



# Multiple endocrine neoplasia type 1 (MEN1): recommendations and guidelines for best practice

Maria Luisa Brandi\*, Carolina R C Pieterman\*, Katherine A English\*, Kate E Lines\*, Omair A Shariq\*, Francesca Marini, Thomas Cuny, Mark A Lewis, Constantine A Stratakis, Nancy D Perrier, Steven G Waguespack, Frederic Castinetti, Gerlof D Valk†, Rajesh V Thakker‡, on behalf of the Delphi Expert Panel‡

Multiple endocrine neoplasia type 1 (MEN1) is characterised by combined occurrence of parathyroid tumours, duodenopancreatic neuroendocrine tumours, and anterior pituitary adenomas. Some patients might also develop thymic and bronchopulmonary neuroendocrine tumours, 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, patients with MEN1 have high morbidity and premature mortality, which can be mitigated by early tumour detection and intervention. Identification of 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 a meta-analysis of the literature, and to use a Delphi approach for the development of consensus statements. 55 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—MEN1, MEN2A, MEN2B (also known as MEN3), MEN4, and MEN5—are recognised and each form is characterised by the development of tumours within specific endocrine glands (table 1). Parathyroid tumours, neuroendocrine tumours of the pancreas and duodenum, and pituitary adenomas are the main manifestations of MEN1.<sup>1,2</sup> Patients with MEN1 might also develop other endocrine tumours, including adrenal cortical tumours, as well as thymic, bronchopulmonary, and gastric neuroendocrine tumours. Non-endocrine tumours associated with MEN1 include facial angiofibromas, collagenomas, and lipomas, and possibly also meningiomas, breast cancer, and melanoma. Thus, patients with MEN1 might 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 neuroendocrine tumours representing the most important disease-related cause of death.<sup>3,4</sup>

The first case reports describing the co-occurrence of multiple endocrine neoplasms were in the early 1900s, which 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 defining features of MEN1. In 1954, a familial basis for MEN1 was established by documenting its occurrence in a father and daughter of one family,<sup>5</sup> and in a father and four daughters of another family.<sup>6</sup> In 1997, the identification of the *MEN1* gene<sup>7,8</sup> facilitated DNA testing to reveal those individuals in a MEN1 family who have a mutation, which is defined in

this Review 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 p 3).<sup>9</sup> The development of genetic testing also facilitated identification of presymptomatic individuals—ie, those who had the mutation but as yet had not developed clinical symptoms or manifestations of MEN1. Such presymptomatic individuals were therefore considered to have genetic MEN1. In 2001,<sup>1</sup> clinical practice guidelines, based on expert opinions, were developed and updated in 2012<sup>2</sup> to advise on the diagnosis and management of patients with MEN1. These guidelines advocated for 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 for in existing guidelines has resulted in patients being diagnosed at earlier stages of the different manifestations. This development frequently poses challenges in clinical management as smaller, mostly indolent, non-functioning (ie, not secreting hormones) pancreatic neuroendocrine tumours, thoracic neuroendocrine tumours, pituitary microadenomas, and adrenal adenomas are identified in patients who are asymptomatic, alongside hormone-secreting neoplasms (eg, parathyroid tumours, gastrinomas, and insulinomas) at very early stages. Furthermore, during the past few decades large multicentre (population-based) and single-centre cohort studies<sup>3,10–15</sup> have provided valuable insights into many aspects of the natural course of MEN1-related

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\*Joint first authors

†Joint corresponding authors

‡Members of the Delphi Expert

Panel are listed in the appendix

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Fondazione FIRMO Onlus

(Italian Foundation for the

Research on Bone Diseases),

Florence, Italy

(Prof M L Brandi PhD,

F Marini PhD); Endocrinology

Unit, IRCCS San Raffaele

Hospital, Milan, Italy

(Prof M L Brandi); Department

of Endocrine Oncology,

University Medical Center

Utrecht, Utrecht, Netherlands

(C R C Pieterman PhD,

Prof G D Valk PhD); Academic

Endocrine Unit, Oxford Centre

for Diabetes, Endocrinology

and Metabolism, Radcliffe

Department of Medicine,

University of Oxford, Oxford,

UK (K A English MBBS,

K E Lines PhD, O A Shariq DPhil,

Prof R V Thakker MD); Oxford

NIHR Biomedical Research

Centre, University of Oxford,

Churchill Hospital, Oxford, UK

(K E Lines, Prof R V Thakker);

School of Biological and

Medical Sciences, Faculty of

Health and Life Sciences,

Oxford Brookes University,

Oxford, UK (K E Lines); Division

of Endocrine Surgery,

Department of Surgery, Mayo

Clinic, Rochester, MN, USA

(O A Shariq); Department of

Surgical Oncology, Section of

Surgical Endocrinology

(O A Shariq, Prof N D Perrier MD)

and Department of Endocrine

Neoplasia & Hormonal

Disorders and the Children's

Cancer Hospital

(Prof S G Waguespack MD),

The University of Texas MD Anderson Cancer Center, Houston, TX, USA; Aix Marseille University, Department of Endocrinology, Centre d'Investigation Clinique 1409 (Prof T Cuny MD) and France and Endo-European Reference network on rare endocrine conditions (Prof F Castinetti MD), La Conception Hospital, Marseille, France; Department of Gastrointestinal oncology, Intermountain Health, Salt Lake City, UT, USA (M A Lewis); EDIMO & Human Genetics and Precision Medicine, Institute for Molecular Biology & Biotechnology, Foundation for Research & Technology Hellas, Heraklion, Greece (Prof C A Stratakis MD); Medical Genetics, H Dunant Hospital and ASTREA Health, Athens, Greece (Prof C A Stratakis); Centre for Endocrinology, Metabolism, William Harvey Research Institute, Barts and The London School of Medicine, Queen Mary University of London, London, UK (Prof R V Thakker)

Correspondence to: Prof Gerlof D Valk, Department of Endocrine Oncology, University Medical Center Utrecht, Utrecht 3584 CX, Netherlands  
g.d.valk@umcutrecht.nl

or Prof Rajesh V Thakker, Academic Endocrine Unit, Oxford Centre for Diabetes, Endocrinology and Metabolism, Radcliffe Department of Medicine, University of Oxford, Oxford OX3 7LJ, UK  
rajesh.thakker@ndm.ox.ac.uk

See Online for appendix

Tumours (estimated penetrance)		Gene, most frequent mutations
MEN1 (11q13)	Parathyroid adenoma (90%); duodenopancreatic tumour (30% to 80%); gastrinoma (40%), insulinoma (10%), non-functioning and pancreatic polypeptide-secreting tumour (20% to 80%), glucagonoma (<1%), and vasoactive intestinal peptide-overproducing neuroendocrine tumour (<1%); pituitary adenoma (~35% to >50%); prolactinoma (~45% to ~80%), clinically non-functioning (15% to ~45%), somatotropinoma (<10%) and corticotropinoma (<5%); associated tumours: adrenal tumours (~40%) adrenal cortical tumour (>90%), pheochromocytoma (<1%), adrenocortical carcinoma (~1%)*; bronchopulmonary neuroendocrine tumour (5% to 30%), thymic neuroendocrine tumour (<10%), gastric neuroendocrine tumour (10%), lipomas (30%), angiofibromas (85%), collagenomas (70%), meningiomas (<10%)	MEN1: codon 83 or 84, 4-bp del (4%); codon 119, 3-bp del (3%); codons 209–211, 4-bp del (8%); codon 418, 3-bp del (4%); codons 514–516, del or ins (7%); intron 4 splice site (10%)
MEN2A (10 cen–10q11.2)	Medullary thyroid cancer (90%); pheochromocytoma (50%); parathyroid adenoma (20% to 30%)	RET: missense (eg, Val804Met [~25%], Cys634Arg [~20%])
MEN2B (also known as MEN3; 10 cen–10q11.2)	Medullary thyroid cancer (>90%); pheochromocytoma (40% to 50%); associated abnormalities (40% to 50%); mucosal neuromas marfanoid habitus; medullated corneal nerve fibres; megacolon	RET: Met918Thr (>95%)
MEN4 (12p13)	Parathyroid adenoma†; pituitary adenoma†; reproductive organ tumours (eg, testicular cancer, neuroendocrine cervical carcinoma)†; potentially adrenal and renal tumours†	CDKN1B: no common mutations identified to date
MEN5 (14q23)	Paraganglioma†; pheochromocytoma†; parathyroid adenoma†; pituitary adenoma†; ganglioneuroma†; ganglioneuroblastoma†	MAX: no common mutations identified to date

Autosomal dominant inheritance of the MEN syndromes has been established. CDKN1B=cyclin dependent kinase inhibitor 1B. MAX=MYC associated factor X. MEN=multiple endocrine neoplasia. RET=Ret proto-oncogene. \*Adrenocortical carcinoma risk is reported to be 10–15% in adrenal tumours >1cm. †Insufficient numbers reported to provide prevalence information.

**Table 1: Types of MEN syndrome, chromosomal locations, characteristic tumours, and associated genetic mutations**

tumours. However, owing to a paucity of evidence-based guidelines, clinical applications of screening and surveillance protocols for MEN1-related tumours vary, even among different centres of excellence.<sup>16</sup>

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).<sup>17</sup> This process identified over 3000 articles published since 2001, although most (~90%) were retrospective series with sparse data that were insufficient to provide high or moderate certainty for the evidence using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach.<sup>18,19</sup> Despite these limitations, we were able to ascertain 37 publications, including 27 retrospective, one prospective cohort study, and nine case series. From these studies, we extracted and analysed data from 1814 patients, allowing us to establish the following recommendations for patients with MEN1. First, subtotal parathyroidectomy, when compared with less than subtotal parathyroidectomy, for treatment of parathyroid tumours causing primary hyperparathyroidism, was associated with a significantly lower risk of primary hyperparathyroidism persistence and recurrence, but a significantly higher risk of post-operative chronic hypoparathyroidism. Second, for non-functioning pancreatic neuroendocrine tumours measuring 2 cm or less, metastatic disease and mortality rates, based on a small number of studies, were not different between the surgery versus active surveillance groups. Third, dopamine agonist responses for prolactinomas in patients with MEN1 and without MEN1 were similar.<sup>17</sup> For all three recommendations, the GRADE levels (scores) were

low or very low certainty. Moreover, due to the complexity of MEN1 and the varying methodological quality of available information, many other questions remained unanswered. For these unanswered questions, we used the Delphi method (figure 1, appendix p 4), a technique for structured quantification of expert opinion,<sup>20</sup> 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 pp 5, 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 pp 5–7), 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 based on their recognised clinical experience, academic excellence, and contributions to professional organisations with remits for endocrine tumours, MEN1, or both. The panel included representatives from 22 countries from five continents (Asia, Australia, Europe, North America, and South America; appendix pp 8–14). Delphi consensus meetings were held for each of the main MEN1-related manifestations (primary

hyperparathyroidism, neuroendocrine tumours, and pituitary adenomas), as well as for paediatric-specific considerations (appendix p 4 and pp 15–25). Initial statements were developed by the Delphi Core Group (appendix pp 6, 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 pp 15–25). “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 p 15,16).

## Recommendations

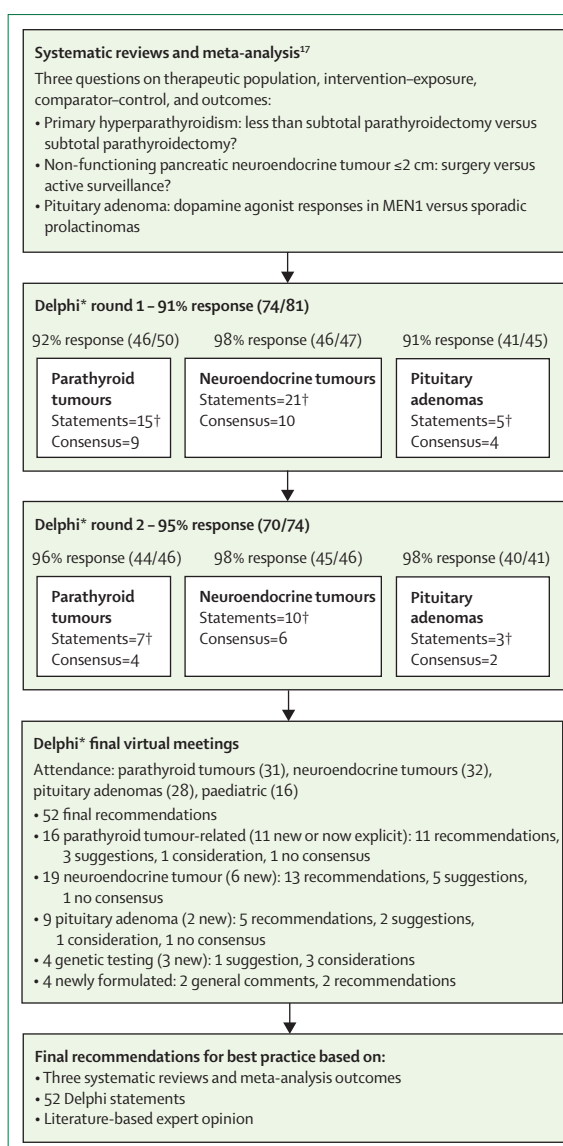
The outcomes of the Delphi proceedings comprised 52 consensus statements (table 2). The statements pertained to: screening, surveillance, sequelae, and treatments of parathyroid tumours (n=16); screening and surveillance of duodenopancreatic (n=14) and thoracic (n=5) neuroendocrine tumours; screening, surveillance and management of pituitary adenomas (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 pp 15–33). These Delphi consensus statements, together with the outcomes from the systematic reviews and meta-analysis,<sup>17</sup> 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 that collaborate nationally and internationally for optimisation of clinical care and research (statement 3).

## Screening recommendations for MEN1-related tumours

The aim of screening for MEN1-related tumours is to enable 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. 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 programme.



**Figure 1: Evidence generation for recommendations for best practice**

A Delphi method was used to develop practical clinical recommendations regarding unanswered questions due to the complexity of MEN1 and the varying methodological quality of available information. This process yielded 52 final recommendations for best practice that will help to provide guidance for health care professionals and patients. MEN1=Multiple endocrine neoplasia type 1.

\*For detailed methodology regarding the Delphi, see appendix (pp 4, 15–33).

†Several statements included sub-statements (appendix pp 26–33).

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.<sup>21,22</sup> Age-related penetrance (ie, the proportion of gene carriers manifesting symptoms or signs of the disease by a given age) has been ascertained: penetrance is low for individuals younger than 10 years and near zero for those younger than 5 years.<sup>1,23–25</sup> Thereafter, penetrance steadily rises to reach over 95% by age 70 years.<sup>1,24–26</sup> Screening

Statement		Statement strength
<b>General</b>		
#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 aged <19 years.	..
#3	Patients with MEN1 should be treated in centres of expertise with high-volume, experienced, multidisciplinary teams. (Unchanged)	Recommendation
#4	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 5 years. Symptoms of MEN1 clinical manifestations should be discussed and shared decision making undertaken regarding screening and surveillance plans. (New)	Recommendation (100%); paediatric meeting
<b>Parathyroid tumours causing primary hyperparathyroidism</b>		
Screening		
#5	Adults with MEN1 should be screened for primary hyperparathyroidism with yearly serum calcium measurements. (Changed, interval similar, parathyroid hormone now omitted)	Recommendation (91%)
#6	Children and adolescents with MEN1 should be screened for primary hyperparathyroidism with serum calcium measurements at 1–3 year intervals. (Changed, enabling longer interval)	Recommendation (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. (Changed, 2001 and 2012 initiated at age 8 years)	Consideration
Management		
#8	To assess renal and skeletal involvement in adults with MEN1 and newly diagnosed primary hyperparathyroidism according to the Guidelines from the Fifth International Workshop on Primary Hyperparathyroidism. (New)	Recommendation (97%)
#9	In children and adolescents with MEN1 and newly diagnosed primary hyperparathyroidism, renal function (creatinine or cystatin C eGFR) should be assessed. (New)	Recommendation (92%)
#10	In asymptomatic children and adolescents with primary hyperparathyroidism, routine dual-energy X-ray absorptiometry assessment is not recommended. For those children undergoing bone mineral density assessment, this needs to be interpreted in the context of age and height. (New)	Recommendation (92%); paediatric
#11	To monitor target organ involvement in adults with MEN1 with primary hyperparathyroidism, if surgery is deferred according to the Guidelines from the Fifth International Workshop on Primary Hyperparathyroidism. (New)	Recommendation (95%)
#12	In asymptomatic children, adolescents, and adults with MEN1, in whom the onset of primary hyperparathyroidism is observed but who do not have evidence of target organ involvement, initial active surveillance is acceptable. (New or now explicit)	Recommendation (adult 90%, paediatric 88%)
#13	Parathyroidectomy is indicated in children, adolescents, and adults diagnosed with MEN1-related primary hyperparathyroidism who are symptomatic or have evidence of target organ involvement. (New or now explicit)	Recommendation (98%)
#14	Irrespective of symptoms, parathyroidectomy is indicated in adults diagnosed with MEN1-related primary hyperparathyroidism, 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. (New or now explicit)	Recommendation (96%)
#15	Parathyroidectomy in children and adolescents diagnosed with MEN1-related primary hyperparathyroidism, 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, is suggested. (New or now explicit)	Suggestion
#16	In patients with MEN1, the presence of a symptomatic gastrinoma should be taken into account when considering the timing of parathyroidectomy. (Unchanged)	Recommendation (96%)
#17	In children, adolescents, and adults with MEN1-related primary hyperparathyroidism, subtotal (3–3.5 gland) parathyroidectomy with concomitant transcervical thymectomy is the recommended index operation, which should be performed by an experienced MEN1 parathyroid surgeon. (2001, 2012 unchanged)	Recommendation (89%)
#18	In selected cases, unilateral clearance can be considered as the index operation for children or adolescents with MEN1-related primary hyperparathyroidism. (New)	Suggestion
#19	There is no consensus on the need nor type of preoperative imaging studies for parathyroid localisation before the index operation in adults. (New or now explicit)	..
#20	The need and type of preoperative imaging for parathyroid localisation before the index operation in children and adolescents are determined on a case-by-case basis. (New or now explicit)	Suggestion
<b>Neuroendocrine tumours</b>		
Duodenopancreatic neuroendocrine tumours: screening		
#21	To screen asymptomatic patients with MEN1 with MRI for the presence of a pancreatic neuroendocrine tumour. (Changed, now stating preference for MRI)	Recommendation (80%)
#22	To perform the first MRI in asymptomatic children at age 10–15 years, the exact age to be at the discretion of the clinician and with shared decision making. (Changed, 2001 20 years, 2012 <10 years)	Recommendation (84%)
#23	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. (Changed, removed screening with glucose and insulin)	Recommendation (100%)
#24	In asymptomatic adults with MEN1, we recommend screening for gastrinoma with fasting serum gastrin. (Unchanged)	Recommendation (95%)

(Table 2 continues on next page)

Statement	Statement strength
(Continued from previous page)	
#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 neuroendocrine tumour is generally not useful. (Changed, removes biochemical screening with chromogranin A, pancreatic polypeptide, glucagon, and vasoactive intestinal peptide)	Recommendation (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 neuroendocrine tumour. (Changed, 2001 every, 2012 yearly)	Recommendation (59% 2 years; 41% 3 years)
Duodenopancreatic neuroendocrine tumours: management	
#28 In patients with MEN1 and stable non-functioning pancreatic neuroendocrine tumours $\leq 2$ 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. (New)	Recommendation (92%)
#29 To perform somatostatin receptor scintigraphy PET–CT or somatostatin receptor scintigraphy PET–MRI in all patients with MEN1 planned for duodenopancreatic surgery. (New)	Recommendation (100%)
#30 Somaostatin PET imaging can have a role in the surveillance of patients with MEN1 and gastrinoma or pancreatic neuroendocrine tumours when the results would affect management. (New)	Suggestion; neuroendocrine tumour meeting
#31 Endoscopic ultrasound can have a role in the surveillance of patients with MEN1 and gastrinoma or pancreatic neuroendocrine tumours when the results would affect management (Changed, more explicit statement about the role)	Suggestion; neuroendocrine tumour meeting
#32 Routine endoscopic ultrasound-guided biopsy is not recommended. (New)	Recommendation (100%); neuroendocrine tumour meeting
#33 Patients with symptoms suggestive of Zollinger–Ellison syndrome should undergo oesophagogastrroduodenoscopy. (Unchanged)	Recommendation
#34 To perform an oesophagogastrroduodenoscopy in patients with MEN1 who have consistently elevated fasting serum gastrin levels to look for signs of Zollinger–Ellison syndrome and gastro-duodenal neuroendocrine tumours. (Unchanged)	Suggestion
Thoracic neuroendocrine tumours: screening	
#35 To screen asymptomatic adults with MEN1 with CT for the presence of a thoracic neuroendocrine tumour. (Changed, now stating preference for CT)	Recommendation (82%)
#36 To initiate thoracic imaging screening at age 20–25 years in asymptomatic patients with MEN1. (Changed; 2001, 20 years; 2012, 15 years)	Recommendation (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 tumour. (Changed compared with 2012 every 1–2 years, similar to 2001 every 3 years in table, 3–5 years in text)	Suggestion
Thoracic neuroendocrine tumours: management	
#38 Active surveillance is an acceptable management strategy for small ( $< 1$ –2 cm) lung neuroendocrine tumours in patients with MEN1. (New)	Suggestion
#39 To perform imaging every 1–2 years taking into account tumour size in patients with MEN1 with small ( $< 1$ –2 cm) lung neuroendocrine tumours and stable growth ( $< 1$ mm/year over $> 1$ year) on active surveillance. (New)	Recommendation (97%)
Pituitary adenomas	
Screening in adults	
#40 To screen asymptomatic adults with MEN1 with MRI for the presence of a pituitary adenoma. (Unchanged)	Recommendation (95%)
#41 In adults with no mass detected by MRI at baseline, persistent absence of features of hypopituitarism or hyperpituitarism and normal hormonal testing, it is recommended that a pituitary MRI is performed every 3–5 years. (Unchanged, 2001 every 3 years in table, 3–5 in text, 2012 every 3 years)	Recommendation (54% 3 years; 43% 5 years)
#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. (New)	Recommendation (94%)
Screening in children	
#43 Physical examination in children with MEN1 should include the evaluation of growth and pubertal development. (New)	Recommendation (100%); paediatric
#44 To screen asymptomatic children with MEN1 with normal growth and development, for pituitary adenomas using prolactin (PRL) and insulin-like growth factor 1 (IGF-1). (Unchanged)	Suggestion
#45 There is no consensus regarding the age to initiate biochemical screening. Initiating biochemical screening from the age of 10 years can be considered. (Changed, 2001 and 2012 start age 5)	Consideration
#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. (Changed)	..

(Table 2 continues on next page)



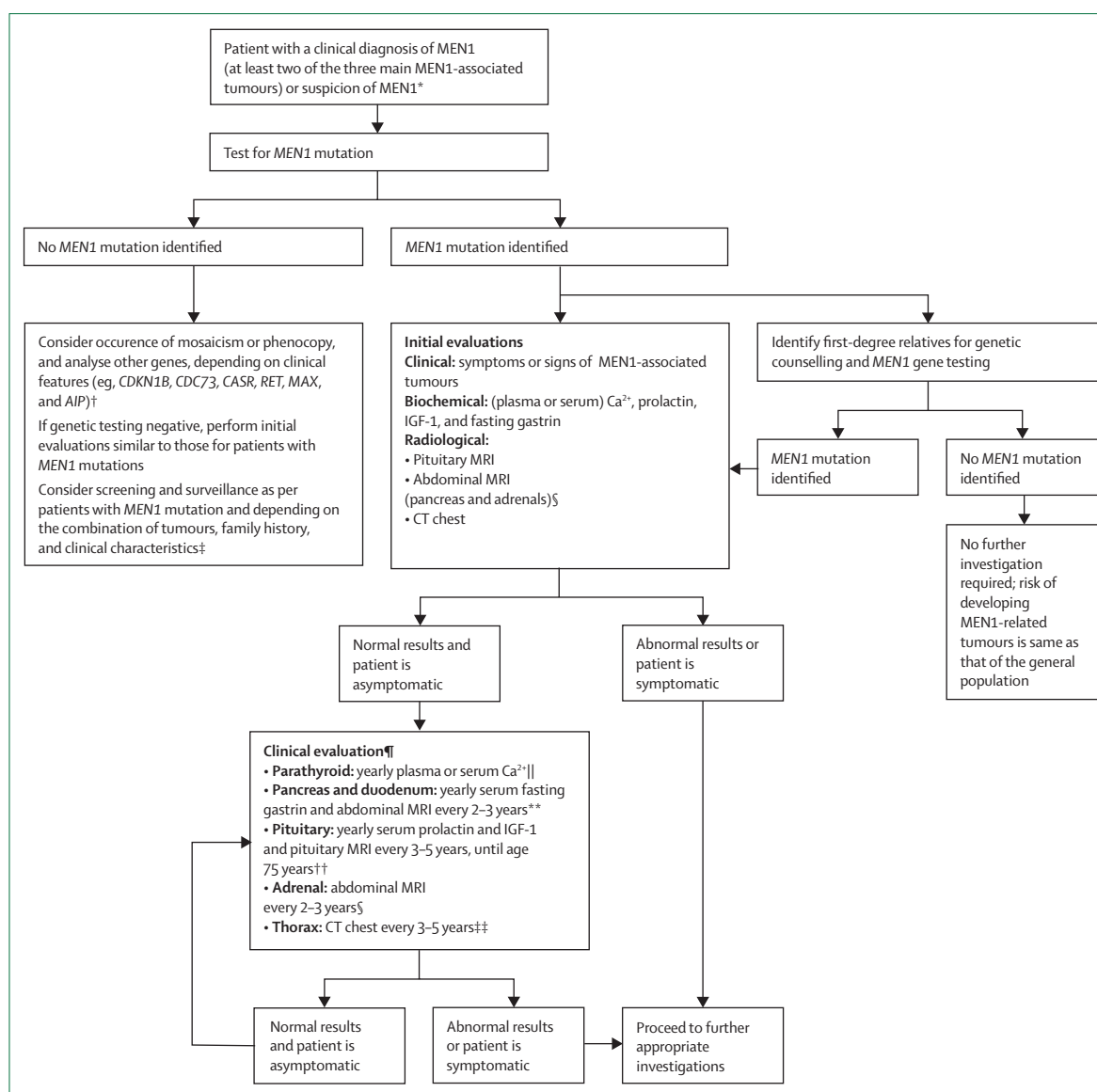
Statement		Statement strength
(Continued from previous page)		
#47	If, after shared decision making, it is decided to screen an asymptomatic child with normal growth and development with pituitary MRI, then the initial scan could be performed from the age of 15 years. (Changed)	Suggestion
Management		
#48	When a pituitary adenoma is diagnosed in a patient with MEN1 management according to sporadic pituitary adenoma guidelines is recommended. (Unchanged)	Recommendation (92%)
<b>Genetic testing in apparently sporadic MEN1-related tumours</b>		
#49	Offer genetic testing including <i>MEN1</i> , to patients with apparently sporadic primary hyperparathyroidism aged <30 years and/or patients with multi-gland disease. (Unchanged)	Suggestion
#50	In patients aged <40 years diagnosed with an apparently sporadic solitary pancreatic neuroendocrine tumour, genetic testing for <i>MEN1</i> can be considered. (New)	Consideration
#51	<i>MEN1</i> genetic testing can be considered in adults aged <30 years with an apparently sporadic, functioning pituitary adenoma (with the exception of a microprolactinoma in women) or a non-functioning pituitary adenoma >1 cm. (New)	Consideration
#52	Genetic testing, including <i>MEN1</i> , should be considered in children and adolescents with an apparently sporadic pituitary adenoma. (New)	Consideration
For statement strength: recommendations are statements that reached consensus in the first two rounds (ie, agreement ≥80%); suggestions are statements with near consensus in the first two rounds (ie, agreement 70–79%); and considerations are statements where opinions among experts were more varied in the first two rounds (ie, agreement 51–69%). The percentage agreement is provided for recommendations. Statements that were not part of the first two questionnaire rounds but have been newly developed in the final meetings are indicated as formulated in the paediatric meeting or formulated in the neuroendocrine tumour meeting. The changes compared with the previous guideline(s) are described for each of the statements. A summary of the final discussions for each statement, with details, nuances, and caveats are provided in the appendix (pp 26–33).		
<b>Table 2: Final Delphi statements</b>		

recommendations are intended for: patients with MEN1 who might be genetically confirmed or obligate carriers (statement 1; figure 2); patients developing endocrine tumours at an early age and hence there is suspicion of MEN1 (statements 49, 50, 51, and 52; figure 3); asymptomatic children of a parent with MEN1 (statement 4; figure 4) and other first-degree relatives of patients with MEN1; and in some cases for patients with clinical MEN1 who do not have *MEN1* mutations (ie, are mutation-negative).<sup>27</sup>

Screening should commence in childhood (statements 4, 6, 7, 22, 23, 25, 43–47; table 3; figure 4) and clinical evaluation, including routine auxological evaluation and assessment of pubertal status, is an essential part of this screening (statement 43). Parents with MEN1 should have an initial consultation (with or without the child present) with a paediatric endocrinologist when the child is aged around 5 years (statement 4). Symptoms of clinical manifestations of MEN1 (with specific emphasis on symptoms of hypoglycaemia and deviation from typical patterns of growth and puberty) should be discussed and shared decision making undertaken regarding screening and surveillance plans (statement 4; figure 4). In asymptomatic children, biochemical screening should consist of serum albumin-adjusted calcium measurements, although some centres might prefer to use ionised calcium, at 1–3-year intervals (statement 6). Additionally, we suggest measuring serum prolactin and insulin-like growth factor 1 (IGF-1) to screen for hormone-secreting (ie, functioning) pituitary adenomas (statement 44; table 3). There is no consensus regarding the need for fasting serum gastrin measurement in childhood (statement 25). Initiating biochemical

screening from the age of 10 years can be considered (statements 7 and 45). We recommend screening for pancreatic neuroendocrine tumours with MRI, starting with an initial scan at age 10–15 years (statement 22; table 3), and repeat scans at 2–3-year intervals if negative (statement 27; table 3). There was no consensus on the benefit of pituitary MRI screening in asymptomatic children with typical growth and development (statement 46), but if screening with pituitary MRI is preferred, then it is suggested that this commences from age 15 years (statement 47; table 3).

Adults are recommended to have a clinical consultation and undergo biochemical screening (figure 2; figure 3) at least once per year and also have regular abdominal, pituitary, and thoracic imaging (table 2; table 3). Screening history and physical examination should be directed towards 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 (statements 5 and 24; table 3), with more specific endocrine function tests being undertaken in individuals who have symptoms or signs of a clinical syndrome. Recommendations for radiological screening include an abdominal MRI, encompassing the pancreas and adrenal glands, every 2–3 years (statements 21 and 27), and MRI of the pituitary every 3–5 years (statements 40 and 41; table 3). Screening for thoracic neuroendocrine tumours, including bronchial



**Figure 2: Flowchart for patients with a clinical diagnosis of MEN1 or who are 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 (ie, 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 pituitary adenoma (radiologically) by age 75 years, can continue screening by clinical exam and biochemistry alone. Index cases with clinical MEN1 and no identified MEN1 mutation (ie, 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 pp 34, 35). Patients with clinical MEN1 and no mutation should undergo initial evaluations and screening similar to those with a MEN1 mutation. However, screening in patients who are MEN1 mutation-negative, who tend to have a more indolent clinical course when compared with patients with MEN1 mutations, should be considered more in the context of the family history and associated clinical phenotypes.<sup>21</sup> \*Suspicion for MEN1, detailed in the panel. †Genes reported to be associated with phenocopies, as detailed in table 1 and appendix (p 35). ‡Detailed in the appendix (p 34). §Abdominal MRI can be performed to screen for pancreatic and adrenal nodules. However, if detailed views of the pancreas cannot be obtained, a dedicated pancreatic MRI is also recommended. ¶Further details in tables 2 and 3 and the appendix (pp 15–33). ||Statements 5–7, table 2.

\*\*Statements 21–27, table 2. ††Statements 41–47, table 2. ‡‡Statements 35–37, table 2.

and thymic neuroendocrine tumours (also referred to as carcinoids), should begin in adulthood, at ages 20–25 years (statement 36). We suggest imaging for

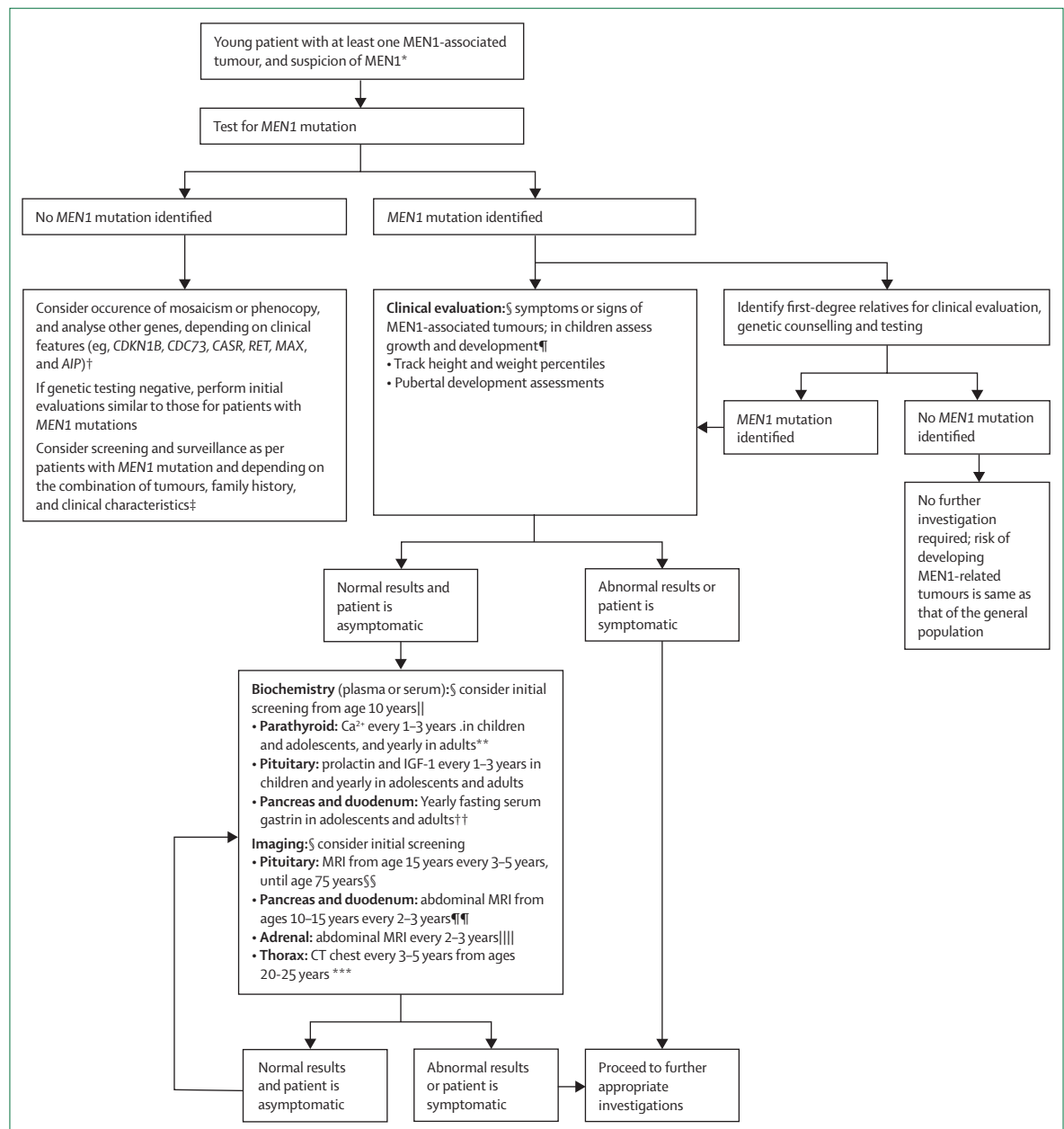
these neuroendocrine tumours using CT every 3–5 years (statements 35–37; table 3), as MRI of the chest is reported to be not the optimal imaging modality for

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.<sup>29,30</sup> Screening for thymic neuroendocrine tumours 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 neuroendocrine tumours with a potentially rapid and aggressive course. MRI screening for pituitary adenomas can be stopped at age 75 years in asymptomatic patients with

negative pituitary imaging and normal biochemistry (statement 42). Screening for breast cancer in women with MEN1 from age 40 years has also been proposed,<sup>31</sup> 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 patients with MEN1

Recommendations will focus on MEN1-specific aspects of the management of tumours. When there is insufficient evidence for MEN1-related tumours, reference to appropriate clinical practice endocrine, neuroendocrine, and oncology guidelines is 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, which are the hallmarks of primary hyperparathyroidism.<sup>4,12,24,32–35</sup> Primary hyperparathyroidism 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

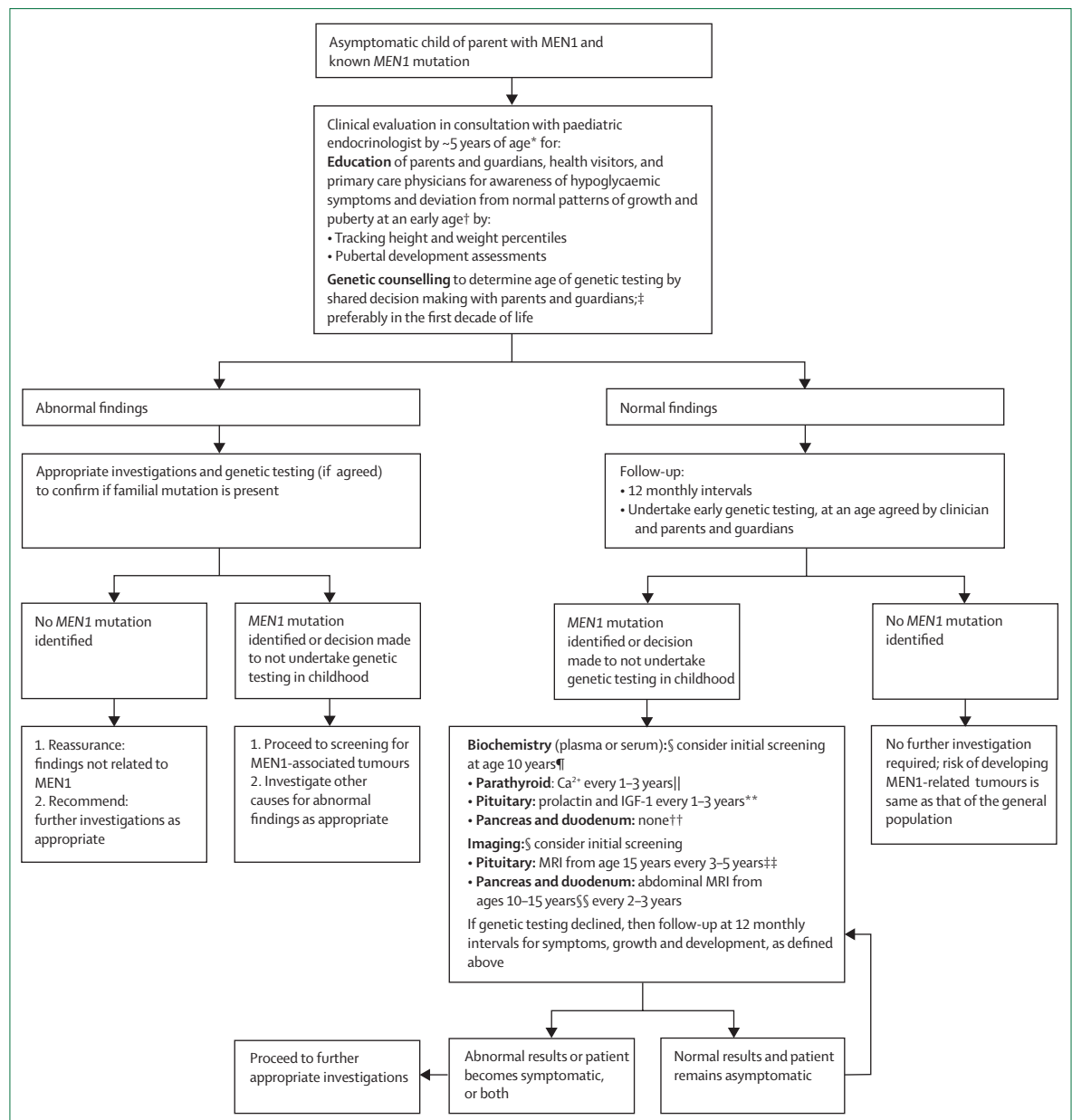
**Figure 3: Flowchart for young patients with at least one MEN1-associated tumour**

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 testing 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, 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 general 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 (figure 2). In children (aged <19 years), the initial clinical evaluation should include a detailed history and examination looking for abnormalities in growth (eg, 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 or guardians, and clinician. If an abnormality is detected, then these individuals should undergo further appropriate tests and treatment. Children younger than 19 years 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 or guardians and clinicians. 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; appendix pp 34, 35). Patients with clinical MEN1 and no MEN1 mutation (ie, MEN1 mutation-negative) should undergo initial evaluations and screening similar to those with MEN1 mutations. However, screening in these patients who are MEN1 mutation-negative, who tend to have a more indolent clinical course when compared with patients with MEN1 mutations, should be considered more in the context of the family history and associated clinical phenotypes.<sup>21</sup> Young patient refers to patients with primary hyperparathyroidism younger than 30 years, patients with pancreatic neuroendocrine tumours younger than 40 years, and patients with pituitary adenomas younger than 30 years; statements 49–52 (panel; appendix pp 15–33). \*Suspicion for MEN1, detailed in panel. †Genes reported to be associated with phenocopies, as detailed in table 1 and appendix (p 35). ‡Detailed in the appendix (p 34).<sup>27</sup> §Further details in tables 2 and 3 and the appendix (pp 15–33). ¶Statement 43, table 2. ||There is no consensus on the exact age to start screening in children (aged <19 years); statements 7, 25, and 45, table 2. \*\*Statements 5–7, table 2. ††Statements 44 and 45, table 2. ‡‡There is no consensus regarding screening with fasting serum gastrin in childhood; statements 23–26, table 2. §§There is no consensus on the benefit of MRI screening for a pituitary adenoma in asymptomatic children with normal growth and development; statements 40–42, 46, and 47, table 2. ¶¶Statements 21, 22, and 27, table 2. ||||Abdominal MRI can be performed to screen for pancreatic and adrenal nodules; however, if detailed views of the pancreas cannot be obtained, a dedicated pancreatic MRI is also recommended. \*\*\*Statements 35–37, table 2.

tumour.<sup>21</sup> Primary hyperparathyroidism is usually asymptomatic in children with MEN1, but might 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) primary hyperparathyroidism, parathyroid disease in MEN1 is multiglandular, with glands often affected asynchronously.<sup>36</sup> The occurrence of parathyroid carcinoma is rare (<1%) in MEN1 and similar to that in patients with sporadic primary hyperparathyroidism.<sup>37</sup> However, the female preponderance seen in sporadic primary hyperparathyroidism is absent in MEN1, and primary hyperparathyroidism in MEN1 is associated with more severe bone mineral loss and kidney complications.<sup>38–41</sup> However, in a 2024 publication of a contemporary cohort, BMD was within the normal range a decade after initial parathyroidectomy, although BMD was still reduced compared with population control individuals.<sup>42</sup> Thus, screening patients with MEN1 for primary hyperparathyroidism is important and, once diagnosed, patients should be evaluated for potential disease sequelae.

### Assessment of target organ involvement

There is scarce evidence available regarding the assessment and monitoring of target organ involvement in MEN1-related primary hyperparathyroidism. Therefore, we recommend following the guidelines from the Fifth International Workshop on Primary Hyperparathyroidism<sup>43</sup> to assess and monitor target organ involvement in adult patients with MEN1 with primary hyperparathyroidism (statements 8 and 11). However, in young (ie, age <30 years), prospectively screened patients with MEN1 at initial diagnosis of primary hyperparathyroidism, assessment of renal and skeletal involvement constitutes more of a baseline measurement than a test to inform or 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 primary hyperparathyroidism 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-h urinary calcium excretion and abdominal imaging only if clinically needed.<sup>43</sup> For evaluation of skeletal involvement, three-site (ie, 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.<sup>43</sup> As patients with MEN1



**Figure 4: Flowchart 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 or guardians, clinicians, and a 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 or 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 and treatment undertaken depending on the 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 programme for *MEN1*. \*In some countries, consultation with a paediatric endocrinologist might be earlier. †Statement 43, table 2 and appendix (pp 15–33). ‡This can be with or without the child present. §Further details in table 2 and the panel. ¶There is no consensus on the exact age to start screening in children; statements 7, 25, and 45, table 2. ||Statements 6 and 7, table 2. \*\*Statements 43–45, table 2. ††There is no consensus regarding screening with fasting serum gastrin in childhood; statement 25, table 2. ‡‡There is no consensus on the benefit of MRI screening for a pituitary adenoma in asymptomatic children with normal growth and development; statements 46 and 47, table 2. §§Statements 22 and 27, table 2.

with primary hyperparathyroidism 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 primary hyperparathyroidism, assessment of renal function is recommended (statement 9), but routine DXA assessment is not recommended (statement 10).

### 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, primary hyperparathyroidism can often be observed from the outset and it is not necessary to operate immediately at the initial diagnosis of primary hyperparathyroidism in these patients (statement 12). Ideally, the timing of the initial operation is planned after shared decision making with the patient, parents or guardians if applicable, the (paediatric) endocrinologist, and the surgeon, taking into account serum albumin-adjusted calcium concentrations, symptoms, and wellbeing, the presence of target organ involvement, and the patient's personal circumstances, including access to an expert parathyroid surgeon, who performs at least 40–50 parathyroidectomies per year (ie, high-volume), and has experience in the challenging procedures required for hereditary forms of primary hyperparathyroidism, paediatric patients, primary hyperparathyroidism without unequivocal preoperative localisation, and reoperations.<sup>44,45</sup> 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, if there are symptoms of primary hyperparathyroidism, or if there is evidence of target organ involvement, or a combination of these (statements 13–15). 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 (statement 16).

Planning for beyond the initial operation also needs to be considered when managing patients with MEN1-related primary hyperparathyroidism, which is a multi-gland disease, although glands might be affected asynchronously. Most 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 subtotal parathyroidectomy with concomitant transcervical thymectomy to remove supernumerary parathyroid

	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 tumours	10 years (annual)*	Calcium	NA	NA
Duodenopancreatic neuroendocrine tumours				
Non-functioning pancreatic neuroendocrine tumour	NA	NA	10–15 years (every 2–3 years)	Abdominal MRI
Gastrinoma	>18 years (annual)	Fasting gastrin†	NA	NA
Insulinoma	5 years (annual)	NA‡	NA	NA
Pituitary adenomas	10 years (annual)§	Prolactin, IGF-1¶	15 years (every 3–5 years)¶	Pituitary MRI**
Adrenal tumours	NA	NA	10–15 years (every 2–3 years) with pancreatic imaging	Abdominal MRI
Thoracic neuroendocrine tumours	NA	NA	20–25 years (every 3–5 years)	CT chest††

N/A=not applicable. \*In children and adolescents, biochemical screening for primary hyperparathyroidism can occur at 1–3-year intervals, whereas in adults, yearly serum calcium measurements should be performed. Further details in statements 5, 6, 7, and the appendix (pp 15–33). †Annual for adults (recommendation 24), but no consensus reached for childhood screening (statement 25). ‡Screening for insulinoma should be performed by careful assessment for hypoglycaemic symptoms and, if present, further biochemical and imaging evaluation is recommended (statement 23). §Consider initiating biochemical screening at age 10 years (statement 45). ¶In children and adolescents, biochemical screening for pituitary adenoma can occur at 1–3-year intervals, whereas in adults, yearly measurements should be performed. ||Imaging screening for pituitary tumours can be stopped at age 75 years in asymptomatic patients with normal pituitary imaging and biochemistry (statement 42). \*\*No consensus on the benefit of MRI screening in asymptomatic children with normal growth and development (statements 46 and 47). ††Statements 35, 36, and 37.

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

glands, performed by an MEN1-experienced, high-volume, parathyroid surgeon, is the recommended initial operation (statement 17).<sup>17</sup> This procedure 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 of 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 (statement 19) before subtotal parathyroidectomy with transcervical thymectomy in patients with MEN1, although most expert centres would undertake an ultrasound to rule out concomitant disease and to inform on benign lymphadenopathy. However, preoperative imaging studies might be indicated in specific circumstances, such as when a unilateral clearance procedure is being considered (statements 19 and 20).

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.<sup>46–48</sup> 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 procedure comes at the expense of higher rates of persistent disease and shorter time to recurrence.<sup>34,47,49</sup> Unilateral clearance additionally limits the options for generating a viable remnant during subsequent operations, which might affect the long-term risk of hypoparathyroidism.<sup>34</sup> Therefore, in general, we recommend that a subtotal parathyroidectomy should be considered the standard-of-care initial operation in patients with MEN1 (statements 17 and 18). If a unilateral clearance is considered, then preoperative imaging is essential.

In patients with MEN1, any residual parathyroid tissue remaining in situ after surgery has the potential to contribute to disease recurrence, and recurrence rates of around 40–60% have been reported following subtotal parathyroidectomy and around 65–70% for less than subtotal parathyroidectomy.<sup>47,50</sup> The highest primary hyperparathyroidism recurrence rates are reported in studies with follow-up durations exceeding 10 years, thereby suggesting that primary hyperparathyroidism will eventually recur in most patients if monitored for long enough.<sup>34,49</sup> Recurrences might also be caused by supernumerary glands, which have been reported in around 10% of patients with MEN1,<sup>49,51</sup> and failure to identify and resect multiple affected glands, which often occurs in patients in whom the diagnosis of MEN1 was not recognised before surgery.

The indications for reintervention for persistent or recurrent MEN1-related primary hyperparathyroidism are generally the same as for index surgery,<sup>43</sup> 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 primary hyperparathyroidism. 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 previous cervical exploration, particularly if the index procedure was performed by a different surgeon, as the results of this could 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 following the surgery. However, total parathyroidectomy as an index operation with parathyroid autotransplantation, which was described as a surgical option in previous guidelines,<sup>1,2</sup> is no longer recommended because of the associated high risks of prolonged

hypoparathyroidism.<sup>34</sup> Further surgical considerations are described in the Fifth International Workshop on Primary Hyperparathyroidism.<sup>52</sup>

The calcimimetic drug, cinacalcet, which is a positive allosteric modulator of the calcium-sensing receptor, can 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.<sup>53,54</sup> However, the effects of long-term cinacalcet treatment on BMD, hypercalciuria, and prevention of nephrolithiasis in patients with MEN1 are not known, although in patients without MEN1 with primary hyperparathyroidism, cinacalcet has been reported not to affect BMD, and also not to increase urinary calcium excretion or occurrence of nephrolithiasis.<sup>55,56</sup> The side-effects (eg, nausea, arthralgia, diarrhoea, and paraesthesia) associated with cinacalcet, which occur in around 33% of patients, limit its long-term use.<sup>57</sup>

Persistent hypoparathyroidism could have a deleterious effect on quality of life with a substantial financial burden.<sup>58</sup> The incidence of long-term hypoparathyroidism, defined as persisting beyond 12 months after surgery for MEN1-related primary hyperparathyroidism, varies from 6% to 30% and depends on the procedure performed and duration of follow-up.<sup>34,49,51,59</sup> The management of hypoparathyroidism in MEN1 follows the same principles outlined in 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.<sup>60</sup> PTH therapy can also be considered in patients whose hypoparathyroidism is inadequately controlled with conventional therapy.<sup>60</sup> In patients with MEN1, 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.<sup>51</sup>

### Duodenopancreatic neuroendocrine tumours

Duodenopancreatic neuroendocrine tumours are common in individuals with MEN1 and can be the presenting feature in 10–20% of cases.<sup>32,33,35,61</sup> Non-functioning pancreatic neuroendocrine tumours, which are either non-hormone secreting or secrete pancreatic polypeptide, which is not associated with any hormonal syndrome or sequelae, are the most frequently diagnosed duodenopancreatic neuroendocrine tumour,<sup>21</sup> followed by duodenal gastrinomas and insulinomas, whereas other functioning pancreatic neuroendocrine tumours (eg, glucagonomas, VIP-omas, somatostatinomas, and tumours secreting ectopic calcitonin, growth-hormone releasing hormone [GHRH], or adrenocorticotrophic hormone [ACTH]) are rare.<sup>21,22,62,63</sup> As such, ectopic hormone secretion from pancreatic neuroendocrine tumours might result in manifestations of pituitary

hormone hypersecretion (eg, acromegaly or gigantism and Cushing's syndrome), and this should be especially considered in children in whom occurrence of pituitary adenomas is rare, as illustrated by GHRH secretion from a pancreatic neuroendocrine tumour causing gigantism in a patient with MEN1.<sup>64,65</sup> Finally, patients with MEN1 might have synchronous or metachronous occurrence of different pancreatic neuroendocrine tumours, such as non-functioning pancreatic neuroendocrine tumours, gastrinomas, and insulinomas.<sup>22</sup>

### Clinical manifestations, diagnosis, and management of non-functioning pancreatic neuroendocrine tumours

The cumulative probability of non-functioning pancreatic neuroendocrine tumours increases steadily, rising from over 8% at age 15 years to 80% by age 80 years.<sup>66</sup> These tumours are mostly detected by surveillance imaging and are only rarely associated with symptoms secondary to local mass effects. However, such tumours represent the leading cause of premature mortality in MEN1 due to distant (ie, hepatic) metastases that can develop in 15–20% of patients.<sup>11,67,68</sup> The outcomes of the systematic review would suggest that active surveillance could be pursued for stable MEN1-associated non-functioning pancreatic neuroendocrine tumours measuring 2 cm or less, 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 events.<sup>17</sup> Moreover, confounding factors could have arisen because of the indication for surgery for non-functioning pancreatic neuroendocrine tumours measuring 2 cm or less that showed growth on serial imaging, and hence there might 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 might be prudent. We therefore suggest that for pancreatic neuroendocrine tumours measuring 2 cm or less under surveillance, imaging intervals should be individualised and based on observed growth rate and absolute size. In newly diagnosed non-functioning pancreatic neuroendocrine tumours measuring 2 cm or less, imaging should be repeated after 6–12 months and, if stable, again after 12 months. If the tumour remains stable with a growth rate less than 1 mm/year, the surveillance interval can be lengthened to every 1–2 years (statement 28). MRI remains the basis for surveillance of non-functioning pancreatic neuroendocrine tumours, with somatostatin receptor scintigraphy-PET imaging and endoscopic ultrasound being reserved for use in circumstances in which their results will affect management (statements 30 and 31). Thus, it is recommended that somatostatin receptor scintigraphy-PET-CT or somatostatin receptor scintigraphy-PET-MRI should be

performed for staging in patients scheduled for duodenopancreatic surgery, as the outcomes might alter the surgical strategy (statement 29). At present, there is no role for routine endoscopic ultrasound-guided biopsy (statement 32). Surgery should be considered for growing non-functioning pancreatic neuroendocrine tumours and those larger than 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,<sup>69,70</sup> with a median age of onset in the third to fifth decade of life.<sup>11,71,72</sup> Despite their small size, local lymph node metastases are reported in around 80% of patients, but these do not appear to have an adverse effect on survival.<sup>67,73</sup> However, distant metastases occur in around 25% of patients and are an important cause of MEN1-related mortality.<sup>73</sup> Hypersecretion of gastrin leads to excessive gastric acid secretion with subsequent peptic ulceration and gastrointestinal bleeding (Zollinger–Ellison syndrome). Traditionally, a diagnosis of gastrinoma is established by a raised fasting gastrin concentration that is elevated at least 10-fold above upper limit of normal, in the absence of proton pump inhibitors, and in association with increased basal gastric acid secretion (gastric pH  $\leq 2$ ).<sup>74–76</sup> However, the widespread use of proton pump inhibitors, the diminished availability of functional tests (eg, secretin stimulation) and assessment of basal acid output, and the high risk of proton pump inhibitor cessation, make it challenging to establish a diagnosis.<sup>76</sup> Therefore, alternative diagnostic criteria have been proposed and these are characteristic symptoms combined with elevated fasting serum gastrin and the presence of a duodenopancreatic neuroendocrine tumour with positive somatostatin receptor scintigraphy imaging (or positive gastrin staining on biopsy), as described in the European Neuroendocrine Tumor Society guidelines.<sup>76</sup> Diagnosis can be even more challenging in prospectively screened patients with MEN1 as they might 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 can occur with larger and more readily visible non-functioning pancreatic neuroendocrine tumours. In this setting somatostatin receptor scintigraphy-PET-CT, MRI, or oesophago-gastroduodenoscopy with endoscopic ultrasound can be particularly useful (statements 30 and 31). Patients who are symptomatic should undergo oesophago-gastro-duodenoscopy, and this is also suggested in all patients with elevated fasting serum gastrin levels to look for



signs of Zollinger–Ellison syndrome, a duodenal primary and gastric neuroendocrine tumour (statements 33 and 34).

Patients with MEN1 and gastrinomas have been reported to have 5-year survival rates of 80–90%, 10-year survival rates of 65–95%, and 20-year survival rates of 60–90%.<sup>76</sup> The goals of treatment are to control symptoms and 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 sequelae with adequate doses of proton pump inhibitors, and this is often highly successful. Thus, the primary goal of surgery for gastrinomas, unlike other functioning pancreatic neuroendocrine tumours associated with MEN1, is to reduce the risk of metastatic disease. However, extensive surgery that 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 might also have concomitant pancreatic neuroendocrine tumours.<sup>76</sup> Apart from a severely elevated fasting serum gastrin, there are no accurate prognostic factors to predict risk of gastrinoma-related distant metastases.<sup>21</sup> 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 patients with MEN1 is 30 years,<sup>77</sup> although insulinomas have been reported in children with MEN1 as young as age 5–6 years.<sup>32,33</sup> Insulinomas typically present with Whipple's triad: hypoglycaemic symptoms, a plasma glucose concentration lower than 3.1 mmol/L (<55 mg/dL), and resolution of symptoms after glucose administration. In prospectively screened patients with MEN1, initial signs and symptoms can be subtle and establishing the diagnosis could take a prolonged time. Most MEN1-related insulinomas are benign and solitary, although up to one-third of patients with MEN1 might have multiple insulinomas that are distributed throughout the pancreas.<sup>77</sup> The diagnosis is established with a 72-h fast, similar to that in patients without MEN1 with insulinomas.<sup>76,78</sup> Preoperative localisation can be challenging due to the presence of other concomitant functioning and non-functioning duodenopancreatic neuroendocrine tumours and it is important to note that the largest tumour identified by imaging might not correspond to the pancreatic neuroendocrine tumour responsible for insulin overproduction. Functional imaging techniques for differentiating insulinomas from other contemporaneous

duodenopancreatic neuroendocrine tumours are currently under investigation. For example, 68Ga-exendin-4 PET–CT uses 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.<sup>16,79</sup> In some cases, selective intra-arterial calcium stimulation and hepatic venous sampling might help to regionalise the insulin-secreting neuroendocrine tumour.<sup>76</sup> Surgery is the mainstay of insulinoma treatment and is associated with excellent long-term hypoglycaemia-free outcomes.<sup>77</sup> 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.<sup>77,80</sup>

### Management of metastatic duodenopancreatic neuroendocrine tumours

In the absence of MEN1-specific evidence regarding the management of advanced or metastatic duodenopancreatic neuroendocrine tumours, we recommend following the current clinical practice guidelines for metastatic duodenopancreatic neuroendocrine tumours that are appropriate for patients with and without MEN1.<sup>76,81–85</sup>

### Gastric neuroendocrine tumours

Type 2 gastric neuroendocrine tumours (also referred to as enterochromaffin-like cell carcinoids) are observed in 15–70% of patients with MEN1 with coexistent hypergastrinaemia and are frequently detected incidentally at the time of upper gastrointestinal endoscopy.<sup>86,87</sup> The tumours are usually small (eg, <1.5 cm) and multiple,<sup>88</sup> and somatostatin receptor scintigraphy might show increased uptake in the stomach. Usually, these gastric neuroendocrine tumours are indolent and can be followed by regular endoscopy. Larger or growing gastric neuroendocrine tumours can be treated by endoscopic resection, although treatment with somatostatin analogues (octreotide or lanreotide), has also been reported to result in regression of these tumours.<sup>89</sup> Gastric surgery can 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%.<sup>87</sup>

### Thoracic neuroendocrine tumours

MEN1-related thoracic neuroendocrine tumours, which comprise bronchopulmonary neuroendocrine tumours and thymic neuroendocrine tumours, are usually non-hormone secreting (ie, non-functioning), although rarely they might secrete hormones.

### Thoracic neuroendocrine tumours and hormonal syndromes

Thoracic neuroendocrine tumours can present with carcinoid syndrome or a syndrome due to ectopic



hormone secretion, such as Cushing's syndrome from ACTH or corticotropin-releasing hormone production, acromegaly from GHRH secretion, hypercalcaemia from PTH-related peptide secretion, or flushing and diarrhoea from hypercalcaemia. The management of these neuroendocrine tumours and syndromes in patients with MEN1 is the same as that reported in clinical practice guidelines for patients without MEN1.<sup>90-94</sup>

### Clinical manifestations, diagnosis, and management of bronchopulmonary neuroendocrine tumours

Bronchopulmonary neuroendocrine tumours in MEN1 generally have an indolent course, with a tumour doubling time of around 12 years and are associated with favourable long-term survival rates.<sup>95,96</sup> Histologically confirmed bronchopulmonary neuroendocrine tumours are observed in approximately 5% of patients with MEN1, although radiologically suspected lesions have a much higher prevalence, ranging from 20% to 30%.<sup>13,97-99</sup> Earlier reports suggested a female predominance, although this has not been supported by studies since 2000.<sup>95,96,99</sup> Bronchopulmonary neuroendocrine tumours are primarily seen in adults, with only two documented cases in adolescents.<sup>12,100</sup>

Small bronchopulmonary neuroendocrine tumours in patients with MEN1 can be followed with active surveillance instead of surgery (statement 38). However, this decision will depend on the tumour size, location, multiplicity, and other patient characteristics, such as other MEN1-related tumours, comorbidities 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 neuroendocrine tumours of 2 cm or less, 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 (statement 39). Bronchopulmonary neuroendocrine tumours 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 neuroendocrine tumours, although this can be considered in fit patients with a high risk of relapse.<sup>92,101,102</sup> Distant metastatic disease is seen in 3–16% of patients with MEN1.<sup>96,103</sup> 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.<sup>85,92,102</sup>

### Clinical manifestations, diagnosis, and management of thymic neuroendocrine tumours

Thymic neuroendocrine tumours have been reported in approximately 2–8% of individuals with MEN1,<sup>95,98,104,105</sup> yet they account for up to 20% of MEN1-related deaths due to their aggressive nature.<sup>11</sup> Over 50% of patients present with distant metastases, with a 10-year survival rate of

33%.<sup>104</sup> The median age at diagnosis is in the fifth decade. Thymic neuroendocrine tumours predominantly develop in male individuals with MEN1, although this sex predominance is reported to be less pronounced in East Asian cohorts.<sup>95,98,104,106</sup> Thymic neuroendocrine tumours are typically non-functional and therefore, screening is dependent upon imaging. A substantial challenge lies in their early detection, as most reported cases have not been identified during routine surveillance.

Screening for thymic neuroendocrine tumours can result in their earlier detection and at a smaller size. Surgery is considered to be the treatment of choice for such locoregional disease.<sup>107</sup> There is no evidence for benefit from routine adjuvant therapy after resection, although the European Society for Medical Oncology 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.<sup>92</sup> In the absence of MEN1-specific evidence regarding the management of advanced or metastatic thymic neuroendocrine tumours, we advise following the treatment guidelines reported for patients without MEN1.<sup>85,92</sup> Complete resection of the thymus is not achievable by transcervical thymectomy performed concomitantly with the index subtotal parathyroidectomy. Therefore, although reducing the thymic tissue volume might lower the risk for thymic neuroendocrine tumour development, these tumours can still occur despite preceding transcervical thymectomy.<sup>108</sup>

### Pituitary adenomas

#### Clinical manifestations, diagnosis, and management of pituitary adenomas

The prevalence of pituitary adenomas ranges from 36–52% and pituitary adenomas might be the first clinical manifestation of MEN1 in around 15% of patients.<sup>14,109-113</sup> The mean age of diagnosis of pituitary adenomas is in the fourth decade, but with a wide range.<sup>23,109-112</sup> Most pituitary adenomas in MEN1 are hormone-secreting (52–85%)<sup>14,109,110,113</sup> and follow a similar distribution to sporadic pituitary adenomas, with prolactinomas being the most common subtype (43–79%), closely followed by clinically non-functioning pituitary adenomas (15–43%),<sup>109-112</sup> somatotrophinomas (4–9%; gigantism or acromegaly), corticotrophinomas (1–4%; Cushing disease), and thyrotrophinomas (<1%). Clinical manifestations of pituitary adenomas in patients with MEN1 are similar to those in patients without MEN1, and it is recommended that their investigation should be according to the appropriate clinical guidelines (statement 48).<sup>2,114-116</sup> Plurihormonal pituitary adenomas are more commonly seen in patients with MEN1 than those without MEN1.<sup>117</sup> These tumours usually co-secrete prolactin and one or more other anterior pituitary hormones, such as growth hormone. Sommatolactotrophinomas (growth hormone-secreting and prolactin-secreting pituitary adenomas) are reported in

around 4% of patients with MEN1. Multifocal pituitary adenomas are infrequent, but still more common than in patients without MEN1 with pituitary adenomas.<sup>117</sup> Pituitary adenomas in patients with MEN1 were previously reported to be larger, more aggressive, and less responsive to surgical and medical treatment, when compared with patients without MEN1,<sup>112,117–119</sup> although this has not been confirmed in independently performed (population-based) studies.<sup>109,110,113</sup> Nevertheless, several studies of MEN1 families have reported young patients with pituitary macroadenomas, that were invasive and therapeutically challenging.<sup>112,117–119</sup> Therefore, asymptomatic individuals with a *MEN1* mutation are advised to commence biochemical screening from age 10 years and radiological screening from age 15 years (table 3). Our systematic review revealed that dopamine agonist (eg, cabergoline, bromocriptine, or quinagolide) resistance in prolactinomas was not more common in patients with MEN1 than patients without MEN1,<sup>17</sup> hence confirming that use of dopamine agonist for treatment of prolactinomas is appropriate in patients with MEN1, although the GRADE levels (scores) for this were very low. Management and treatment of MEN1-associated pituitary adenomas is similar to that in patients without MEN1, and we recommend following the appropriate clinical practice guidelines for pituitary adenomas (statement 48).<sup>93,94,114–116,120–123</sup>

### Adrenal cortical tumours

#### Clinical manifestations, diagnosis, and management of adrenal cortical tumours

Adrenocortical adenomas have been reported in around 40% of patients with MEN1 by age 80 years,<sup>24</sup> compared with 10% in the general population.<sup>124</sup> The prevalence of adrenocortical adenomas in patients with MEN1 is reported to range from over 3% to around 25%<sup>3,14,111,125</sup> with a mean age of diagnosis of 40–47 years.<sup>14,24,111,125</sup> Most patients are asymptomatic, as most of these tumours are non-functioning, although manifestations of hormonal hypersecretion occur in less than 10% of patients, and among these primary hyperaldosteronism (Conn's syndrome) and ACTH-independent Cushing's syndrome are the most common.<sup>125,126</sup> Pheochromocytomas, which are tumours of the adrenal medulla and one of the main manifestations of MEN2 (table 1), are reported to occur rarely in patients with MEN1, and represent less than 2% of adrenal tumours.<sup>127,128</sup> Pheochromocytomas occurring in patients with genetically proven MEN1 (ie, 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,<sup>127,128</sup> 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 adrenocortical carcinoma is around 1% in patients with MEN1, but it is higher (ie, 10–15%) in patients with

MEN1 with adrenal tumours larger than 1 cm.<sup>126</sup> If functional, adrenocortical carcinomas most commonly secrete cortisol or sex steroids, or both. Biochemical investigation (eg, plasma renin and aldosterone concentrations, low-dose dexamethasone suppression test, plasma and urinary metanephrines, and serum dehydroepiandrosterone sulfate in all individuals and testosterone in female individuals) should be undertaken for those with symptoms or signs suggestive of functioning adrenal tumours, adrenocortical carcinoma, or tumours larger than 1 cm.<sup>2</sup> 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 adrenocortical adenomas as most are benign.<sup>2</sup> However, the risk for malignancy is increased if the tumour has a diameter larger than 4 cm, although adrenocortical carcinomas have been identified in tumours smaller than 4 cm in patients with MEN1.<sup>2,126</sup> Surgery is recommended for adrenal tumours that are larger than 4 cm in diameter, have atypical or suspicious radiological features (eg, increased Hounsfield units on unenhanced CT) and are 1–4 cm in diameter, or show measurable growth over a 6-month interval.<sup>2,126</sup> The treatment of functioning (ie, secreting) adrenal tumours in patients with MEN1 is similar to that for tumours occurring in patients without MEN1.<sup>2,124,129</sup>

### Non-endocrine manifestations

#### Breast cancer

Women with MEN1 might have a 2–3 fold increased risk of breast cancer developing at an earlier age, when compared with the general population.<sup>31,130</sup> Studies of breast cancer in women with MEN1 have reported menin expression to be reduced<sup>131</sup> or increased,<sup>132</sup> 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 (eg, 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 programme in other countries.<sup>31</sup> 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

Patients with MEN1 can develop angiofibromas and collagenomas of the skin and lipomas, which occur in

around 30% of patients with MEN1.<sup>131</sup> 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.<sup>131</sup> Leiomyosarcomas or other sarcomas rarely occur, and it is important to note that on [<sup>18</sup>F]fluorodeoxyglucose ([<sup>18</sup>F] FDG)-PET-CT, hibernomas (benign rare brown fat tumours) might be mistaken for these malignant lesions.<sup>133,134</sup> Melanoma has been reported in some patients with MEN1, but at present there is not sufficient evidence to consider this as part of MEN1.<sup>131</sup>

### Meningiomas and ependymomas

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

### Genetic testing in the diagnosis of MEN1

A diagnosis of MEN1 can be established in an individual by one of three criteria (panel). First, on the basis of the occurrence of two or more main MEN1-associated endocrine tumours (ie, parathyroid neoplasms, duodeno-pancreatic neuroendocrine tumours, and pituitary adenomas), which is referred to as clinical MEN1. Second, due to 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 third, by identification of a germline *MEN1* mutation in an individual, who might be asymptomatic and has not yet developed serum biochemical or radiological abnormalities indicative of tumour development, referred to as genetic *MEN1*. However, the diagnosis of genetic *MEN1* can be challenging to establish if a DNA sequence variant of uncertain (or unknown) significance (also known as VUS; appendix p 3) is identified. This scenario 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 five-category classification of DNA sequence variants.<sup>9</sup> 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 there is 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 p 3).<sup>9</sup> A diagnosis of genetic *MEN1* can also be challenging to establish if patients with clinical MEN1 are found to not have a *MEN1* mutation (ie, *MEN1* mutation-negative; appendix p 34), whereas

#### Panel: Suggested approach for *MEN1* germline mutation analysis in a clinical setting

##### Value in clinical setting

- Aids in diagnostic confirmation
- Identifies germline mutation carriers in a family for screening and development of tumours, thereby facilitating early diagnosis and treatment
- Identifies the 50% of family members who do not have the *MEN1* mutation, thereby alleviating the anxiety and burden of disease from these individuals and their offspring

##### Who should be tested?

- Index case patients with two or more classical MEN1-associated tumours
- First-degree relatives of a family member with a known *MEN1* germline mutation, clinical MEN1, or family history suggestive of endocrine tumours
- Suspicion of MEN1:
  - Primary hyperparathyroidism: individuals with apparently sporadic primary hyperparathyroidism younger than 30 years,\* multi-gland primary hyperparathyroidism,\* or family history of primary hyperparathyroidism or other MEN1-associated disorders
  - Pancreatic neuroendocrine tumours: individuals with a gastrinoma† or multiple pancreatic neuroendocrine tumours† at any age, or apparently sporadic pancreatic neuroendocrine tumours younger than 40 years‡
  - Pituitary adenomas: adults younger than 30 years with apparently sporadic, functioning pituitary adenomas (with the exception of microprolactinoma in female individuals), or non-functioning pituitary adenoma larger than 1 cm;‡ children and adolescents younger than 19 years with an apparently sporadic pituitary adenoma‡
  - Individuals with a thymic neuroendocrine tumour†§ at any age
  - Atypical for MEN1 (ie, development of two non-classical tumours; eg, parathyroid and adrenal tumours)†

##### When should testing be done?

Within the first decade of life or at clinical diagnosis

##### Where should testing be performed?

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

\*Genetic testing suggested; statement 49, table 2 and appendix (pp 15–33).<sup>42</sup> †Genetic testing recommended.<sup>28</sup> ‡Genetic testing should be considered; statements 50–52, table 2. §25% of reported thymic neuroendocrine tumours are MEN1-associated.<sup>21</sup>

diagnoses of clinical MEN1 and familial MEN1 might be confounded by the occurrence of phenocopies (appendix p 35).<sup>2,16,25,136</sup>

### Variants of uncertain significance

Most (~75%) of *MEN1* variants identified in patients are disease-causing mutations (ie, pathogenic or likely pathogenic), based on the ACMG and the AMP classification<sup>9</sup> (appendix p 3), as they are nonsense mutations or frameshifting alterations that predict truncations of the menin protein.<sup>14,24,137</sup> However, the remaining variants (~25%) are missense and in-frame indels, and a subset of these would be classified as variants of uncertain significance.<sup>24</sup> Interpretation of variants of uncertain significance following *MEN1* genetic testing is a major challenge and poses difficulties in making clinical decisions for patients with MEN1.<sup>24,138</sup> For example, of 122 *MEN1* missense variants identified from the French oncogenetics network of neuroendocrine

tumours (TENGEn), around 60% were classified to be pathogenic or likely pathogenic variants using TENGEn criteria but less than 30% were classified as pathogenic or likely pathogenic variants using the ACMG–AMP guidelines; importantly, 20 of the ACMG–AMP variants of uncertain significance were found in patients with clinically authentic MEN1 disease.<sup>138</sup> Such variances in the classification of *MEN1* missense variants can have major adverse effects on the clinical management of patients and their families. TENGEn therefore proposed locus-specific adjustments based on assessments of the patient's phenotype and family history, to the ACMG–AMP framework, for use in interpreting *MEN1* missense variants.<sup>138</sup> Other studies have used in silico thermodynamic and structural analysis of menin to further evaluate the pathogenicity of a variant of uncertain significance (appendix p 3). 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.<sup>9,138</sup>

#### **MEN1 mutation-negative patients and phenocopies**

Between 10% and 30% of patients with clinical MEN1 (ie, having two or more MEN1-associated tumours) have not been found to have a germline *MEN1* mutation (ie, *MEN1* mutation-negative; appendix p 34).<sup>27</sup> However, such patients might have mutations in non-coding regions that are not usually interrogated by current genetic testing methods,<sup>139</sup> somatic mosaicism,<sup>140–142</sup> coincidental occurrence of two separate tumours,<sup>143</sup> or represent phenocopies<sup>144</sup> (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 (a method that detects abnormal copy numbers of DNA in specific regions of the genome), or next-generation sequencing multigene (ie, 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 or whole-genome sequencing, which might detect *MEN1* mutations in around 50% of such patients<sup>145</sup> and identify *MEN1* mosaic mutations.<sup>140–142</sup> Patients with clinical MEN1 but who are so-called true negative for a *MEN1* mutation, might represent phenocopies, and have a mutation in another gene that is more typically associated with a different disease (appendix p 35).<sup>144</sup> Such genes can include *CDKN1B*, *RET*, and *MAX*, whose mutations are associated with MEN4, MEN2, and MEN5, respectively (table 1), or *CDC73*, *CASR*, and *AIP* genes (appendix p 35).<sup>144,146</sup> However, the frequencies of *CDKN1B*, *MAX*, *CDC73*, *CASR*, *RET*, and *AIP* mutations in patients who are *MEN1* mutation-negative are not known, although it was estimated that patients

with *CDKN1B* mutations might account for around 3% of MEN1-like individuals,<sup>147</sup> but a recent study of 5600 patients with suspected MEN1 has reported that only four (0.07%) of 5600 patients had *CDKN1B* mutations.<sup>148</sup> At present, we recommend that *MEN1* mutation-negative patients should be tested for mutations of *CDKN1B*, *MAX*, *CDC73*, *CASR*, *RET*, and *AIP*, depending on their clinical phenotype and while noting that other as yet unreported genes might be involved.<sup>143</sup> Moreover, patients with clinical MEN1 who do not have an identified mutation in the *MEN1* gene or other endocrine neoplasia associated genes should be identified, as they are reported to have a more favourable prognosis, have less aggressive disease, and have median ages of first and second tumour manifestation 13 years and 9 years later, respectively, when compared with patients with *MEN1* mutation.<sup>27,149</sup> 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 (age 87 years vs 73 years).<sup>4,27</sup>

Phenocopies have also been reported in the context of familial MEN1, in which a member of the kindred has a clinical manifestation of MEN1 (eg, pituitary adenoma or primary hyperparathyroidism), but is subsequently found not to harbour the familial *MEN1* mutation (ie, 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 identify 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 or 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 (panel). 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 (panel).<sup>150</sup> *MEN1* mutational analysis can 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 (panel) in an index case with two or more *MEN1*-associated endocrine tumours; a first-degree relative of a *MEN1* mutation carrier expressing familial *MEN1* (ie, having symptoms, signs, biochemical, or radiological evidence for one or more *MEN1*-associated tumours); asymptomatic first-degree relatives of a known *MEN1* mutation carrier; and patients with suspicious or atypical *MEN1* (statements 49–52; panel).<sup>150</sup> 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; figure 3). Delays in diagnosis of *MEN1* are common, and a median lag-time of around 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.<sup>151</sup> The delay in diagnosis might be due to multiple reasons, including the relevant information not being available to the patient (or doctors) because they might be unaware of relevant family history. This unawareness might be due to medical information not being shared between family members (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.<sup>151</sup> Also, patients with *MEN1* are naturally anxious about disease occurrence for themselves and their relatives, and this might be compounded by the investigations and regular surveillance screening.<sup>2</sup> There are also potential ethical issues to consider for predictive testing, and therefore individuals should receive appropriate genetic counselling. Presently, approximately 90% 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 or guardian consent, is recommended in the first decade of life.

### Accredited genetic diagnostic laboratories

We recommend that genetic testing be undertaken in accredited genetic diagnostic laboratories (panel) and include DNA sequence analysis using an appropriate method that will detect abnormalities (eg, variants and indels) involving all exonic and splice site regions of the *MEN1* gene. The identified DNA sequence variants (eg, single nucleotide variants and indels) should then be assessed for variant pathogenicity using validated methods, with many testing laboratories adopting the ACMG–AMP guidelines.<sup>28</sup>

### Conclusion

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. Despite the availability of over 3000 studies published during the past decade on the management of tumours of the parathyroids, pancreatic islets, and anterior pituitary in patients with *MEN1*, only 37 (1·2%) of 3048 met the inclusion criteria for our systematic reviews, which nevertheless provided three recommendations for management of these tumours in patients with *MEN1*.<sup>17</sup> We therefore used the Delphi method to address gaps and controversies in screening and surveillance practices for *MEN1* and developed an additional 52 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 patients with *MEN1* having surveillance abdominal MRIs. There is also a need for biomarkers that allow for accurate risk stratification of neuroendocrine tumours, prediction of aggressive pancreatic neuroendocrine tumours, personalised and

### Search strategy and selection criteria

The recommendations outlined in this Review were established by a multidisciplinary group that was convened to undertake systematic reviews and a 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. In brief, MEDLINE Ovid, Embase Ovid, The Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials), and Web of Science were searched from Dec 1, 2001, (ie, after publication of the first *MEN1* guidelines) until Dec 22, 2024, with a combination of free text and MeSH terms without any language restrictions. In addition, to ensure that 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”, “neuroendocrine tumours”, “*MEN1* mutation”, “parathyroid tumours”, “primary hyperparathyroidism”, “pancreatic islet tumours”, “pituitary adenomas”, “prolactinomas”, “somatotrophinomas”, “corticotrophinomas”, “thyrotrophinomas”, “somatolactotrophinomas”, “non-functioning pituitary adenomas”, “gigantism”, “acromegaly”, “Cushing disease”, “adrenal adenomas”, “adrenal cortical tumours”, “Conn’s syndrome”, “Cushing syndrome”, “adrenal carcinomas”, “phaeochromocytomas”, “bronchial carcinoid”, “bronchopulmonary neuroendocrine tumours”, “thoracic neuroendocrine tumours”, “thymic carcinoid”, “hormonal syndromes”, “carcinoid”, “breast cancer”, “lipomas”, “skin tumours”, “melanoma”, “meningiomas”, “ependymomas”, “genetic testing”, “variants of uncertain significance”, “phenocopies”, and “genetic counselling”, and articles published after Dec 1, 2001, until Dec 22, 2024, were selected.

risk-based management strategies, and early detection of thymic neuroendocrine tumours. To enable such research, prospective and well annotated cohorts of patients with MEN1 with clinical biobanks and global collaborations are needed. These will be crucial for facilitating clinical trials and exploring the effectiveness of targeted, non-invasive, or minimally invasive early interventions. In genetic testing, better variant of uncertain significance 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 probable 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.

#### Contributors

MLB, GDV, RVT, CRCP, SGW, FC, NDP, MAL, and CAS were responsible for the conceptualisation of the project and MLB, GDV, and RVT provided resources. MLB, GDV, and RVT were responsible for project supervision, and RVT for project administration. MLB, GDV, RVT, CRCP, SGW, FC, OAS, TC, KEL, FM, and KAE were members of the systematic review working group. GDV was Delphi lead and CRCP was Delphi co-lead; MLB, RVT, SGW, FC, OAS, TC, FM, and KAE were members of the Delphi core group. RVT, GDV, and CRCP were responsible for the methodology. GDV, RVT, CRCP, OAS, KEL, and KAE wrote the original draft, and MLB, GDV, RVT, CRCP, SGW, FC, OAS, TC, KEL, FM, KAE, NDP, MAL, and CAS undertook review and editing of the draft. All authors gave final approval of the version to be published. RVT had the final decision to submit for publication.

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