Working Groups

International Writing Committee		
Name	Role	Discipline
Rajesh Thakker	Project administration Supervision Systematic review Working Group Delphi Core Group Conceptualisation Methodology Resources Writing – original Draft Writing – Review and editing	Endocrinology
Maria Luisa Brandi	Supervision Systematic review Working Group Delphi Core Group Conceptualisation Resources Systematic Review Writing – Review and editing	Endocrinology
Gerlof Valk	Supervision Systematic review Working Group Delphi Lead Conceptualisation Methodology Resources Delphi Writing – original Draft Writing – Review and editing	Endocrinology
Carla Pieterman	Systematic review Working Group Delphi co-Lead Conceptualisation Methodology Project Administration Writing – original Draft Writing – Review and editing	Endocrinology
Steven G. Waguespack	Systematic review Working Group Delphi Core Group Conceptualisation Writing – Review and editing	Endocrinology Paediatric Endocrinology
Frederic Castinetti	Systematic review Working Group Delphi Core Group Conceptualisation Writing – Review and editing	Endocrinology
Omair Shariq	Systematic review Working Group Delphi Core Group Writing – original Draft Writing – Review and editing	Endocrine Surgery
Thomas Cuny	Systematic review Working Group Delphi Core Group Writing – Review and editing	Endocrinology
Kate Lines	Systematic review Working Group Writing – original Draft	Biochemistry, molecular oncology

	Writing – Review and editing	
Francesca Marini	Systematic review Working Group Delphi Core Group Writing – Review and editing	Biology
Katherine English	Systematic review Working Group Delphi Core Group Writing – original Draft Writing – Review and editing	Endocrinology
Nancy Perrier	Conceptualisation Writing – Review and editing	Endocrine Surgery
Mark Lewis	Conceptualisation Writing – Review and editing Patient perspective	Patient representative Oncology
Constantine Stratakis	Conceptualisation Writing – Review and editing	Paediatrics Endocrinology, Medical Genetics
Systematic Review Working Group		
Rajesh Thakker	Supervision Parathyroid Systematic review Pituitary Systematic review	Endocrinology
Gerlof Valk	Supervision NET systematic Review	Endocrinology
Maria Luisa Brandi	Supervision Parathyroid Systematic review	Endocrinology
Steven G. Waguespack	Supervision Pituitary Systematic review	Endocrinology Paediatric endocrinology
Frederic Castinetti	Supervision Pituitary Systematic review	Endocrinology
Omair Shariq	Parathyroid Systematic review	Endocrine Surgery
Thomas Cuny	Pituitary Systematic review	Endocrinology
Kate Lines	Pituitary Systematic review	Biochemistry, molecular oncology
Francesca Marini	Parathyroid systematic review	Biology
Carla Pieterman	NET systematic review	Endocrinology
Katherine English	NET systematic review Pituitary systematic review	Endocrinology
Silvia Minozzi Zuzana Mitrova Rosella Saulle	Supervision Methodology and analysis	Epidemiology
Delphi Core Group		
Gerlof Valk	Lead	Endocrinology

	NET Statements NET concise literature overview	
Carla Pieterman	Co-Lead NET statements NET concise literature overview	Endocrinology
Rajesh Thakker	Member Parathyroid Statements Parathyroid concise literature overview Pituitary Statements Pituitary concise literature overview	Endocrinology
Maria Luisa Brandi	Member Parathyroid Statements Parathyroid concise literature overview	Endocrinology
Omair Shariq	Member Parathyroid Statements Parathyroid concise literature overview	Endocrine Surgery
Francesca Marini	Member Parathyroid Statements Parathyroid concise literature overview	Biology
Frederic Castinetti	Member Pituitary Statements Pituitary concise literature overview	Endocrinology
Thomas Cuny	Member Pituitary Statements Pituitary concise literature overview	Endocrinology
Katherine English	Member Pituitary Statements Pituitary concise literature overview	Endocrinology
Steven Waguespack	Member Pituitary Statements Paediatric Statements Pituitary concise literature overview	Endocrinology Paediatric endocrinology

Supplementary table 3. Delphi Consensus Expert Panel

Name	Discipline	Country	Institute	Para P/F	PIT P/F	NET P/F	Paed
Gerlof Valk*	E	NL	University Medical Center Utrecht	Y / Y	Y / Y	Y / Y	Y
Carla Pieterman*	E	NL	University Medical Center Utrecht	Y / Y	Y / Y	Y / Y	Y
Maria Luisa Brandi*	E	IT	University Vita-Salute san Raffaele	Y / Y	Y / Y	Y / N	N
Frederic Castinetti*	E	FR	Aix Marseille University / La Conception Hospital	Y / N	Y / Y	Y / N	N
Thomas Cuny*	E	FR	Aix Marseille University / La Conception Hospital	N / N	Y / N	N / Y	N
Katherine English*	E	GB	University of Oxford	Y / Y	Y / Y	Y / Y	N
Omair Shariq *	ES	US	University of Oxford Mayo Clinic Rochester Currently: The University of Texas MD Anderson Cancer Center	Y / Y	N / Y	Y / N	Y
Rajesh Thakker*	E	GB	University of Oxford Queen Mary University London (QMUL)	Y / Y	Y / Y	Y / Y	Y
Steven G. Waguespack*	Paed E / E	US	The University of Texas MD Anderson Cancer Center	Y/Y	Y/Y	Y/Y	Y
Andrew Arnold	E	US	University of Connecticut School of Medicine	Y / Y	Y / N	N / N	N
Detlef K. Bartsch	ES	DE	Philipps-University Marburg	N / N	N / N	Y / Y	N
Albert Beckers	E	BE	University of Liège	N / N	Y / Y	N / N	N
Jérôme Bertherat	E	FR	Hospital Cochin	N / N	Y / N	N / N	N
Sanjay Kumar Bhadada	E	IN	PGIMER, Chandigarh, India	Y / Y	N / N	N / N	N
John P Bilezikian	E	US	Columbia University	Y / Y	N / N	N / N	N
Jenny Blau	E	US	NIDDK/NIH	Y / Y	Y / Y	Y / Y	N
Arthur Braat	NM	NL	University Medical Center Utrecht Princes Máxima Center Utrecht Netherlands Cancer Institute, Amsterdam	N / N	N / N	Y / Y	N
Luis Cardoso	E	PT	Coimbra Hospital and University Centre / i3S – Institute for Research and	Y / Y	Y / Y	Y / Y	N

			Innovation in Health of the University of Porto				
Ruth Casey	E	GB	University of Cambridge and National Institute for Health Research	Y / N	Y / Y	Y / Y	N
Bart Clarke	E	US	Mayo Clinic Rochester	Y / N	N / N	N / N	N
Rory Clifton-Bligh	E	AU	Royal North Shore Hospital University of Sydney	Y / Y	Y / Y	Y / Y	N
Mehul Duttani	Paed E	GB	UCL GOS Institute of Child Health	Y / N	Y / N	Y / N	N
Paolo de Coppi	Paed S	GB	Great Ormond Street Hospital	Y / N	N / N	Y / N	Y
Wouter de Herder	E	NL	Erasmus MC & Erasmus MC Cancer Institute	Y / N	Y / Y	Y / Y	N
Gerard Doherty	S	US	Harvard Medical School	N / N	N / N	Y / Y	N
Ghada El-Hajj Fulcihan	E	LB	American University of Beirut	Y / Y	N / N	N / N	N
Francesca Giusti	E	IT	Donatello Bone Clinic	Y / Y	N / N	N / N	N
Simona Grozinsky-Glasberg	E	IL	The Hebrew University	N / N	N / N	Y / Y	N
David Goltzman	E	CA	McGill University / McGill University Health Centre	Y / N	N / N	N / N	N
Jamie van Gompel	NS	US	Mayo Clinic Rochester	N / N	Y / Y	N / N	N
Pierre Goudet**	ES	FR	Dijon University Hospital	N / N	N / N	Y / Y	N
Ashley Grossman	E	GB	Queen Mary University of London; Green Templeton College, University of Oxford; ENETS Centre of Excellence, Royal Free Hospital	Y / Y	Y / Y	Y / Y	N
Mark Gurnell	E	GB	University of Cambridge and Addenbrooke's Hospital	N / N	Y / Y	N / N	N
Thorvardur Halfdanarson	MO	US	Mayo Clinic Rochester	N / N	N / N	Y / Y	N
Daniel Halperin	MO	US	The University of Texas MD Anderson Cancer Center Currently Emory.	N / N	N / N	Y / Y	N
Maurizio Iacobone	ES	IT	University of Paduva	Y / Y	N / N	N / N	N
Smita Jha	E	US	NIH/NIDDK	Y / Y	Y / Y	Y / Y	Y
Gregory Kaltsas	E	GR	National and Kapodistrian University of Athens	Y / Y	Y / Y	Y / Y	N
Niki Karavitaki	E	GB	University of Birmingham / University Hospitals	N / N	Y / Y	N / N	N

			Birmingham NHS Foundation Trust				
Tom Kurzwinski	E	GB	University College Hospital London / Great Ormond Street Hospital for Children	Y / N	N / N	Y / Y	Y
Edward Laws	E	US	Brigham and Women's Hospital	N/ N	Y / N	N / N	N
Manuel Lemos	E / G	PT	University of Beira Interior	Y / N	Y/ Y	Y / Y	N
Mark Lewis**	Patient/ MO	US	Intermountain Health	Y/ N	Y / N	Y / N	N
Agnès Lingart	Paed	FR	Paris Saclay University / Bicêtre Paris Saclay hospital,	Y/ N	Y /N	Y / N	N
Maya Lodish	Paed E	US	University of California San Francisco	Y/ N	Y / N	Y / N	Y
Michael Mannstadt	E	US	Massachusetts General Hospital and Harvard Medical School	Y / N	N / N	N / N	N
Ann McCormack	E	AU	St Vincent's Hospital/ Garvan Institute of Medical Research / University of New South Wales	N /N	Y / Y	N / N	N
Ian McCutcheon	NS	US	The University of Texas MD Anderson Cancer Center	N/ N	Y / Y	N / N	N
Shlomo Melmed	E	US	Cedars-Sinai Medical Center	N/ N	Y / Y	N / N	N
Leon Moons	GE	NL	University Medical Center Utrecht	N / N	N / N	Y / N	N
Bernadette van Nesselrooij	MG	NL	University Medical Center Utrecht	Y/ Y	Y/ Y	Y/ Y	Y
Dermot O'Toole	GE	IE	St Vincent's University Hospital & St James Hospital & Trinity College	N / N	N / N	Y / Y	N
Nancy Perrier**	ES	US	The University of Texas MD Anderson Cancer Center	Y / Y	N / N	N /N	Y
Gérald Raverot	E	FR	INSERM / Lyon 1 University / "Groupement Hospitalier Est" Hospices Civils de Lyon	N/ N	Y / Y	N / N	N
Yumie Rhee	E	KR	Yonsei University College of Medicine	Y / Y	Y / N	Y / Y	N
Samira Sadowski	ES	US	NIH/NCI	N /N	N / N	Y / N	N
Camilla Schälén-Jantti	E	FI	Helsinki University Hospital and University of Helsinki	Y / Y	Y / Y	Y / Y	N
David Scott-Coombes	ES	GB	University Hospital of Wales	Y / Y	N /N	Y /N	N
Andreas Selberherr	S	AT	Evangelisches Krankenhaus Wien	N / N	N /N	Y / N	N

Dolores Shoback	E	US	University of California, San Francisco / San Francisco Department of Veterans Affairs Medical Center	Y / Y	N / N	N / N	Y
Shonni Silverberg	E	US	Columbia University College of Physicians & Surgeons	Y / Y	N / N	N / N	N
William Simonds	E	US	NIH/NIDDK	Y / Y	N / N	N / N	N
Catherine Skefos	GC	US	The University of Texas MD Anderson Cancer Center	Y / Y	Y / Y	Y / Y	N
Peter Snyder	E	US	University of Pennsylvania	N / N	Y / N	N / N	N
Constantine Stratakis**	Paed/E/MG	GR	Foundation for Research & Technology Hellas (FORTH) / European University of Cyprus School of Medicine / NIH/NICHD	N / N	Y / N	N / N	Y
David Taieb	NM	GT	Aix-Marseille University	N / N	N / N	Y / Y	N
Amit Tirosh	E	IE	Sheba Medical Center	N / N	N / N	Y / Y	N
Francesco Tonelli	S	IT	University of Florence	Y / Y	N / N	Y / Y	N
Annemarie Verrijn Stuart	Paed E	NL	University Medical Center Utrecht	Y / N	Y / N	Y / N	Y
Menno Vriens	ES	NL	University Medical Center Utrecht	Y / Y	N / N	Y / Y	N
Jonathan Wasserman	Paed E	CA	The Hospital for Sick Children	Y / N	Y / N	Y / N	Y
Staffan Welin	IM	SE	Uppsala University	N / N	N / N	Y / Y	Y
John Wysolmerski	E	US	Yale School of Medicine	Y / N	N / N	N / N	N
Ye Lei	E	CN	Ruijin Hospital / Shanghai Jiao Tong University School of Medicine	Y / Y	Y / Y	Y / Y	N

Read and approved final draft but not part of the Delphi Panel

Delmar Muniz Lourenço Junior	E	BR	University of São Paulo School of Medicine (FMUSP); Endocrine Genetics Unit, Laboratory of Cellular and Molecular Endocrinology (LIM-25), Division of Endocrinology and Metabolism. Hospital das Clínicas, Division of Endocrinology and Metabolism, FMUSP. Institute of Cancer of the State of São Paulo (ICESP), Division of Endocrine Oncology, FMUSP.
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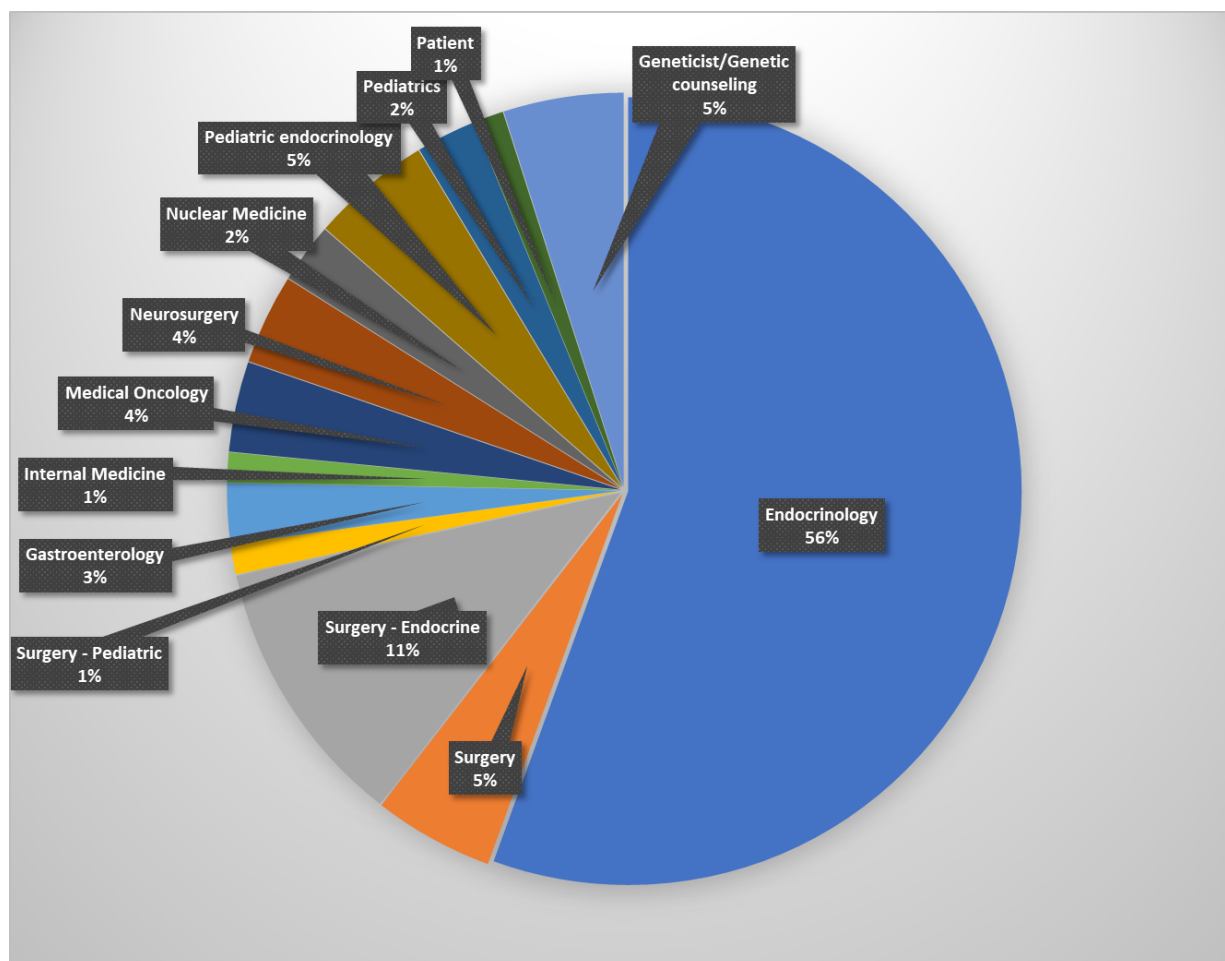
Marta Korbonits	E	GB	Barts and the London School of Medicine and Dentistry, Queen Mary University of London
Jes Sloth Mathiesen	S	DK	Odense University Hospital

Names in bold indicate the Delphi Core Group Leads. * Delphi Core Group Members ** members of the international Writing Committee

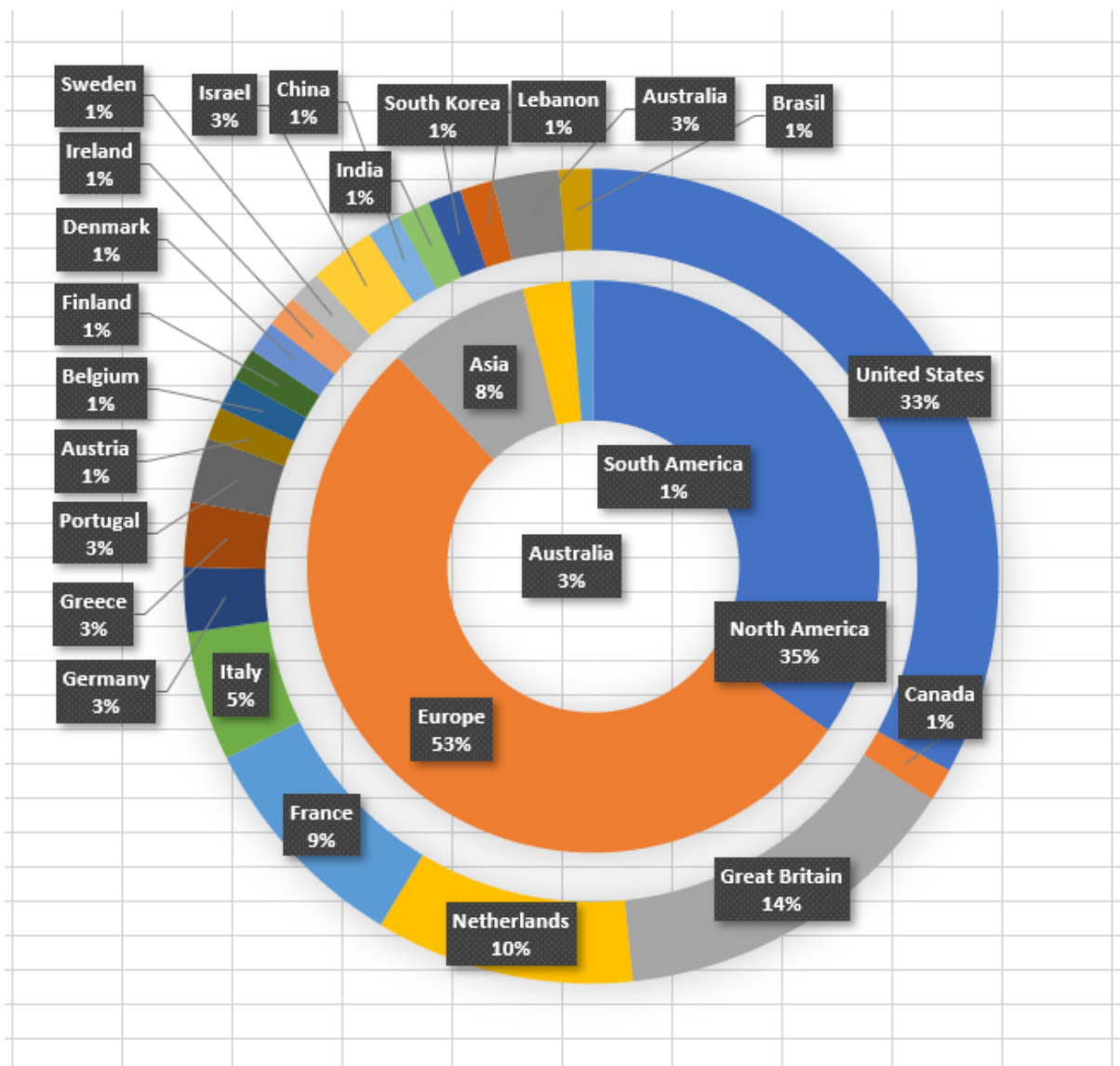
ES – endocrine surgery; E – endocrinology; F – attended Final meeting; G – genetics; GE – gastroenterology; IM – internal medicine; MG – medical genetics; MO – medical oncology; NET – neuroendocrine tumour Delphi; NM – nuclear medicine; NS – neurosurgery; N – no; P – part of the panel; Paed – paediatric meeting; Paed E – paediatric endocrinology; Para – parathyroid Delphi; PIT – pituitary Delphi; S – surgery and Y – yes.

Supplementary figure 2

Supplementary figure 2A: Composition of the expert panel by discipline



Supplementary figure 2B: Composition of the expert panel by Continent and Country



Appendix Delphi Consensus

Methods

A Delphi consensus was held, one for each of the main MEN1-related manifestations primary hyperparathyroidism, neuroendocrine tumours, and pituitary tumours. With the Delphi proceedings we aimed to address controversies that exist in screening and surveillance practices due to lack of guidance, as well as controversies in timing and extent of initial parathyroidectomy. Each Delphi consensus consisted of three rounds, two individual questionnaire rounds and a final digital meeting (See Supplementary figure 1, appendix p4).

In Q1 2023 and based on two recent review publications from the Delphi Core group leads^{2,3}, the Delphi Core Group (See Supplementary table 2, appendix pp5-7) prepared a concise literature overview regarding the Delphi Consensus topics. Based on the available literature, recommendations from the 2012 Clinical Practice Guidelines for MEN1⁴, and the expert opinion of the core group, the statements for the first round were developed. For the first round, we developed 15 parathyroid statements, 5 pituitary statements and 21 NET statements including sub-statements (See supplementary tables 4, 5 and 6, appendix pp28-35). These statements were subsequently built into Castor EDC⁵ as three questionnaires. The literature overview (See references at the end of this section appendix pp23-27) was included in the questionnaires as background. Experts could respond to each of the statements with *agree*, *disagree* or *unable to answer-not my expertise*, and a free text field was provided for comments. Consensus was defined as $\geq 80\%$ agreement. The *unable to answer/not my expertise* votes were not considered as part of the denominator.

The experts invited for the Delphi Consensus Expert Panel were selected based on their recognized clinical experience, academic excellence, and contributions to professional organizations dealing with specific endocrine tumours and/or MEN1 as well as to have global representation (Supplementary table 3, Supplementary figure 2, appendix pp8-13). Experts could be part of one or more of the three topic-specific Expert Panels: Parathyroid, Pituitary or NET. We set 10 as the minimum of experts for each panel. This is based on the fact that, if there are 10 experts and 8 of them agree (80% agreement), the chance of this occurring if there is disagreement among all the experts of the world is $<0.05^6$.

Results from Round 1 were compiled by the Delphi Core Group. Based on the free text comments and statements that did not reach consensus, follow-up statements were developed for Round 2, amounting to 7 parathyroid statements, 3 pituitary statements and 10 NET statements including sub-statements (See supplementary tables 4,5 and 6, appendix pp28-35). These statements were likewise built into Castor EDC⁵ and sent around as three questionnaires with similar answer options and comment boxes as in the Round 1.

The Delphi Core Group compiled results from Round 1 and Round 2 and developed the proposals for the final statements. Four final virtual meetings were organized with the Core Group and the Expert Panel to discuss and vote upon the final statements: Parathyroid, Pituitary, NET, and a separate Paediatric meeting to discuss statements pertaining to children/adolescents (<19 years). Initially, we did not plan a separate paediatric final meeting as the paediatric questions were part of the topic-specific questionnaires. However, after reviewing the results of the first two rounds, it was decided to discuss the final paediatric statements in a separate meeting attended by paediatric subspecialists and adult specialists with paediatric experience. In preparation for the final virtual meeting, all Expert Panel members were sent the outcome of the first two rounds together with the proposed final statements. Wording of the final statements reflects the level of consensus. We use “**recommend**” for statements that reached consensus in the first two rounds (agreement $\geq 80\%$), “**suggest**” for statements with near consensus (agreement 70-80%) and “**consider**” for statements where opinions among experts are more varied (agreement 51-70%). During the final meetings, all statements were discussed. For statements that had not yet reached consensus, the formulated suggestions and considerations were discussed, amended if necessary, voted upon (*agree*, *disagree*, *not my expertise*, or *abstain*), and incorporated if there was agreement of $\geq 80\%$ of the total *agree/disagree* votes. In the final meetings, 6 additional statements were formulated, that were not part of the first two rounds.

In Round 1, 142 questionnaires were distributed (50 parathyroid, 45 pituitary and 47 NET) to a total of 81 international experts, of whom 74 (91%) responded (See supplementary table 3, appendix pp8-11). Response rates for the individual questionnaires were 92% for parathyroid, 91% for pituitary, and 98% for NET. Supplementary figure 2, appendix pp12-13, details the composition of the expert panel. Outcomes of the first round can be seen in Supplementary tables 4, 5 and 6, appendix pp28-35 for parathyroid, NET, and pituitary, respectively. Questionnaires for Round 2 were sent

to the 74 experts who contributed to Round 1, of whom 70 responded, leading to a 95% response rate for Round 2. Response rates for the individual questionnaires of round 2 were 96% for parathyroid, 98% for pituitary, and 98% for NET. Overall, 86% of the invited experts completed both rounds. Outcomes of Round 2 can likewise be seen in Supplementary tables 4, 5 and 6, appendix pp28-35. The final virtual meetings were attended by 31, 28, 32, and 16 experts for the parathyroid, pituitary, NET, and paediatric meetings, respectively. Experts could take part in multiple meetings. Overall, 78% of the Expert Panel members who answered Round 1 were present at one or more of the final virtual meetings.

General Statements

Statement #1. The statements in these Delphi proceedings pertain to patients with genetically confirmed MEN1 or those who are obligate carriers.

Statements are not intended for patients with a clinical MEN1 diagnosis with negative genetic testing or in whom a diagnosis of MEN1 is uncertain.

Statement #2. In accordance with the WHO definition, children and adolescents are defined as people age <19 years.

Statement #3. Recommendation. Patients with MEN1 should be treated in centres of expertise with high-volume, experienced multidisciplinary teams.

Due to the complexity and rarity of the disorder, patients with MEN1 should be followed by expert multidisciplinary teams that collaborate nationally and internationally for optimization of clinical care and research.

Statement #4. Recommendation. Parents with MEN1 should have an initial consultation (with or without the child present) with a paediatric endocrinologist when the child is around the age of five years. Symptoms of MEN1 clinical manifestations should be discussed and shared decision-making undertaken regarding screening and surveillance plans.

Meeting with a paediatric endocrinologist when the child is around the age of five years allows parental education about signs and symptoms of paediatric MEN1 (with specific emphasis on symptoms of hypoglycaemias and deviation from normal patterns of growth and puberty) and facilitates timely detection of those very rare, early symptomatic manifestations. Additionally, there can be a shared discussion about current screening and surveillance recommendations and how to apply these to the individual child and family.

Parathyroid

Screening

Statement #5. Recommendation. Adults with MEN1 should be screened for primary hyperparathyroidism with yearly serum calcium measurements.

Statement #6. Recommendation. Children and adolescents with MEN1 should be screened for primary hyperparathyroidism with serum calcium measurements at 1–3-year intervals.

Statement #7. Consideration. In asymptomatic children, there is no consensus regarding the age at which to initiate screening. Screening starting at the age of 10 can be considered.

In recommending serum calcium as a screening test for PHPT, the expert panel considered that screening should pick up clinically relevant disease, not necessarily detect the earliest onset of disease, and that cumulative costs and ease of measurement should be taken into consideration in a lifelong screening program.

To allow for personal preference and local capabilities, it is not specified whether to measure ionized calcium or albumin-corrected total calcium. In the setting of screening, the expert panel deemed the measurement of intact parathyroid hormone (iPTH) unnecessary because, in asymptomatic patients with a normal calcium level, iPTH would not alter management.

For the paediatric population, arguments that factored into the recommendation of a screening interval of 1-3 years were: (1) the goal of screening is to detect disease that needs intervention, (2) the importance of longitudinal measurements to adequately judge progression, and (3) that the burden of blood testing is not trivial and can be a

traumatic event in children. The precise interval can be individualized by the clinician with parent/guardian input, considering the current calcium level and other factors relevant to the individual patient.

Although there was consensus that age 15 years was too late, there was no consensus at which age to initiate screening (Supplementary table 4, appendix pp28-30 R1.2). In published cohorts of paediatric MEN1, a diagnosis of PHPT before the age of 10 occurred in <10%, is rarely symptomatic, and only exceptionally was parathyroid surgery performed before the age of 10⁷⁻¹¹. The expert panel felt that a general screening recommendation should not aim to capture rare outliers at the expense of unnecessary screening for most children. However, some experts advocated for an earlier start to capture those outliers as well.

Assessment of target organ involvement

Statement #8. Recommendation. To assess renal and skeletal involvement in adults with MEN1 and newly diagnosed PHPT according to the Guidelines from the Fifth International Workshop on Primary Hyperparathyroidism.

There is a paucity of evidence regarding assessment and monitoring of target organ involvement in MEN1-related PHPT. Therefore, the experts panel refers to the guidelines from the Fifth International Workshop on Primary Hyperparathyroidism¹² to assess target organ involvement at the time of PHPT diagnosis in patients with MEN1. However, patients with MEN1 are on average 2 decades younger at the time of PHPT diagnosis than patients with sporadic PHPT and have an equal gender distribution^{13,14}. Moreover, many patients with MEN1 are now prospectively screened from an early age, allowing actual observation of the onset of the PHPT. In these young, prospectively screened patients, assessment of renal and skeletal involvement constitutes more of a baseline measurement than a test to inform/dictate management decisions. In this setting, the timing of the initial assessment of target organ involvement can be left to the managing clinician, to prevent over-screening for which no evidence exists. This particularly applies to bone mineral density (BMD) assessment with dual-energy X-ray absorptiometry (DXA) in young adults.

Statement #9. Recommendation. In children/adolescents with MEN1 and newly diagnosed PHPT, renal function (creatinine- or cystatin C-based eGFR) should be assessed.

Statement #10. Recommendation. In asymptomatic children/adolescents with PHPT, routine DXA assessment is not recommended. For those children undergoing BMD assessment, DXA needs to be interpreted in the context of age and height.

Although renal dysfunction is a late sign and almost never seen in paediatric patients with MEN1, the expert panel considered that renal dysfunction should not be missed, and determining the eGFR is easily combined with other blood tests in hypercalcaemic children. If renal involvement is seen in children and adolescents, it is usually nephrolithiasis. However, there are no data that routine renal ultrasound adds to the management of paediatric patients with MEN1-related PHPT and preventing an unnecessary surveillance burden in this population is essential. Similarly, there are no data that routine DXA adds to the management of paediatric MEN1 patients, in whom the use of cortical bone BMD is not recommended (<https://iscd.org/learn/official-positions/pediatric-positions/>) . Furthermore, DXA results in children and adolescents may be misinterpreted by not considering age, height and pubertal status when interpreting Z-scores (T-scores should not be used).

Statement #11. Recommendation. To monitor target organ involvement in adults with MEN1 with PHPT if surgery is deferred according to the Guidelines from the Fifth International Workshop on Primary Hyperparathyroidism.

In patients with MEN1-related PHPT in whom it is decided to not yet perform a parathyroidectomy, monitoring of renal and skeletal involvement is important. However, evidence for any particular monitoring scheme in MEN1-related PHPT is lacking. Therefore, the expert panel refers to recommendation from sporadic PHPT guidelines. Regarding renal involvement, these guidelines recommend performing yearly creatinine clearance (preferred over eGFR) and abdominal imaging or 24-h urine only if clinically needed. For skeletal involvement three-site DXA is recommended every 1-2 years unless BMD is normal. As patients with MEN1 are often much younger than patients with sporadic

PHPT, the frequency of DXA monitoring should be decreased in younger adults with MEN1 to prevent multiple investigations for which no evidence exists, and which are often without clinical consequences.

Timing of index operation

Statement #12. Recommendation. In asymptomatic children, adolescents, and adults with MEN1, without evidence of target organ involvement, in whom the onset of PHPT is observed, initial active surveillance is acceptable.

Statement #13. Recommendation. Parathyroidectomy is indicated in children, adolescents and adults diagnosed with MEN1-related PHPT who are symptomatic or have evidence of target organ involvement.

Statement #14. Recommendation. Irrespective of symptoms, parathyroidectomy is indicated in adults diagnosed with MEN1-related PHPT, in whom total calcium levels are consistently >1 mg/dl (0.25 mmol/L) above the upper limit of the reference range of the specific assay used.

Statement #15. Suggestion. We suggest parathyroidectomy in children and adolescents diagnosed with MEN1-related PHPT, in whom total calcium levels are consistently >1 mg/dl (0.25 mmol/L) above the upper limit of the reference range of the specific assay used.

In patients diagnosed by predictive genetic testing who are subsequently prospectively screened, PHPT can often be observed from the outset. With statement PHPT.6, the expert panel conveyed the message that it is not necessary to operate immediately at the initial diagnosis of PHPT in these patients. Ideally, the timing of the initial operation is planned after shared decision-making with the patient, parents/guardians if applicable, the (paediatric) endocrinologist, and the surgeon, taking into account calcium levels, symptoms and well-being, the presence of target organ involvement (which has ideally been prevented), and the patient's personal circumstances, including access to a high-volume parathyroid surgeon. Parathyroidectomy is usually indicated if total calcium levels consistently exceed 1 mg/dl (0.25 mmol/L) above the upper limit of the reference range of the specific assay used or if there are symptoms of PHPT and/or evidence of target organ involvement. This does not suggest delaying surgery until there is target organ involvement or a severely elevated calcium level is present, but rather preventing. The evidence base, however, for a causal relation between PHPT and elevated gastrin (biochemical effect) or G-cell hyperplasia (cell proliferation effect) in patients with MEN1 is tenuous^{15,16}. Nevertheless, the expert panel felt that the presence of a symptomatic gastrinoma may constitute a relative indication for parathyroidectomy. these complications by individualized timing of the initial parathyroidectomy.

Statement #16. Recommendation. *In patients with MEN1, the presence of a symptomatic gastrinoma should be taken into account when considering the timing of parathyroidectomy.*

It has been hypothesized that, given the presence of the calcium-sensing receptor on G-cells, the hypercalcemia of PHPT may contribute to G-cell hyperplasia in patients with MEN1, with the increased proliferation increasing the chances of the second hit in the G-cells, leading to neoplasia¹⁵.

Type of index operation

Statement #17. Recommendation. In children, adolescents, and adults with MEN1-related PHPT, subtotal (3 to 3½ gland) parathyroidectomy with concomitant transcervical thymectomy is the recommended index operation, which should be performed by an experienced MEN1 parathyroid surgeon.

Statement #18. Suggestion. In selected cases, unilateral clearance can be considered as the index operation for children or adolescents with MEN1-related PHPT.

There are considerations beyond those of the initial operation when managing patients with MEN1-related PHPT, which is, by definition, a multigland disease, although glands may be affected asymmetrically. After initial subtotal parathyroidectomy, the 10-year recurrence rate is 72% (95% CI 64-79)¹⁶. Hence, most patients will experience recurrence and consequently require additional surgical intervention at some point during their lives, and operations after the index procedure inevitably have a higher risk of complications. The goal of management is to maintain a (near) normal calcium level for as long as possible with as few operations as possible, preventing or limiting target organ involvement while avoiding permanent post-operative hypoparathyroidism. The initial operation also needs to facilitate safe reoperation. In the hands of an MEN1-experienced, high-volume parathyroid surgeon, a subtotal

parathyroidectomy with concomitant transcervical thymectomy (TCT) is the recommended initial operation to achieve these goals. This means a bilateral cervical exploration with visualization of all four parathyroid glands, where three glands and/or a portion of the fourth gland are removed, leaving a tagged and viable remnant. The rationale behind a transcervical thymectomy is to remove any ectopic glands located in the thymus, as around one fifth of patients have intra-thymic parathyroid glands¹⁶⁻¹⁸. In theory, reducing the amount of thymic tissue may also decrease the risk for thymic NET development. However, a complete removal of the thymus is usually not achievable transcervically and a thymic NET can still occur after TCT¹⁹.

Recently, a unilateral clearance (unilateral exploration removing both parathyroids and the cervical thymus in only one side of the neck) has been considered as the initial operation in children, adolescents and young adults when disease is grossly limited to one side of the neck²⁰⁻²². The argument in favour of this approach is the avoidance of postoperative hypoparathyroidism during an important stage of life and with the understanding that the inevitable reoperation will be performed in an unoperated side of the neck. This, however, comes at the expense of a higher rate of persistent disease and a shorter time to recurrence^{16,21,23}. Unilateral clearance additionally limits the options for creating a viable remnant during subsequent operations, which may impact the long-term risk of hypoparathyroidism²³. Therefore, in general, a subtotal parathyroidectomy should be considered the standard-of-care initial operation in patients with MEN1. In children and adolescents with an indication for surgery who have gross unilateral disease, unilateral clearance can be considered in selected cases as the risks may be weighed differently compared with adults, especially in pre-pubertal children. In adults and paediatric patients alike, the final decision is always a well-informed shared decision between the patient, parents/guardians as applicable, and the medical team.

Statement #19. There is no consensus on the need nor type of pre-operative imaging studies for parathyroid localization before the index operation in adults.

Most centres use ultrasound to rule out concomitant disease and to inform about benign lymphadenopathy.

Statement #20. Suggestion. The need and type of pre-operative imaging for parathyroid localization before the index operation in children and adolescents are determined on a case-by-case basis.

The expert panel considered that pre-operative imaging is not needed to determine the type of operation in standard-of-care initial subtotal parathyroidectomy in patients with MEN1. However, there may be other indications for pre-operative imaging studies as determined by the individual surgeon. In children and adolescents, when a unilateral clearance is considered, pre-operative imaging is essential.

Neuroendocrine tumours

Duodenopancreatic NETs

Screening

Statement #21. Recommendation. To screen asymptomatic patients with MEN1 with magnetic resonance imaging (MRI) for the presence of a pancreatic NET.

In recommending MRI as the preferred modality to screen for pancreatic (Pan)NETs, the expert panel considered that screening should detect clinically relevant PanNETs and placed high value on the lack of ionizing radiation exposure and non-invasive nature of MRI. MRI also shows a higher diagnostic accuracy compared with computed tomography (CT)²⁴⁻²⁶, with diffusion-weighted imaging and fat-suppressed T2-weighted sequences being the most sensitive²⁴. Reported sensitivities for MRI range from 65 to 88%^{25,26}. Endoscopic ultrasound (EUS) has a higher diagnostic accuracy for smaller PanNETs^{26,27}. However, it is invasive, operator dependent, performs less homogeneous throughout the pancreas and may identify additional small non-functioning (NF)-PanNETs that often have no clinical consequences and thus do not change management. Somatostatin receptor (SSTR) positron emission tomography (PET)/CT is not recommended as a regular screening tool due to the associated radiation exposure and the fact that an SSTR-PET/CT positive lesion not visible on MRI would rarely be clinically significant²⁸. Some experts suggested that, rather than as routine screening, SSTR-PET/CT could be employed in a single instance as baseline screening because preliminary data show that, based on a negative baseline SSTR-PET/CT, a longer interval to subsequent

screening might be possible^{28,29}. However, most experts felt that more evidence would be needed before such an approach could be broadly advocated.

Statement #22. Recommendation. To perform the first MRI in asymptomatic children between ages 10-15 years, the exact age to be at the discretion of the clinician and with shared decision making.

Initiation of pancreatic imaging in childhood/adolescence already reached consensus in Round 1 (Supplementary table 5, appendix pp31-33). Experts were divided, however, whether the starting age should be 10 or 15 years. In the final paediatric meeting concerns of over-screening were expressed, given that a clinically relevant NF-PanNET before the age of 15 is very rare, and insulinomas (the most frequently occurring functional PanNET in childhood/adolescence) are almost always symptomatic². Therefore, imaging screening in childhood/adolescence mainly serves to detect NF-PanNETs. Clinically relevant (size >2 cm or rapid growth) NF-PanNETs are estimated to occur in 2.5% by age 13.5 and in 5% by age 17.8 years³⁰.

Statement #23. Recommendation. Children, adolescents, and adults with MEN1 should be screened for insulinoma by careful assessment for hypoglycaemic symptoms. For symptomatic patients we recommend further biochemical evaluation as per established guidelines.

Careful assessment of symptoms and education of patients and family members is the most important screening tool for insulinoma in patients with MEN1. Parental/guardian education is particularly important because insulinomas are the most common functional PanNET before the age of 19 years and can, although rarely, occur at a very young age². Although in the first round near consensus existed for screening asymptomatic patients with fasting glucose, in the final meeting this was not endorsed and screening by symptoms only was recommended, with a low threshold for further evaluation. The main reason to no longer recommend screening with fasting glucose in all patients was the fact that a random normal fasting glucose does not rule out hyperinsulinism³¹ and thus may provide a false sense of security and less attention to carefully assessing signs and symptoms. Conversely, slightly low fasting glucose levels (i.e. 55-68 mg/dL [3.0-3.8 mmol/L]) in patients without signs and symptoms may trigger unnecessary investigations.

Statement #24. Recommendation. In asymptomatic adults with MEN1, we recommend screening for gastrinoma with fasting serum gastrin.

Statement #25. There is no consensus on screening asymptomatic children with fasting serum gastrin for the presence of a gastrinoma.

Fasting serum gastrin (FSG) is the main modality to screen for gastrinoma in adults with MEN1 and facilitates early gastrinoma detection. However, it is important to realize that, even in patients with MEN1, there may be other common causes of mildly elevated FSG, such as the use of potent gastric acid anti-secretory agents, most commonly proton pump inhibitors, *Helicobacter pylori* infection and atrophic gastritis, all of which are associated with achlorhydria/hypochlorhydria in contrast to the hyperchlorhydria seen with gastrinoma. In the particular setting of MEN1, hypercalcemia may also contribute to elevation of FSG; however, the scientific evidence is ambiguous^{32,33}, see also PHPT.10.

Statement #26. Recommendation. In asymptomatic patients with negative abdominal imaging, additional biochemical screening for the presence of a pancreatic neuroendocrine tumour is generally not useful.

The expert panel felt that, in the setting of a negative screening MRI and the absence of signs and symptoms indicative of a functional pancreatic NET, additional blood tests beyond gastrin would not be useful in the screening for a pancreatic NET. This is based on the evidence that chromogranin A, pancreatic polypeptide, and glucagon have a low diagnostic accuracy for the detection of PanNETs²⁶. Additionally, with a negative screening MRI and the absence of signs and symptoms, blood tests to screen for functioning NETs such as glucagonoma or a vasoactive intestinal peptide-producing tumour have no added value.

Statement #27. Recommendation. To perform pancreatic imaging every 2-3 years in adults with MEN1 who have a negative baseline MRI, normal serum gastrin and no signs or symptoms of a (functioning) duodenopancreatic neuroendocrine tumour.

The expert panel recognizes that there are no studies directly investigating the optimal screening frequency after a negative baseline MRI. The recommendation of the expert panel is based on the demonstrated slow growth (average

growth rates 0.1-1.32 mm/year²⁶) and indolent behaviour of most MEN1-related small NF-PanNETs²⁶, as well as cohort studies showing that initial observation of NF-PanNETs <2 cm is safe^{34,35}.

Surveillance

Statement #28. Recommendation. In patients with MEN1 and stable NF PanNETs <2 cm with growth rates <1 mm/year (for more than 1 year) on active surveillance, we recommend performing imaging every 1-2 years, taking into account tumour size.

With this statement the expert panel aims to individualize the follow-up of NF-PanNETs <2 cm based on observed growth rate and absolute size, and to enable extended surveillance intervals up to 2 years when size and growth rate allow. The recommendation is based on the observed indolent growth rate of NF-PanNETs <2 cm in 10 observational studies (7 combined in a systematic review)^{26,36-40} and a low incidence of new lesions^{26,40,41}. Additionally, the risk of metastatic disease is low, although not absent, in NF-PanNETs <2cm⁴². To enable this approach, it is important to first observe the PanNET behaviour. In newly diagnosed NF-PanNETs <2cm, imaging should be repeated after 6-12 months and, if stable, again after 12 months. If the tumour remains stable with a growth rate <1mm/year, the surveillance interval can be lengthened. Within the expert panel there was consensus that the interval should not be increased beyond two years, with only 8% of experts (See supplementary table 5, appendix pp31-33 R2.5) in favour of a 3-yr interval. The panel recognizes that the stated definition of “stable” is expert opinion based on knowledge of PanNET behaviour in patients with MEN1.

Statement #29. Recommendation. To perform SSTR-PET/CT or SSTR-PET/MRI in all patients with MEN1 planned for duodenopancreatic surgery.

Statement #30. Suggestion. SSTR-PET imaging can play a role in the surveillance of patients with MEN1 and gastrinoma or PanNET when the results would affect management.

Because of the superior sensitivity of SSTR-PET imaging^{28,43-46}, especially for detection of loco-regional lymph node metastases, the expert panel unanimously recommends that all patients with MEN1 undergo SSTR-PET staging before planned surgery as this may alter the surgical strategy. This recommendation is also in line with the role of SSTR-PET in the initial staging of sporadic functioning and NF-PanNETs⁴⁷⁻⁵². Although its routine use cannot be recommended, SSTR-PET imaging is suggested in specific scenarios during duodenopancreatic NET surveillance when it may alter management. One area where SSTR-PET may become particularly valuable is the diagnosis and staging of (suspected) gastrinoma, as evidenced from a small retrospective study⁴³.

Statement #31. Suggestion. EUS can play a role in the surveillance of patients with MEN1 and gastrinoma or PanNET when the results would affect management.

Statement #32. Recommendation. Routine EUS-guided biopsy is not recommended.

The expert panel felt that EUS should be reserved for specific situations where the results obtained from EUS would affect management. Like SSTR-PET imaging, it can be very valuable in the diagnosis and surveillance of gastrinoma. Other scenarios in which EUS might affect management include the pre-operative planning of certain cases, the assessment of atypical lesions or those with unexpectedly high growth rates, and the evaluation of suspected functional PanNETs with negative cross-sectional imaging. In line with a recent international consensus statement, the expert panel emphasizes that routine biopsy of MEN1-related pancreatic NETs is not necessary⁵³.

Statement #33. Recommendation. Patients with symptoms suggestive of Zollinger-Ellison Syndrome (ZES) should undergo esophagogastroduodenoscopy (EGD).

Statement #34. Suggestion. To perform an EGD in patients with MEN1 who have consistently elevated fasting serum gastrin levels to look for signs of ZES and gastro-duodenal NETs.

Patients with normal FSG levels without symptoms suggestive of ZES do not need to undergo esophagogastroduodenoscopy (EGD). In patients with symptoms and/or consistently elevated FSG, EGD may be combined with EUS.

Thoracic NETs

Screening

Statement #35. Recommendation. To screen asymptomatic adults with MEN1 with CT for the presence of a thoracic NET.

Although there was consensus (82%) in Round 1 among the expert panel that CT is the most appropriate modality to screen for thoracic (lung and thymic) NETs (R1.1-R.1.4, Supplementary table 5, appendix pp31-33), no consensus was reached on whether this should be low-dose or contrast-enhanced CT. Given the lifelong follow-up in patients with MEN1, contrast and ionizing radiation exposure is not trivial, and this should be considered. SSSTR-PET/CT has limited utility in detecting small primary lung NETs⁵⁴.

Statement #36. Recommendation. To initiate thoracic imaging screening between ages 20-25 years in asymptomatic patients with MEN1.

Given that there are only anecdotal reports of thoracic NETs in patients with MEN1 below the age of 20², the expert panel felt screening in adolescence could not be justified. Therefore, the recommendation to initiate screening at the age of 15 years from the previous guidelines⁴ has been updated to initiate screening in the age range 20-25 years.

Statement #37. Suggestion. To perform thoracic imaging every 3-5 years in adults with MEN1 who have negative baseline imaging and no signs or symptoms of a thoracic neuroendocrine tumour.

The expert panel recognises that there are no studies directly investigating the optimal screening interval in the case of negative baseline imaging. No consensus was reached on this statement in the first two rounds, where the majority (77%) of the panel was in favour of extending the screening interval beyond 2 years (R1.6 Supplementary table 5, appendix pp31-33), although experts were divided between recommending 3 years (56%) or 5 years (48%). Concerns expressed with a 5-year interval were potentially missing a thymic NET or a rare aggressive lung NET. The final suggestion is based on the demonstrated slow growth and indolent behaviour of most MEN1-related small lung NETs^{55,56}, the rarity of thymic NETs among patients with MEN1, and considering the potential harm of more frequent CT-scanning over the lifespan.

Surveillance

Statement #38. Suggestion. Active surveillance is an acceptable management strategy for small (<1-2 cm) lung NETs in patients with MEN1.

This is based on the demonstrated indolent behaviour of small MEN1-related lung NETs⁵⁵ and excellent long-term outcomes and is in line with the most recent European Society of Medical Oncology clinical practice guidelines for lung and thymic NETs⁵⁷.

Statement #39. Recommendation. To perform imaging every 1-2 years taking into account tumour size in patients with MEN1 and stable (growth <1 mm/year over >1 year) small (<1-2 cm) lung NETs on active surveillance.

With this statement the expert panel aims to individualize the follow-up of small lung NETs based on observed growth rate and absolute size and enable surveillance intervals to be extended up to 2 years when size and growth allow. To enable this approach, it is important to first observe the behaviour of the lung NET. In newly diagnosed lung NETs <2cm, imaging should therefore initially be repeated after 6-12 months and when stable again after 12 months. If the tumour remains stable subsequent increases in the surveillance interval can be made. The recommendation is based on the observed indolent growth rate of small pulmonary NETs under surveillance^{55,58-60} and on the low risk of metastatic disease. The panel recognizes that the stated definition of “stable” is expert opinion based on knowledge of lung NET behaviour in patients with MEN1.

Pituitary

Screening in adults

Statement #40. To screen asymptomatic adults with MEN1 with MRI for the presence of a pituitary adenoma.

Statement #41. Recommendation. In adults with no mass detected by MRI at baseline, persistent absence of features of hypo- or hyperpituitarism and normal hormonal testing, we recommend performing an MRI of the pituitary every 3-5 years.

Patients with MEN1 should be screened for the presence of a pituitary adenoma by careful assessment of signs and symptoms, as well as biochemical screening for hypersecreting adenomas. Additionally, the expert panel recommends screening with pituitary MRI, especially for timely detection of clinically relevant NF pituitary adenomas. Only in rare situations when MRI is not available should pituitary CT be considered. Regarding the screening interval in asymptomatic patients, nearly all (97%) experts recommend either a three- or five-year interval, with the proportion of experts considering three or five being nearly equal (R2.2 Supplementary table 6, appendix pp34-35). During the final round the panel felt that, given the slow progression of pituitary adenomas while under surveillance⁶¹⁻⁶³ and the ability to detect functioning lesions with history, physical examination and biochemical screening, a five-year interval would suffice for most patients. More frequent screening may be considered for some, and age also factors into this decision. The final recommendation provides for a screening interval of 3-5 years, consistent with the opinions of the expert panel and the 2012 (3 years)⁴ and 2001 (5 years)⁶⁴ MEN1 clinical practice guidelines.

Statement #42. Recommendation. In asymptomatic patients with no pituitary adenoma history, who have negative pituitary imaging and normal hormone testing, imaging screening can be stopped at the age of 75 years while continuing clinical and biochemical screening.

This recommendation pertains to patients who are prospectively screened and reach the age of 75. The expert panel recognises that there are no data available on the incidence of pituitary adenomas in prospectively screened patients with MEN1 over the age of 70 years. Considering (1) that the collective experience of the panel indicates this situation is rarely encountered and (2) most clinically relevant adenomas will be detected by the continued clinical and biochemical evaluations, the expert panel felt it safe to recommend stopping routine MRI screening and replacing this by performing imaging on indication only from age 75 onwards.

Screening in children

Statement #43. Recommendation. Physical examination in children with MEN1 should include the evaluation of growth and pubertal development.

In children with MEN1, pituitary adenomas can lead to alterations in linear growth, weight, and pubertal development. When present this will most often reflect relative deceleration and delayed or halted puberty associated with prolactinoma. Weight gain and a decline in growth velocity would be expected in most patients with Cushing disease. The rare patients who have a growth hormone-producing adenoma in childhood leading to gigantism present with accelerated growth. Therefore, routine auxologic evaluation of the child with MEN1 is an important aspect of screening for pituitary adenomas in children.

Statement #44. Suggestion. To screen asymptomatic children with MEN1 with normal growth and development for pituitary tumours using prolactin (PRL) and Insulin-like Growth Factor 1 (IGF-1).

Statement #45. Consideration. There is no consensus regarding the age to initiate biochemical screening. Initiating biochemical screening from the age of 10 years can be considered.

Among the expert panel there was near consensus (76% agree) that biochemical screening is indeed indicated in asymptomatic children/adolescents with MEN1 who have normal growth and development (R2.1, Supplementary table 6, appendix pp34-35). Considerations leading to this consensus include: 1) the fact that laboratory tests are already advised in children with MEN1 to screen for PHPT (see statement PHPT.2) and therefore there is no additional patient burden from checking PRL and IGF-1 at the same time, 2) prolactinomas are the most common functioning adenoma in children with MEN1² and are easily diagnosed through biochemical testing, 3) growth hormone-producing adenomas are very rare, but missing them has important consequences, and 4) early signs and symptoms may be subtle, and depending solely on disturbances in growth/puberty may lead to a delayed diagnosis and an adenoma that may be more challenging to treat.

Although there was consensus that screening should start before puberty, there was no consensus at which age to initiate this screening (R2.1, Supplementary table 6, appendix pp34-35). In published cohorts of paediatric MEN1, a diagnosis of a pituitary adenoma before the age of 10 occurred in <5% and no interventions were needed before age 10^{7,9,10,65}. There are published reports of exceptional cases with functioning adenomas and/or macro-adenomas requiring treatment before the age of 10^{66,67}, but the expert panel felt that a general screening recommendation should not aim to capture these rare outliers at the expense of unnecessary screening for the majority of children. However, some experts advocated for an earlier start to capture those outliers as well.

Statement #46. There is no consensus on the benefit of MRI screening in asymptomatic children with normal growth and development for the presence of a pituitary adenoma.

Statement #47. Suggestion. To perform the initial MRI from the age of 15 years if, in shared decision making, it is decided to screen asymptomatic children with normal growth and development with pituitary MRI.

There is no consensus that, in addition to history, physical examination (including growth and pubertal status) and biochemical screening, screening with pituitary MRI is of benefit in children with MEN1. Most NF pituitary adenomas described in children with MEN1 are micro-adenomas that do not require intervention, and only rarely are NF macro-adenomas diagnosed that require surgery. Considering that screening should ideally be used to identify clinically relevant disease, not necessarily disease at its earliest stage, concern was expressed by paediatric experts that MRI screening in otherwise asymptomatic children with normal growth and hormone testing would only serve to detect clinically irrelevant micro-adenomas, leading to a higher patient burden without a clear benefit.

With statement PIT.8 the expert panel aims to stress that, if it is decided to perform a pituitary MRI for screening of NF tumours in asymptomatic children, this should not be performed in young children who require sedation.

Management

Statement #48. Recommendation. When a pituitary tumour is diagnosed in a patient with MEN1, we recommend management according to sporadic pituitary tumour guidelines.

Recent data do not support the premise that MEN1-related pituitary tumours are more aggressive and warrant different management⁶¹⁻⁶³. Although this evidence is derived from non-comparative observational studies, these independent cohorts all have similar results. Therefore, once a pituitary adenoma is diagnosed, the expert panel recommends management following regular tumour-specific guidelines.

When to consider MEN1 genetic testing in patients with apparently sporadic MEN1-related tumours?

The Delphi core group and expert panel aimed to provide guidance regarding genetic testing for MEN1 in patients with apparently sporadic PHPT, PanNET or pituitary tumours, specifically for those patients without evidence of other MEN1-related tumours and a non-contributory family history.

Parathyroid

Statement #49. Suggestion. Offer genetic testing, including MEN1, to patients with apparently sporadic PHPT <30 years of age and/or patients with multi-gland disease.

This suggestion aligns with recommendations from the ACMG¹, the Fifth International Workshop on Primary Hyperparathyroidism¹² as well as the previous MEN1-guidelines⁴.

Pancreas

Statement #50. Consideration. In patients aged <40 years diagnosed with an apparently sporadic solitary PanNET, genetic testing for MEN1 can be considered.

There was no consensus among the expert panel on the topic of genetic testing in apparently sporadic PanNETs (Supplementary table 5, appendix pp31-33 R1.12, R2.6, R2.7 and R1.13, R2.8). In the final meeting, agreement was reached that MEN1 genetic testing can be considered in patients <40y with an apparently sporadic PanNET. This was mostly based on an externally validated prediction model from de Laat *et al.* that showed a 5% risk of MEN1 in

patients aged 40y with a PanNET⁶⁸, a threshold in line with genetic testing recommendations for other conditions such as breast cancer.

Pituitary

Statement #50. Consideration. MEN1 genetic testing can be considered in adults below 30 years of age with an apparently sporadic, functioning pituitary adenoma (except for a micro-prolactinoma in women) or a non-functioning pituitary adenoma larger than 1cm.

Statement #51. Consideration. Genetic testing, including MEN1, should be considered in children/adolescents (<19 years) with an apparently sporadic pituitary adenoma.

Considering the relatively high prevalence of pituitary adenomas in the general population, especially micro-prolactinomas in young females, and the very rare occurrence of *MEN1* germline mutations in this group, the expert panel emphasizes that, in most cases, there is no indication to pursue *MEN1* genetic testing in patients without other associated tumours or a suspicious family history. In young adults (19-30y) finding an *MEN1* germline mutation is less rare in macro-adenomas, particularly prolactinomas⁶⁹. Therefore, *MEN1* genetic testing can be considered in young adults with non-functioning macroadenomas, macro-prolactinomas and other hypersecreting pituitary adenomas. Additionally, testing of other relevant genes may be considered. In patients <19 years, the yield is higher and a diagnosis of a pituitary adenoma in this population should at least trigger referral for genetic testing, including *MEN1*, especially in young patients with somatotroph adenomas. This is also consistent with the recommendations in the recently published consensus guidelines for the diagnosis and management of pituitary adenomas in childhood and adolescence⁷⁰.

As part of the discussion, some experts favoured using serum calcium as a steppingstone to genetic assessment, i.e., monitoring calcium levels to identify patients with MEN1, who are likely to develop PHPT at a young age. On the other hand, other experts were not in favour of this approach, stating that serum calcium may not be elevated for years after a pituitary adenoma diagnosis in MEN1, leading to a lack of clarity as to when to stop calcium screening, a question that would be more directly answered via genetic testing.

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Supplementary table 4. Outcomes of the Parathyroid Delphi Round 1 and Round 2			
Parathyroid - Outcomes of the first two rounds Round 1 (R1) n=46 Round 2 (R2) n=44	Agree	Disagree	Unable to answer/ not my expertise (n)
Screening			

R1.1 In the absence of signs/symptoms of PHPT, assessment of plasma calcium in patients with MEN1 should be performed annually	91%	9%	1
If disagree, [...] should be performed every 5 years	25%		
If disagree, [...] should be performed every 3 years	25%		
If disagree, [...] should be performed every 2 years	50%		
R1.2 Asymptomatic children with MEN1 should undergo biochemical screening for PHPT	98%	2%	2
If agree, biochemical evaluation for PHPT in asymptomatic children with MEN1 should start at age 5	43%		3
If disagree, biochemical evaluation for PHPT in asymptomatic children with MEN1 should start at age 10	45%		
If disagree, biochemical evaluation for PHPT in asymptomatic children with MEN1 should start at age 15	13%		
Assessment of target organ involvement			
R1.3 In patients with MEN1 and asymptomatic PHPT, biochemical assessment of renal involvement should include measurement of creatinine clearance or estimated glomerular filtration rate (eGFR) and 24-hour urinary calcium excretion	93%	7%	2
If agree, in patients with MEN1 and asymptomatic PHPT this should be performed every year	73%		
If disagree, in patients with MEN1 and asymptomatic PHPT this should be performed every 2 years	22%		
If disagree, in patients with MEN1 and asymptomatic PHPT this should be performed every 3 years	5%		
R1.4 In patients with MEN1 and asymptomatic PHPT, assessment of renal involvement should include abdominal imaging to detect nephrocalcinosis or nephrolithiasis	77%	23%	2
If agree, in patients with MEN1 and asymptomatic PHPT this should be performed every year	45%		1
If disagree, in patients with MEN1 and asymptomatic PHPT this should be performed every 2 years	27%		
If disagree, in patients with MEN1 and asymptomatic PHPT this should be performed every 3 years	24%		
If disagree, in patients with MEN1 and asymptomatic PHPT this should be performed every 5 years	0%		
Disagree to all	3%		
R1.5 In adults with MEN1 and asymptomatic PHPT, assessment of skeletal involvement should include measurement of bone mineral density (BMD) at the lumbar spine, hip and distal radius using dual-energy X-ray absorptiometry (DXA)	100%	0%	5
If agree, In adults with MEN1 and asymptomatic PHPT this should be performed every year	33%		1
if disagree, in adults with MEN1 and asymptomatic PHPT this should be performed every 2 years	43%		
if disagree, in adults with MEN1 and asymptomatic PHPT this should be performed every 3 years	10%		
if disagree, in adults with MEN1 and asymptomatic PHPT this should be performed every 5 years	10%		
disagree to all	5%		
R2.1 At the time of PHPT diagnosis in adults with MEN1, investigations of target organ damage should be performed as recommended in sporadic PHPT	97%	3%	4
R2.2 In adults with MEN1-related PHPT without objective symptoms and without target organ damage where the decision is made to observe, monitoring of target organ damage can be performed according to practice recommendations in sporadic PHPT	95%	5%	4
R2.3 At the time of diagnosis of PHPT in children with MEN1, baseline investigations for target organ damage should include eGFR	87%	13%	14

R2.4 At the time of diagnosis of PHPT in children with MEN1, baseline investigations for target organ damage should include renal ultrasound	89%	11%	9
Timing of index operation			
R1.6 Concomitant gastrinoma is an additional indication for parathyroidectomy in patients with MEN1-associated PHPT	84%	16%	9
R1.7 Parathyroidectomy is indicated at the time of diagnosis in all adults with MEN1 and asymptomatic PHPT WITHOUT evidence of target organ involvement, when they manifest hypercalcemia, regardless serum calcium levels	10%	90%	5
If disagree, parathyroidectomy is indicated in adults with asymptomatic PHPT WITHOUT target organ involvement when the serum calcium level is >1 mg/dL/0.25 mmol/L above the upper limit of normal	75%		1
If disagree, parathyroidectomy should be deferred until documented target organ involvement in adults with MEN1 and asymptomatic PHPT, regardless serum calcium levels	17%		
Disagree to all	8%		
R1.8 Parathyroidectomy is indicated at the time of diagnosis in all children with MEN1 and asymptomatic PHPT WITHOUT evidence of target organ involvement, when they manifest hypercalcemia, regardless serum calcium levels	12%	88%	6
If disagree, parathyroidectomy is indicated in children/adolescents with MEN1 and asymptomatic PHPT in the absence of target organ involvement when the serum calcium level is >1 mg/dL / 0.25 mmol/L above the upper limit of normal	44%		3
If disagree, parathyroidectomy should be deferred until adulthood in children with MEN1 and asymptomatic PHPT WITHOUT evidence of target organ involvement, regardless serum calcium levels	41%		
Disagree to all	17%		
Type of index operation			
R1.9 In patients with MEN1-associated PHPT, subtotal parathyroidectomy is the index operation of choice	89%	11%	2
If disagree, in patients with MEN1-associated PHPT, total parathyroidectomy with or without parathyroid auto-transplantation is the index operation of choice	20%	80%	
R1.10 Transcervical thymectomy should be performed at the time of parathyroidectomy in patients with MEN1-associated PHPT	85%	15%	
R1.11 Preoperative localization studies (ultrasonography, nuclear imaging or four-dimensional computed tomography) should be routinely utilized before index (sub)total parathyroidectomy in adults with MEN1-associated PHPT	66%	34%	5
R1.12 In selected adults with MEN1-associated PHPT and a concordant focus of disease on preoperative localization studies, less-than-subtotal parathyroidectomy can be considered	71%	29%	8
R1.13 Preoperative localization studies (ultrasonography, sestamibi imaging or four-dimensional computed tomography) should be routinely utilized before index parathyroidectomy in children with MEN1-associated PHPT to determine if a less-than-subtotal parathyroidectomy may be preferred	76%	24%	5
R2.5 In children and young adults, single gland excision should be considered the preferred index operation when there is concordant imaging evidence of a single enlarged parathyroid gland	47%	53%	4
If disagree, In children and young adults, unilateral clearance should be considered the preferred index operation when there is concordant imaging evidence of a single enlarged parathyroid gland	56%	44%	3
R2.6 In children and young adults, unilateral clearance should be considered the preferred index operation when there is concordant imaging evidence of two or more enlarged parathyroid glands on one side of the neck	70%	30%	7

Genetic testing in apparently sporadic PHPT			
R1.14 MEN1 genetic testing should be recommended in patients who develop PHPT <40 years of age AND who have a negative family history (e.g. apparently sporadic PHPT)	69%	31%	1
If disagree, MEN1 genetic testing should be recommended in patients who develop PHPT <30 years of age AND who have a negative family history (e.g. apparently sporadic PHPT)	65%	36%	
R1.15 MEN1 genetic testing should be recommended in patients with PHPT and evidence of multiglandular involvement, WITHOUT a reported familial history of MEN1 or other hereditary forms of PHPT (e.g HPT-JT, FIHP, FHH)	78%	22%	1
R2.7 In patients with apparent single gland disease, NO suspicious family history AND NO signs of other syndromal manifestations, genetic counseling and testing should be considered			
Always	5%		
Only below 40	46%		
Only below 30	49%		

Statements from the first round are shown in white, statements from the second round in grey. Follow-up questions to a particular answer have a lighter font. For statements that reached consensus percentages are given in bold. Abbreviations: FHH familial hypocalciuric hypercalcaemia; FIHP familial isolated hyperparathyroidism; HPT-JT hyperparathyroidism jaw-tumor; MEN1 Multiple Endocrine Neoplasia Type 1; PHPT primary hyperparathyroidism

Supplementary table 5. Outcomes of the NET Delphi Round 1 and Round 2

NET outcomes of the first two rounds Round 1 (R1) n=46 Round 2 (R2) n=45	Agree	Disagree	Unable to answer/ not my expertise (n)
A. DUODENOPANCREATIC NETS			
Screening			
R1.1 MRI is the preferred method of screening for pancreatic NETs in asymptomatic patients with MEN1	80%	20%	5
R1.2 EUS is the preferred method of screening [...]	27%	73%	6
R1.3 SSTR-PET/CT is the preferred method of screening [...]	20%	80%	6
R1.4 Radiological screening for PanNETs in asymptomatic patients with MEN1 should be initiated before the age of 19	80%	20%	5
If agree, radiological screening for PanNETs [...] should be initiated at the age of 5 years	12%		
If disagree, radiological screening for PanNETs [...] should be initiated at the age of 10 years	42%		
If disagree, radiological screening for PanNETs [...] should be initiated at the age of 15 years	42%		
Disagree to all	3%		
R1.5 In asymptomatic adults with MEN1 WITHOUT evidence for duodenopancreatic NETs on imaging AND normal biochemistry the interval for radiological screening can be extended beyond 1 year	83%	18%	6
If agree, the interval for radiological screening can be extended to 5 years	21%		1
If disagree, the interval for radiological screening can be extended to 4 years	-		
If disagree, the interval for radiological screening can be extended to 3 years	48%		
If disagree, the interval for radiological screening can be extended to 2 years	27%		
R2.1 In patients with MEN1 without evidence of PanNETs on imaging, who have normal biochemistry and absence of signs and symptoms of functioning PanNETs, the recommended interval for abdominal radiological screening is:			4
Every 2 years	59%		
Every 3 years	41%		
Biochemical screening for duodenopancreatic NETs in asymptomatic patients without evidence for duodenopancreatic NETs on radiological exam should include:			
R1.6.1 Biochemical screening [...] should include chromogranin A	38%	63%	6
R1.6.2 Biochemical screening [...] should include glucagon	39%	61%	8
R1.6.3 Biochemical screening [...] should include pancreatic polypeptide	32%	68%	9
R1.6.4 Biochemical screening [...] should include VIP	27%	73%	9
R1.6.5 Biochemical screening [...] should include gastrin	95%	5%	7
R1.6.6 Biochemical screening [...] should include glucose	79.5%	20.5%	7
R1.6.7 Biochemical screening [...] should include insulin	49%	51%	7
R2.2 Chromogranin A is NOT a suitable biomarker to screen for non-functioning pancreatic neuroendocrine tumors in patients with MEN1 without evidence of pancreatic NETs on imaging	93%	7%	4

R2.3 Pancreatic Polypeptide is NOT a suitable biomarker to screen for non-functioning pancreatic neuroendocrine tumors in patients with MEN1 without evidence of pancreatic NETs on imaging	86%	14%	8
R2.4 Glucagon is NOT a suitable biomarker to screen for non-functioning pancreatic neuroendocrine tumors in patients with MEN1 without evidence of pancreatic NETs on imaging	89%	11%	8
R1.7 Only children with symptoms suspicious of hypoglycemia should undergo biochemical testing for insulinoma	76%	24%	8
R1.8 Only children with symptoms suspicious of gastrinoma should undergo biochemical testing for gastrinoma (gastrin)	59%	41%	7
R1.9 All patients with MEN1 (regardless of symptoms or gastrin levels) should be screened with esophagogastroduodenoscopy (EGD) for gastroduodenal NETs and signs of ZES	15%	85%	7
If disagree, all patients with elevated gastrin levels (regardless if symptomatic) should be screened with EGD	76%		
If disagree, only symptomatic patients with MEN1 AND elevated gastrin levels should be screened with EGD	24%		
Surveillance			
R1.10 In stable NF-PanNETs <2cm the interval for radiological surveillance can be extended beyond 1 year	67%	33%	7
If agree, [...] interval for radiological surveillance can be extended to every 3 years	35%		
If disagree, [...] interval for radiological surveillance can be extended to every 2 years	65%		
R2.5 In patients with MEN1 with stable NF-PanNETs <2 cm (growth <1 mm/year over more than one year) imaging can be repeated after:			5
2 years	92%		
3 years	8%		
R1.11 Patients with MEN1 planned to undergo duodenopancreatic surgery should have a SSSTR-PET/CT performed pre-operatively	100%	0%	
Genetic testing in apparently sporadic NETs			
R1.12 In every patient (irrespective of the age) diagnosed with a functioning or non-functioning PanNET WITHOUT family history of MEN1-related tumors (i.e. apparently sporadic PanNET), MEN1 genetic testing should be recommended	36%	67%	2
If disagree, genetic testing should only be recommended in patients below age 40	68%		
If disagree, genetic testing should only be recommended in patients below age 30	14%		
If disagree, genetic testing should only be recommended in patients below age 20	7%		
Disagree to all	11%		
R2.6 For a patient with a unifocal NF PanNET, who has NO other manifestations suggestive of MEN1 and NO suspicious family history, genetic testing for MEN1 should be considered:			4
Always	10%		
Only below 40 years	49%		
Only below 30 years	24%		
Only in childhood	17%		
R2.7 For a patient with a unifocal insulinoma, who has NO other manifestations suggestive of MEN1 and NO suspicious family history, genetic testing for MEN1 should be considered:			5
Always	17%		
Only below 40 years	48%		
Only below 30 years	23%		
Only in childhood	12%		
R1.13 In every patient (irrespective of the age) diagnosed with a gastrinoma WITHOUT family history of MEN1-related tumors (i.e. apparently sporadic gastrinoma), MEN1 genetic testing should be recommended	66%	34%	2

If disagree, genetic testing should only be recommended in patients below age 40	73%
If disagree, genetic testing should only be recommended in patients below age 30	7%
If disagree, genetic testing should only be recommended in patients below age 20	7%
Disagree to all	13%

R2.8. For a patient with gastrinoma, who has NO other manifestations suggestive of MEN1 and NO suspicious family history, genetic testing for MEN1 should be considered:		3
Always	50%	
Only below 40 years	31%	
Only below 30 years	17%	
Only in childhood	2%	

B. THORACIC NETS

Screening			
R1.1 The preferred modality for radiological screening for thoracic NETs is MRI	15%	85%	12
R1.2 [...] is contrast-enhanced standard dose CT	38%	62%	12
R1.3 [...] is low-dose CT (without contrast enhancement)	44%	56%	12
R1.4 [...] is SSSTR-PET/CT	15	85%	12
R1.5 Radiological screening for thoracic NETs should start in childhood (i.e < age 19),	16%	84%	8
If disagree, radiological screening for thoracic NETs should start at age 20	69%		3
If disagree, radiological screening for thoracic NETs should start at age 25	14%		
If disagree, radiological screening for thoracic NETs should start at age 30	17%		
R2.1 In patients with MEN1 without sign/symptoms of thoracic NETs, radiological screening for thoracic NETs should be initiated around the age of 20-25 years	86%	14%	10
R1.6 In patients with MEN1 WITHOUT evidence of thoracic NETs the screening interval can be extended beyond 2 yr	77%	23%	11
If agree, in pt with MEN1 WITHOUT evidence of thoracic NETs the screening interval can be extended to 5 yr	48%		
If disagree, in pt with MEN1 WITHOUT evidence of thoracic NETs the screening interval can be extended to 3 yr	56%		
Surveillance			
R1.7 For patients with MEN1 and cT1N0 (radiologically suspected) thoracic NETs active surveillance can be considered	71%	29%	12
If agree to question R1.7,			
R1.8 In patients with MEN1 and stable cT1N0 thoracic NETs the surveillance interval can be extended beyond 1 year	75%	25%	
R2.2 In patients with MEN1 and a cT1N0 (radiologically diagnosed) lung NET which has been stable on repeat imaging for at least 1 year the recommended surveillance interval is 1-2 years	97%	3%	7

Statements from the first round are shown in white, statements from the second round in grey. Follow-up questions to a particular answer have a lighter font. For statements that reached consensus percentages are given in bold. EGD - esophagogastroduodenoscopy; EUS - endoscopic ultrasound; MEN1 - multiple endocrine neoplasia type 1; MRI - magnetic resonance imaging; NET - neuroendocrine tumour; PanNET - pancreatic neuroendocrine tumour; SSSTR-PET/CT - somatostatin receptor positron emission computed tomography; VIP - vasoactive intestinal peptide; yr – year and ZES - Zollinger-Ellison syndrome.

Supplementary table 6. Outcomes of the Pituitary Delphi Round 1 and Round 2

Pituitary outcomes of the first two rounds Round 1 n=41 Round 2 n=40	Agree	Disagree	Unable to answer/ not my expertise (n)
Screening in children			
R1.1 Appraisal of signs/symptoms of pituitary disease and assessment of growth and pubertal development suffice for screening for pituitary adenomas in children (i.e. no biochemical and/or radiological screening in asymptomatic children)	50%	50%	3
If disagree, on asymptomatic children, a pituitary MRI examination is recommended for diagnosing pituitary adenomas	67%	33%	1
If agree, MRI should be performed starting at the age of 5 years	1/12		
If disagree, MRI should be performed starting at the age of 10 years	8/12		
If disagree, MRI should be performed starting at the age of 15 years	3/12		
If disagree, in asymptomatic children, laboratory testing is recommended for diagnosing pituitary adenomas	95%	5%	
If agree, laboratory testing should begin at the age of 5 years	5/18		
If disagree, laboratory testing should begin at the age of 10 years	12/18		
If disagree, laboratory testing should begin at the age of 15 years	1/18		
If agree, laboratory testing should include both prolactin and IGF1	15/18		
If disagree, laboratory testing should include prolactin only	3/18		
R2.1 Asymptomatic children with MEN1 should be screened in childhood for the presence of a pituitary adenoma using history, physical examination, assessment of growth charts and pubertal development, If all this is normal, screening for the presence of a pituitary adenoma in asymptomatic children should additionally include			
Laboratory only	31%		
MRI only	12%		
Laboratory and MRI	43%		
Neither	14%		
MRI (MRI only + laboratory and MRI)	54%		
For those who answered MRI: In asymptomatic children the initial screening MRI should be performed between 10 and 15 years or age	89%	11%	
Laboratory (Laboratory only + laboratory and MRI)	76%		
For those who answered laboratory: initial laboratory tests should be performed			
Between age 5 and 9	42%		
Between age 10 and 14	50%		
Between age 15 and 19	8%		
Screening in adults			
R1.2 In the absence of signs/symptoms of pituitary disease, adults with MEN1 should undergo an MRI exam for a pituitary adenoma	95%	5%	4
If agree, in the absence of signs/symptoms of pituitary disease, patients should undergo an MRI exam every yr	9%		1
If disagree, [...] should undergo an MRI exam every two years	18%		
If disagree, [...] should undergo an MRI every three years	44%		
If disagree, [...] should undergo an MRI every five years	29%		
R2.2 In asymptomatic adults with MEN1 who have unremarkable biochemical screening for pituitary adenoma AND a normal baseline pituitary MRI, an MRI pituitary is recommended every:			
2 years	3%		
3 years	54%		
5 years	43%		
R1.3 If no prior history of a pituitary adenoma, testing for pituitary adenomas in asymptomatic patients with MEN1 should be lifelong	56%	44%	5
If disagree, testing for pituitary adenomas can stop after 55 years of age	4/16		
If disagree, [...] can stop after 60 years of age	4/16		
If disagree, [...] can stop after 65 years of age	4/16		
If disagree, [...] can stop after 70 years of age	4/16		

R2.3 In a prospectively screened patient with MEN1 who reaches the age of 75 years without having developed a pituitary adenoma, further screening with MRI can be stopped	94%	6%	5
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Management

R1.4 In MEN1 patients with pituitary disease identified, the medical and surgical treatment should be the same as for sporadic pituitary adenomas	92%	8%	3
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Genetic testing in apparently sporadic Pituitary Adenoma

R1.5 In every patient diagnosed with a functioning pituitary adenoma or a non-functioning pituitary adenoma > 1cm without family history of pituitary tumors (i.e. apparently sporadic pituitary adenoma), MEN1 genetic testing should be recommended,	12%	88%	1
If disagree, genetic testing should be recommended only in patients below age 40	26%		
If disagree, genetic testing should be recommended only in patients below age 30	43%		
If disagree, genetic testing should be recommended only in patients below age 20	17%		
Disagree	14%		

Statements from the first round are shown in white, statements from the second round in grey. Follow-up questions to a particular answer have a lighter font. For statements that reached consensus percentages are given in bold.

IGF1 - insulin-like growth factor-1; MEN1 - multiple endocrine neoplasia type 1; MRI - magnetic resonance imaging; yr - year

Supplementary table 7. *MEN1* mutation-negative patients

Definition of *MEN1* mutation-negative patient

- Patient with clinical MEN1 (2 of the 3 main MEN1-related tumours) who does not have mutation of *MEN1* (10-30% of cases)

Additional genetic testing required

- Undertake DNA sequence analysis for mutations in genes known to cause MEN1 phenocopies^a e.g. *CDKN1B*, *MAX*, *CDC73*, *CASR*, *RET* and *AIP*, tailored to the phenotype
- If above genetic testing fails to identify mutations then consider repeat testing using another bioinformatic pipeline or libraries, before using WES or WGS

Importance of identifying MEN1 mutation-negative patients

- *MEN1* mutation-negative patients reported to have a more favourable prognosis
- Have less aggressive disease, with median age of first tumour manifestation 13 years later, and median age of second tumour manifestation 9 years later, when compared to patients with *MEN1* mutation
- Third tumour manifestations rarely identified in *MEN1* mutation-negative patients
- Median survival is 14 years greater than those with a *MEN1* mutation (87 *versus* 73 years of age)

WES - whole exome sequencing. WGS – whole genome sequencing.

^a Many genetic diagnostic laboratories include these genes on targeted- or virtual- panels that use next generation sequencing (NGS) when testing for *MEN1* mutations.

Supplementary table 8. Multiple Endocrine Neoplasia Type 1 (MEN1) phenocopies and associated genes

Disease	Phenotypes	Gene	Genomic location	Gene function
HPT-JT	Tumours of: Parathyroids, jaw (maxilla and mandible), kidney, uterus, pancreas and pituitary	<i>CDC73</i>	1q31.2	Tumour suppressor that encodes parafibromin, a subunit of the polymerase II-associated factor (PAF) protein complex, which associates with the RNA polymerase II subunit POLR2A and a histone methyltransferase complex
FHH1, NSHPT & PHPT.	Hypercalcemia, and tumours of : parathyroids, colon, pituitary, pancreas, prostate and breast.	<i>CASR</i>	3q21.1	Encodes the calcium sensing receptor (CaSR), a G-protein coupled receptor (GPCR) that maintains mineral ion homeostasis.
FIPA	Tumours of: pituitary and parathyroids	<i>AIP</i>	11q13.2	Encodes tumour suppressor protein that interacts and colocalises with the PKA subunits PRKAR1A & PRKACA
Carney complex	Tumours of: Thyroid, pituitary, adrenal, heart, skin, breast, testes	<i>PRKAR1A</i>	17q24.2	Regulator of cAMP-dependent protein kinase

HPT-JT - Hyperparathyroidism-Jaw Tumour; FHH1 - Familial hypocalciuric hypercalcemia type 1; NSHPT - Neonatal severe hyperparathyroidism; PHPT - Primary hyperparathyroidism; FIPA - Familial isolated pituitary adenoma; PKA - protein kinase A; PRKAR1A – PKA R1-alpha; PRKACA – PKA C-alpha ; *CDC73* – cell cycle division 73; *CASR* – Calcium sensing receptor; *PRKAR1A* - Protein Kinase CAMP-Dependent Type I Regulatory Subunit Alpha; *AIP* - aryl hydrocarbon receptor-interacting protein