# Management impact: effects on quality of life and prognosis in MEN1

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## Abstract

Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant endocrine tumor syndrome, caused by inactivating mutations of the *MEN1* tumor suppressor gene at 11q13 locus, which predisposes to develop tumors in target neuroendocrine tissues. As the positional cloning and identification of the causative gene in 1997, genetic diagnosis, by the sequencing-based research of gene mutations, has become an important tool in the early and differential diagnosis of the disease. Application of the genetic test, in MEN1 index cases and in first-degree relatives of mutated patients, has been constantly increasing during the last two decades, also thanks to the establishment of multidisciplinary referral centers and specific genetic counseling, and thanks to the wide availability of high throughput instruments for gene sequencing and gene mutation identification. The *MEN1* genetic test helps the specific diagnosis of probands, and allows the early identification of asymptomatic carriers, strongly contributing, together with progressions in tumor diagnostic techniques and in pharmacological and surgical therapeutic approaches, to the reduction of morbidity and mortality associated with the syndrome. International clinical guidelines for MEN1 have been drafted by panels of specialists in the field, with the main goal to improve the management of the disease and grant patients a better quality of life. Here, we review main recommendations and suggestions derived by the last published general guidelines in 2012, and by most recent published studies about MEN1 syndrome diagnosis, clinical management, therapeutic approaches and patients' quality of life.

**Key Words**

- multiple endocrine neoplasia type 1 (MEN1)
- *MEN1* gene
- international MEN1 guidelines
- clinical management

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## Introduction

Multiple endocrine neoplasia type 1 (MEN1) predisposes to the development of multiple endocrine and non-endocrine tumors in various organs in a single patient. Although the great majority of MEN1 tumors are generally not aggressive, and many of them present a long-term indolent course remaining asymptomatic for years (particularly non-functioning tumors; NFTs), malignant progression, metastatic tumors, as well as excessive hormone-related syndromes and derived complications, manifest in a significant percentage of patients, being responsible for a severely compromised quality of life (QoL) and reduction in life expectance. The recognition of MEN1 tumors in their early stage, the early-started targeted treatments for the control of hormone production and prevention of over-secretion-related complications, and the surgical removal of tumors before their excessive growth, surrounding tissue invasion and metastases development are the best approaches to reduce negative clinical impact of MEN1. In this light, a delay in diagnosis negatively influences patients' QoL and

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survival; the necessity of early diagnosis and intervention is, thus, strongly felt.

Genetic test revealed as a fundamental tool for the early, and even pre-symptomatic, diagnosis and together with constant progressions in tumor diagnostic techniques and in pharmacological and surgical therapies, it has contributed in the last two decades, and still contributes, to the reduction of MEN1-associated morbidity and mortality.

## Twenty years of the *MEN1* gene discovery: from the bench to the bedside

MEN1 has been first described by Erdheim in 1903, but only five decades later its hereditary nature was recognized. The syndrome is caused by inactivating mutations of the tumor suppressor gene *MEN1*, positionally cloned in 1997 at 11q13 locus (Chandrasekharappa *et al*. 1997). The identification and genetic characterization of the causative gene, opened the possibility to the genetic testing and to the early and pre-symptomatic diagnosis of the disease. Over 1500 *MEN1* loss-of-function different mutations (1341 germinal and 203 somatic variants) have been described up to September 2015 (Lemos & Thakker 2008, Concolino *et al*. 2016), the great majority of them giving a truncated protein unable to reach the nucleus and exert its anti-oncogenetic functions. Approximately 10% of patients have *de novo* mutations, developed at embryonic level, and, thus, lack of a family history.

Genetic test of *MEN1* is recommended for clinical index cases with two or more MEN1-associated endocrine tumors (for the confirmation of clinical diagnosis), for first-degree relatives and family members of known *MEN1* mutation carriers, and also for patients with suspicious MEN1 phenotype (i.e. hyperparathyroidism before the age of 30, a multiglandular involvement, multiple and/or recurring pancreatic neuroendocrine tumors (pNETs) at any age). Asymptomatic members of a mutation-bearing family should undergo genetic screening as early as possible, better before the age of 5 years. A positive *MEN1* genetic test is indication for periodic biochemical and imaging screenings for MEN1-associated tumor detection, and for the early choice of the appropriate surgical and/or pharmacological treatment. Unfortunately, no correlation between the specific *MEN1* mutation or a specific affected region of the gene and the MEN1 clinical phenotype has been described. It is not possible to foresee clinical manifestations based on the result of genetic test, and, thus, to personalize tumor prevention; all MEN1 patients and mutations carriers undergo the same standardized and periodical clinical surveillance program (Table 1), according to the MEN1 clinical practice guidelines (Brandi *et al*. 2001, Thakker *et al*. 2012).

The identification of pedigree members who do not bear the familial *MEN1* mutation is indication for them to be excluded from any further investigation for MEN1-associated tumors (they present the same risk of developing the syndrome of the normal population) strongly contributing in reducing costs for unnecessary screenings.

Genetic testing consists of sequencing *MEN1* coding region (exons 2–10) and splicing sites. It allows to identify point mutations and small intra-exon deletions/insertions, but fails the identification of large intragenic deletions (estimated to represent up to 10% of *MEN1* mutations) (Lemos & Thakker 2008). In case of a *MEN1* negative sequencing test in a MEN1 family or in a clinically defined MEN1 patient, a gene dosage procedure (i.e. Southern blot analysis or multiplex ligation-dependent probe amplification (MLPA)), able to detect copy number change and gross intra-genic deletions, insertions or rearrangements, should be performed. If both sequencing and allele copy dosage screenings resulted negative, haplotype analysis of 11q13 locus, with flanking microsatellite markers, should be considered to identify individuals bearing the *MEN1* 'causative' familial haplotype, in a family with at least two affected individuals spanning at least two generations.

The presence of a phenocopy should be suspected in presence of a negative *MEN1* genetic test, by sequencing, gene dosage and 11q13 haplotype analyses. Phenocopies are estimated to account for up to 5% of MEN1-like cases (Turner *et al*. 2010), and their recognition, by specific genetic tests, is important for differential diagnosis and correct clinical and therapeutic management of patient. Principal MEN1 phenocopy is the multiple endocrine neoplasia type 4 (MEN4), a recently identified hereditary endocrine tumor syndrome causes by loss-of-function mutations of the *CDKN1B* tumor suppressor gene encoding the $p27^{kip1}$ inhibitor of the cyclin-dependent kinase 2. Other, rarer, MEN1 phenocopies are due to mutations in genes encoding members of the cyclin-dependent kinase inhibitor (CDKN) family, such as *CDKN1A* ($p21^{cip1}$), *CDKN2B* ($p15^{Ink4b}$) or *CDKN2C* ($p15^{Ink4c}$). All together mutations in these four *CDKN* genes are suspected to cover less than 2% of clinical MEN1 patients without a *MEN1* mutation (Turner *et al*. 2010); genetic screening of these genes is suggested in these cases, starting from *CDKN1B*.



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**Table 1** Recommended biochemical and imaging surveillance program for MEN1-associated main tumors in MEN1 patients and in *MEN1* mutation carriers.

| **Tumor** (estimated frequency) | **Suggested starting age** (years) | **Biochemical screening** (frequency) | **Imaging analysis** (frequency) |
|---|---|---|---|
| **Parathyroid adenoma (over 90%)** | 8 | – Morning fast serum calcium and PTH (annually)<br>– Morning fast serum ionized calcium[a] (annually) | None[b] |
| **Anterior pituitary tumors (30–40%):** | 5 | | Head non-contrast MRI (every three-five years)[c] |
| PRL-secreting adenoma (prolactinoma) (20%) | | Morning fast serum PRL (annually) | |
| Somatotropin (GH)-secreting adenoma (somatotropinoma) (10%) | | Morning fast serum IGF-1 (annually) | |
| GH-PRL-secreting adenoma (5%) | | Morning fast serum PRL and IGF-1 (annually) | |
| Corticotropin (ACTH)-secreting adenoma (corticotropinoma) (<5%) | | Cortisol and ACTH in blood samples taken at different times of the day (annually) | |
| LH-secreting adenoma (rare) | | Morning fast serum LH (annually) | |
| FSH-secreting adenoma (rare) | | Morning fast serum FSH (annually) | |
| Thyrotropin (TSH)-secreting adenoma (rare) | | Morning fast serum TSH and thyroid hormones (annually) | |
| Non-functioning adenomas (<5%) | | None | |
| **GEP-NETs (30–80%):** | | Serum chromogranin A[d] (annually) | |
| Gastrinoma (40–55%) | 20 | – Morning fast serum gastrin (annually)<br>– Gastric acid output[e] (annually)<br>– Secretin-stimulated gastrin[f] (annually)<br>– Selective Arterial Secretagogue Injection (SASI) | None[g] |
| Insulinoma (10–30%) | 5 | – Fasting glucose (annually)<br>– Morning fast insulin (annually)<br>– Selective Arterial Secretagogue Injection (SASI)[h] | None |
| Glucagonoma (<3%) | <10 | | |
| VIPoma (<1%) | <10 | Morning fast glucagon (annually) | None |
| Non-functioning tumors and PPoma (20–55%) | <10 | Morning fast plasma VIP (annually) | None |
| | | Serum chromogranin A and PP (annually) | MRI, CT scan or EUS of the abdomen (annually) |
| **Carcinoids (over 3%):** | 15 | None (they are typically non-secretory tumors)[i] | |
| Foregut/stomach (10%) | | | EUS of the stomach (annually)<br>Gastroscopy examination (with biopsy) in gastric NETs with hypergastrinemia and in gastric carcinoids type II (every three years) |
| Lung/bronchi (3.4–13.3%) | | | Low-dose CT scan of chest for bronchopulmonary carcinoids (every one-two years) |
| Thymus (2–8.2%) | | | Low-dose CT scan and MRI of the neck and chest for thymic carcinoids (every one-two years)[j] |

*(Continued)*



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**Table 1** Continued.

| **Tumor** (estimated frequency) | **Suggested starting age** (years) | **Biochemical screening** (frequency) | **Imaging analysis** (frequency) |
|---|---|---|---|
| **Adrenal lesions (40%):**<br><br>Adrenal cortical tumors (40%)<br>Pheocromocytoma (<1%) | <10 | Plasma renin, aldosterone, low-dose dexamethasone suppression test, urinary cathecolamines and/or metanephrynes[k] | Abdominal imaging by MRI or CT scan (annually with pancreatic imaging) |

[a]Inonized calcium should be checked if calcium results to be normal or to be intermittently high in presence of a PTH higher than normal reference range.
[b]Neck ultrasound and Tc99 scintigraphy (sestamibi) are suggested for pre-operatory neck exploration before parathyroidectomy (usually in patients with hypercalcemia and hypercalciuria) for the localization of enlarged, extra-numerary and/or ectopic parathyroid glands.
[c]Head MRI is usually the imaging technique of choice for the detection of pituitary adenoma since it is more detailed than CT scan and it identifies pituitary macroadenomas and most of microadenomas. MRI might not detect microadenomas smaller than 3 mm. sensitivity and specificity for secreting pituitary tumors is approximately 90%, diagnostic accuracy in detecting non-functioning microadenoma is less established.
[d]Serum concentration of chromogranin A is still the most valuable marker of GEP-NETs; its concentration is elevated in about 100% of gastrinomas, 80% of neuroendocrine tumors of the small intestine and 69% of non-functioning pancreatic neuroendocrine tumors. However, sensitivity of this dosage for non-functioning tumors is relatively low (33–58%).
[e]Gastric acid output is measured if gastrin level is high. The occurrence of both high fasting serum gastrin concentration and increased basal gastric acid secretion (gastric pH <2) is indication of a gastrinoma.
[f]Secretin-stimulated gastrin is measured if both gastrin level and gastric acid output are high.
[g]Gastrinoma imaging is suggested after a biochemical diagnosis, only to localize tumors before surgery intervention. Due to the small size (<0.5–1 cm) of duodenal and pancreatic gastrinomas in MEN1, mostly of them are usually missed by somatostatin receptor scintigraphy or other conventional imaging. Multi-slice CT scan is the highest sensibility technique able to acquire an entire anatomic region without gaps. EUS can be used for pancreatic gastrinomas, but it fails in recognize small adenoma in the duodenum. Intraoperative EUS of the duodenum and of the pancreas has a higher sensitivity than pre-operative imaging. Somatostatin receptor scintigraphy is highly recommended for lymph node and liver metastases.
[h]SASI test, performed using secretin as a secretagogue, locates gastrinomas by determines the arteries feeding the tumor. It has been shown to have a high predictive value in the Japanese experience, but similar accuracy was not reproduced in other studies (Tonelli *et al*. 2012).
[i]Biochemical dosages of urinary 5-hydroxyindolacetic acid and of serum chromogranin A are not helpful for carcinoid diagnosis.
[j]CT scan demonstrated a 95% sensitivity for detecting thymic carcinoids and it is superior to chest MRI in detecting intrathoracic lesions.
[k]These biochemical investigations are recommended only for patients with signs and symptoms of functioning adrenal tumors and/or with an identified tumor larger than 1 cm.
ACTH, Adrenocorticotropic hormone (corticotropin); CT, Computed tomography; EUS, Endoscopic ultrasounds; FSH, Follicle-stimulating hormone; GEP-NETs, Gastro-entero-pancreatic neuroendocrine tumors; GH, Growth hormone; IGF-1, Insulin-like growth factor-1; LH, Luteinizing hormone; MRI, Magnetic resonance imaging; PP, Pancreatic polypeptide; PTH, Parathyroid hormone; PRL, Prolactin; TSH, Thyroid stimulating hormone; VIP, Vasoactive intestinal peptide.



Other genes to be considered for mutation screening are *CDC73* (also called *HRPT2*, a tumor suppressor gene encoding parafibromin), *CaSR* (encoding the calcium-sensing receptor), *GNA11* (encoding the G-protein alpha 11), *AP2S1* (encoding the adaptor protein 2 sigma 1) for the differential diagnosis of syndromic and familial primary hyperparathyroidism, respectively, in hyperparathyroid-jaw tumor (HPT-JT) syndrome and familial benign hypocalciuric hypercalcemias (FHH1, FHH2 and FHH3), and *AIP* a tumor suppressor located on 11q13 (encoding the aryl hydrocarbon receptor-interacting protein) associated with familial isolated pituitary adenomas. *CDC73, CaSR, GNA11* and *AP2S1* screening is recommended in MEN1-negative individuals with primary hyperparathyroidism and a familial history of the disease. *AIP* mutation testing is suggested in all children and adolescents with prolactinoma or somatotropinoma.

The suggested approach for genetic screening, and related diagnostic surveillance, in MEN1 is schematized in Fig. 1.

The future of genetic diagnosis will be the application of high throughput next-generation sequencing (NGS), that allows the enlargement of nucleotide sequencing from single gene to multi-gene-disease-targeted panels and up to the entire genome, using platforms and instruments capable of producing hundreds of gigabytes of genetic data in a single run, and to include also the non-coding and regulatory regions of genes, that are, at the moment, usually excluded in Sanger's sequencing analysis. In particular, NGS-targeted multi-gene sequencing, using a platform including an endocrine inherited tumor-related selected panel of genes, will be useful for the differential and early diagnosis of MEN1 and other inherited endocrine syndromes. Time and cost for performing NGS screening are progressively decreasing, granting, in a near future,

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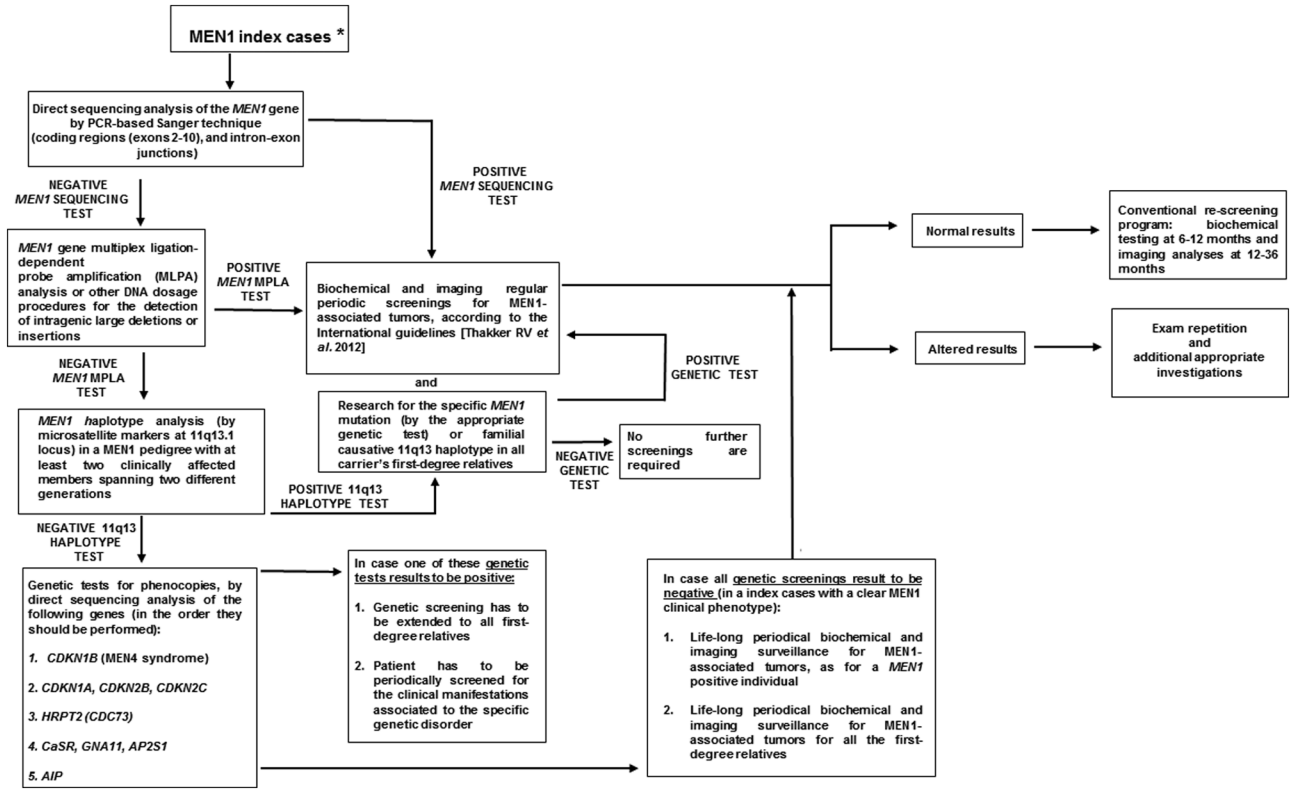


**Figure 1**
Schematic representation of suggested approach for MEN1 syndrome genetic testing in a clinical setting. Genetic screening is indicated to: (1) confirm clinical diagnosis in index cases, (2) identify asymptomatic carriers among first-degree relatives of a mutated subject, (3) identify non-mutated family members. A MEN1 index case (*) is considered: (1) a patient meeting clinical criteria for MEN1 (i.e. two or more MEN1-associated tumors, or one MEN1-associated tumor and a first-degree relative with MEN1), (2) a suspicious MEN1 patient (i.e. multiple parathyroid adenoma before the age of 40, recurrent primary hyperparathyroidism (PHPT) after surgery, gastrinoma and/or multiple pancreatic neuroendocrine tumors (pNETs) at any age), (3) an atypical MEN1 phenotype (i.e. development of one main MEN1-associated tumor and of one non-classical and/or rare MEN1 tumor, such as parathyroid adenoma in association with adrenal gland tumor).



the possibility of a more and more capillary application of this technique.

## Clinical practice guidelines for MEN1: recommendations and suggestions. An evolving story

The first consensus statement, edited by an international panel of specialists in the area of MEN syndromes, was published in 2001 on both MEN1 and MEN2, according to data deriving from the Seventh International Workshop on Multiple Endocrine Neoplasias (Brandi *et al*. 2001). These clinical guidelines have been updated, for MEN1, in 2012 (Thakker *et al*. 2012), after a systematic review of literature and according to novel findings about the clinic aspects and genetic bases of MEN1 syndrome, the constant improvement of diagnostic tools, the published surgical practice for MEN1 tumors and the availability of new drugs for the control of hormone over-production-associated manifestations of the disease. Guidelines include a complete and detailed list of recommendations and suggestions for the diagnosis, treatment and management of the syndrome.

Prior to 1980, approximately 80% of deaths were caused by pNETs, mostly due to gastrinoma-derived gastric acid hypersecretion that causes multiple duodenal ulcers and severe gastro-intestinal bleeding and perforation. Improvements in pharmacological therapy, controlling the excessive gastric acid secretion and the hormone excess-derived syndrome, have strongly reduced mortality related to these complications. Nevertheless, despite the advances in treatment of MEN1 tumors and associated functional syndromes, the life expectancy of patients remains shorter than normal population (death mean age: 55 years) (Norton *et al*. 2015*a*). MEN1 probands present a mean interval of survival of 18 years after the clinical diagnosis. Causes of death have changed in the last decades, and they are now prevalently due to

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the malignant progression of neuroendocrine tumors (NETs), mostly pNETs and thymic carcinoids, which are responsible for 40–50% and 12–24% deaths, respectively. Moreover, the increased life expectance in MEN1 patients has increased, at the same time, morbidity and mortality due to the development of other syndrome-related tumors, such as adrenal tumors, gastric and bronchopulmonary carcinoids, neurofibromas, meningioma, ependymoma, breast cancer, which manifest with a higher frequency in MEN1 patients with respect to normal population (Ito & Jensen 2016). Therefore, further enhancements of techniques and methods for the earliest identification of MEN1-related tumors at their early stage, as well as the development of tailored, specific, effective and safe therapies are still required. Currently, recognition, localization, staging and follow-up of MEN1 NETs are performed by tumor marker measurements in serum and urine, and by imaging, such as computed tomography (CT) scan of chest, abdomen and pelvis, magnetic resonance imaging (MRI) of chest, abdomen and liver, endoscopic ultrasounds (EUS) of stomach and abdomen, contrast-enhanced abdominal CT and non-contrast MRI of the head. The rationale for an aggressive surveillance approach in MEN1 patients and asymptomatic carriers is based on the presumption that the early pre-symptomatic detection of MEN1 neoplasias may reduce the associated mortality (Thakker *et al*. 2012), but, at the moment, there are no clear data to support the notion that more frequent and numerous biochemical and imaging examinations can lead to improved survival outcomes in MEN1. Moreover, the ratio between diagnostic benefits of imaging and risks due to periodical exposure to ionizing radiation should be taken into account. Indeed, recent data have demonstrated to 3-fold increase in the per capita individual radiation exposure from medical diagnostic radiation sources over the past 25 years (Casey *et al*. 2017), and it has been estimated that exposure to ionizing radiation for diagnostic purposes may account for 2% of all tumors (Flasar & Patil 2014). This oncogenic relative risk could also be higher in patients with a genetic tumor-predisposing syndrome, bearing a mutation in genes involved in DNA repair or tumor suppression, such as *MEN1*, who constantly undergo repeated exposure to diagnostic doses of ionizing radiation (Allan 2008). Very recently, Casey and coworkers (Casey *et al*. 2017), retrospectively investigated, for the first time, the effective dose (ED) of ionizing radiation received by a cohort of 43 MEN1 patients to evaluate if the cumulative radiation exposure in surveillance program increases the oncogenic risk. Authors failed in finding an association between the high mean ED in their cohort and the secondary tumor induction, but that could be due to the relatively short period of the retrospective study (only 8 years). Prospective studies, with longer follow-up are required to establish the real risk of secondary tumors caused by repeated radiation exposure in MEN1 patients; the optimal imaging surveillance protocol in MEN1 remains to be defined.

Etchebehere and coworkers compare NET lesion detectability among somatostatin receptor scintigraphy (SRS) with $^{99m}$Tc-hydrazino nicotinamide (HYNIC)-octreotide SPECT/CT, $^{68}$Ga-DOTATATE PET/CT and whole-body diffusion-weighted (WB DWI) MRI (Etchebehere *et al*. 2014). $^{68}$Ga-DOTATATE PET/CT seems to be more sensitive for detecting well-differentiated NET lesions, pulmonary lesions and metastases in lymph nodes (Schraml *et al*. 2013) and for the staging of NETs. WB DWI MRI revealed as an efficient new method with high accuracy and without ionizing radiation exposure, showing a comparable overall primary lesion detection rate to $^{68}$Ga-DOTATATE PET/CT, but superior in detecting liver and bone metastases. SSRS SPECT/CT should be used only when $^{68}$Ga-DOTATATE PET/CT and WB DWI MRI are not available.

Unfortunately, to date, there is a lack of controlled clinical trials to evaluate the efficacy of diagnostic techniques and approaches in MEN1 and the effectiveness of surgical and/or pharmacological interventions for tumors associated with this syndrome. Many diagnostic recommendations, as well as data about surgery and drugs, are derived from long-term experiences of specialists in the area, from clinical work of numerous specialist referral centers worldwide, and from trials performed on sporadic counterparts of MEN1-associated tumors.

## Quality of life in patients with MEN1

The diagnosis of a tumor is a shock and a great challenge for patients and their families. This is followed by lack of patient's personal control over the current treatment method and uncertainty of its outcome. Feelings of depression, anxiety and fear are very common and are normal responses to this life-changing experience. Physical symptoms such as pain, nausea or extreme tiredness (fatigue) can also manifest. All these considerations are even more true after a diagnosis of MEN1 by which a patient becomes aware of the certainty of develop multiple and often recurrent tumors during his



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life. Some studies investigated psychological and physical responses after a diagnosis of cancer, but only one has been specifically conducted about the QoL of MEN1 individuals and psychosocial consequences of the disease diagnosis. Berglund and coworkers analyzed health related QoL (HRQoL) in 29 Swedish MEN1 patients through the administration of four questionnaires (Hospital Anxiety and Depression Scale (HADS), Impact of Event Scale (IES), Life Orientation Test (LOT) and Short Form-36 (SF-36)), first at one in-hospital stay and then at home 6 months later (Berglund *et al*. 2003). On the basis of medical record data, patients were divided into three levels of disease severity, named as 0, 1 and 2. The '0' level means that the MEN1 diagnosis has not been verified and no surgery or medical treatment have been yet initiated. The '1' level corresponds to a verified MEN1 diagnosis with a limited disease, associated with one or more performed surgeries. The '2' level is a verified MEN1 diagnosis with an extensive disease, for which several surgeries have been already performed and pharmacological treatments have been administered. SF-36 scores resulted lower for general health and social functioning with respect to normal population. Approximately 70% of MEN1 patients were defined as pessimists about their uncertain future with the fear of what might happen to themselves, their children and other relatives. This pessimism may also concern the uncertainty regarding the progression of the disease and how this might impact negatively upon their daily activities, and their ability to maintain their present work situation. Authors evidenced that patients presenting higher burden disease and undergoing extensive treatments may need some support for their psychosocial distress, after discharge from hosital.

Later on in 2007, Strømsvik and coworkers (Strømsvik *et al*. 2007) conducted a qualitative study on 29 Swedish patients with MEN1 exploring how they live with the disease. Patients have been encouraged to report any psychological, physical and social limitations in their daily activity and in their job life and to judge how these limitations influence their general QoL. The study showed that most participants tried to adjust their novel situation by changing lifestyle and focusing on nutrition and physical activity. They reported a shift in priorities after developing MEN1 or learning about their personal risk. Changing values help the patients managing the situation. Surprisingly, a majority of them described themselves as being healthy, despite disease severity, surgery, pharmacological treatments and other physical and psychological symptoms. Participants reported that interpersonal relationships with family and friends were one of the most valuable aspects in their lives. Moreover, the majority of participants indicated overall satisfaction with being in a clinical surveillance and follow-up program, under the supervision of specialist health care providers, since this grants to start therapy immediately at the time of tumors development, with a higher possibility to be positively cured. Regarding job situations and environments, result of tests evidenced a patient's sense of control by going on, normally, with their job lives, and only a soft sense of fear about disease-related professional limitations.

Various non-disease-specific QoL tests have been evaluated in sporadic NETs, but, to date, no conclusive data have been published. Although there are evidences suggesting a correlation between disease symptoms and tumor burden with QoL, further perspective trials are warranted to understand the impact of disease diagnosis and progression on physical and psychological QoL of patients and families (Chau *et al*. 2013). Unfortunately, no specific questionnaires measuring HRQoL in MEN1 or other hereditary tumors have been developed yet, and generic questionnaires may overlook some general aspects but skip more specific tracts of the disease. Targeted perspective trials in MEN1 individuals are surely required to design optimal HRQoL evaluation tests for this syndrome. Indeed, an increased knowledge about MEN1, not only about genetic and clinical features but also on the psychosocial aspects of the disease, may help to provide patients with optimal care, psychological support and a better QoL for them and their families.

## Parathyroid adenomas

Primary hyperparathyroidism (PHPT), due to parathyroid hyperplasia and/or adenoma, is the most common (approximately 90% of cases by the age of 40 and nearly 100% by 50) and, usually, the first endocrine manifestation in MEN1, with a common age of onset in the early third decade of life (20–25 years). PHPT in MEN1 can present a long-term asymptomatic course and it is usually recognized by the incidental finding of elevated serum level parathyroid hormone (PTH) in association with hypercalcemia or, in some cases, with normocalcemia. Diagnostic screening includes annual dosage of intact serum PTH and calcemia (Table 1). Patients with hypercalcemia should undergo continuous surveillance, including annual calciuria, imaging of the urinary tract (to prevent nephrolithiasis) and bone



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mineral density (BMD) evaluation by dual-energy X-ray absorptiometry (DXA). MEN1 patients generally develop multiple poly-glandular parathyroid adenomas, and usually all four parathyroids are affected during lifetime. The great majority of parathyroid tumors show loss of heterozygosity (LOH) at 11q13, suggesting that the complete loss of wild type menin in parathyroid cells is a fundamental step for adenoma development. Tumors are different in time of development and size, and each one has to be considered as an independent clonal adenoma, as confirmed by the different pattern of 11q13 LOH found in any single tumor, even from the same patient (Dwight *et al.* 2002). *MEN1* LOH in multiple glands, within the same individual, is ultimately caused by independent genetic changes that arise randomly in any single gland and that are presumably driven by still unknown genetic, epigenetic, physiological and/or environmental factors. An early gland hyperplastic phase has been suggested, by not certainly proven. Recently, it has been suggested that MEN1 parathyroid tumorigenesis could be under the control of a 'negative feedback loop' between miR-24-1 and menin, which mimics the second hit of Knudson's hypothesis, silencing the expression of the second wild type copy of *MEN1* in a post-transcriptional, still reversible, epigenetic manner, before the irreversible genetic deletion/inactivation of the second wild type allele (Luzi *et al.* 2012). This LOH-based mechanism of single gland independent tumorigenesis causes a non-synchronous enlargement of parathyroids at the time of neck exploration and surgery, and it is considered to be responsible for the high rate of tumor recurrences after partial and subtotal parathyroidectomy.

Surgery is the treatment of choice for the control of hypercalcemia. Timing of surgery has not clearly defined yet and it should be decided based on single patient clinical characteristics. Parathyroidectomy is usually performed in patients with notable hypercalcemia in association with hypercalciuria to prevent and/or reduce the associated clinical consequences of high calcium levels, such as severe reduction of BMD, nephrolithiasis, gastric hypersecretion, mental disturbs, vomiting, abdominal and bone pain, etc. Surgery to correct PHPT and hypercalcemia is fundamental in MEN1 patients with Zollinger–Ellison syndrome (ZES), since the restoring of normal calcium level contributes to reduce gastric acid output, ameliorating the clinical findings of ZES and reducing the risk of peptic ulcers. Type of operation for parathyroid surgery in MEN1 patients is still controversial: Some authors suggest minimal invasive surgery with ablation of only the enlarged glands, others suggest subtotal removal of 3.5 glands, and some others total parathyroidectomy with heterotopic auto-transplantation of fresh or cryopreserved normal parathyroid tissue into the brachioradialis muscle of the non-dominant forearm (Norton *et al.* 2015*b*). Partial and subtotal parathyroidectomy have both high probability of recurrences (i.e 40–60% within 10–12 years after surgery), and patients have to be annually monitored for this possibility; conversely, re-inplant after total parathyroidectomy presents a high incidence of graft failure and subsequent permanent hypoparathyroidism. Considering the presence of an after-surgery PHPT-free period, some surgeons have suggested to surgically remove only parathyroid gland/glands that appear to be enlarged and adenomatous (that presumably have already lost both wild type copies of *MEN1*), and do not touch parathyroids appearing normal in volume (presumably still retaining the second wild type copy of the gene and still being normally functioning), to delay, mostly for young patients, the surgical-derived hypoparathyroidism. Indeed, post-surgical permanent hypoparathyroidism is an irreversible complication of total parathyroidectomy, which is more difficult to be treated and controlled than PHPT and is responsible for a great reduction of the general QoL. In this light, the choice of parathyroid surgery approach has to be defined based on every single patient personal and clinical features; it should primarily take into account three main goals: (i) to restore normal calcium level (reducing and/or preventing secondary damages due to long-term elevated serum calcium concentration) and maintain normocalcemia, for as long as possible before recurrence occurs; (ii) to avoid or to delay, for as long as possible, permanent post-surgical hypoparathyroidism; and (iii) to facilitate any possible future surgery for recurrences.

Intraoperative dosage of PTH is suggested to monitor the correct ablation of all adenomatous and/or hyperplastic parathyroids (Nilubol *et al.* 2013); measurement has to be performed 5–10 min after the removal of the last abnormal gland, and a decreasing of at least 50% of intact serum PTH (with respect to basal level before surgery) is indicative of a correct ablation of all pathological parathyroid tissue (with a clinical sensibility of about 87% after 5 min and approximately 95% after 10 min). Transcervical thymectomy is recommended at the time of neck surgery, especially in men and patients with a family history of thymic carcinoids.

Some MEN1 patients require re-operation to cure recurrent and/or persistent PHPT; a novel neck intervention is often difficult, can create definitive and/or recurrent tissue injuries (i.e laryngeal nerve) and it is associated to



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increased morbidity. Moreover, in some cases re-operation can be not indicated due to the clinical and emotional condition of patients, or patients could refuse to undergone a second intervention. Recently, a retrospective study evaluated safety and efficacy of multiple percutaneous parathyroid ethanol ablation (PEA) treatment (average of 2.2 real-time sonographic-guided intra-parathyroid ethanol injections per patient) in 37 MEN1 patients with recurrent PHPT, demonstrating this technique as able to safely and effectively control hyperparathyroidism with a low rate of hypocalcemia and permanent complications, when performed by an experienced radiologist (Singh Ospina *et al*. 2015). However, PEA cannot replace primary parathyroid surgery, but it might represent a possible viable and safer alternative to re-operation, to control recurrent PHPT when a second intervention is not indicated. Moreover, PEA is not a definitive therapy, as demonstrated by the short duration of normal calcium level after the procedure, and it requires to be repeated when hypercalcemia recurs.

PHPT can also be pharmacologically controlled by calcimimetics (i.e. cinacalcet), a class of calcium-sensing receptor agonists that demonstrated to reduce PTH release by parathyroid cells and, at the same time, to control cell growth. Cinacalcet normalizes serum calcium in 70–80% of patients with PHPT. This effect is maintained over 5 years. Serum calcium increases back to baseline levels when the treatment is stopped. This drug neither impacts BMD value nor lowers biochemical markers of bone turnover. There are no documented effects on hypercalcemic symptoms, renal stones or QoL (Khan *et al*. 2017). A study conducted on the patients with end-stage renal disease (ESRD) and related PHPT showed that parathyroidectomy improved QoL, whereas cinacalcet did not (van der Plas *et al*. 2017). For these reasons, today, cinacalcet is not recommended as a first-line treatment choice for the general management of PHPT, but it is suggested as an alternative to parathyroid surgery in patients not meeting the criteria for parathyroidectomy, for those who failed a previous intervention, or for those presenting recurrence who refuse to undergo any further surgical interventions. This drug has demonstrated to be well tolerated and safe in MEN1 patients, and to be able to restore normal calcium homeostasis (Moyes *et al*. 2010, Giusti *et al*. 2016).

## Anterior pituitary tumors

Anterior pituitary tumors in MEN1 have a variable incidence from 15 to 50% in different series, with a mean age of onset in the fourth decade of life, and early cases described by the age of 5 years. Even though pituitary tumors are relatively benign, they can cause significant morbidity due to hormone hypersecretion, hypopituitarism and compression of adjacent structures (principally optic chiasm with subsequent severe headaches and visual field defects). Clinical manifestations are similar to sporadic pituitary adenomas and depend on secreted hormone/hormones and size of tumors. Approximately 60% of these tumors secrete prolactin (PRL), 25% secrete growth hormone (GH), 5% secrete adrenocorticotropic hormone (ACTH) and the remaining presumably being NFTs. MEN1 pituitary adenomas tend to be larger in size than sporadic counterparts (84% vs 24%), to present a more aggressive behavior and to have a reduced response to pharmacological therapy (particularly prolactinoma; 56% vs 10%), necessitating an early surgery (Vergès *et al*. 2002). In this light, early diagnosis, by genetic test in carrier's relatives, is fundamental to prevent tumor growth and to control, as soon as possible, hormone release. Indeed, in MEN1 children and adolescents, conversely to adults, pituitary tumors are the second most frequent manifestation of the disease maybe because they, even if still asymptomatic, are earlier diagnosed thanks to the periodic diagnostic program immediately started at the time of genetic diagnosis. This early identification of pituitary tumors and the subsequent early-started specific therapy help in the reduction of damages due to the prolonged exposition to excessive pituitary hormones and/or in preventing tumor growth and derived compression of pituitary-adjacent structures. However, no genotype-phenotype correlation is observed and all mutation carriers have to be periodically screened for all MEN1 pituitary tumor types, according to the same screening protocol (Table 1). Life-long diagnostic follow-up is indicated because tumors may recur after surgery. Current guideline suggested screenings consist of annual measurement of plasma PRL and insulin-like growth factor-1 (IGF-1), and head MRI every 3–5 years (Thakker *et al*. 2012) (Table 1). However, recently Livshits and coworkers suggested that annual dosage of PRL alone could be not sufficient to early detect pituitary adenoma, and that MRI scan should be performed at a more frequent interval than 3–5 years (Livshits *et al*. 2016). Indeed, the finding of an elevated PRL, in association with a negative MRI scan, could, falsely, suggest the presence of a small microprolactinoma (undetectable by imaging scan), but it could be really due to a non-functioning pituitary tumor causing intrasellar compression (even in case of small microadenomas) or compression of pituitary



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stalk, both responsible for increase in PRL level even in absence of a PRL-secreting tumor (Arafah *et al*. 2000). These non-functioning adenomas are not detected by annual biochemical analysis but they can grow rapidly compressing and damaging adjacent structures. Authors suggested that the head MRI scan should be performed every 1–2 years in all MEN1 patients (Livshits *et al*. 2016).

Therapy of pituitary adenomas in MEN1 is the same of sporadic tumors. The first-line therapy for prolactinomas is principally based on pharmacological control of PRL over-secretion with dopamine agonists (bromocriptine and cabergoline); trans-sphenoidal surgery and radiotherapy are usually reserved for drug-resistant tumors, whose growth and hormone release cannot be controlled by pharmacological therapy, and for macroadenomas compressing adjacent structures and generating neuro-ophthalmological compliances. Conversely, for GH-secreting tumors the approach of choice is trans-sphenoidal surgery; administration of somatostatin analogs (SSAs; octreotide or lanreotide) for the control of GH over-secretion is reserved for second line therapy or for patients not eligible for surgery.

## Gastro-entero-pancreatic neuroendocrine tumors (GEP-NETs)

GEP-NETs clinically affect 30–80% of MEN1 patients, and 80–100% in postmortem studies. They are typically multiple tumors, arising as single independent event following the LOH at 11q13. The appearance is often as diffuse microadenomatosis (multiple tumors > 0.5 cm) of the pancreas and the duodenum; a small percentage of MEN1 patients (less than 13%) develop macro-tumors (>2 cm), mostly of them being non-secreting tumors. GEP-NETs are classified in functioning GEP-NETs and NFTs. Functioning GEP-NETs includes gastrin-secreting tumors (gastrinomas; approximately 50% of MEN1 patients), insulin-secreting tumors (insulinomas; 10–30% of MEN1 patients), glucagon-secreting tumors (glucagonoma; less than 3% of MEN1 patients), vasoactive intestinal peptide (VIP)-secreting tumors (VIPoma; less than 1% of MEN1 patients). Functioning tumors may result in the associated clinical syndrome of hormone excess. NFTs do no secrete hormone or may release some hormonally-inactive peptides, such as pancreatic polypeptide (PP), chromogranin A, neurotensin, neuron-specific enolase or ghrelin.

Gastrinoma is the most frequent functioning GEP-NET in MEN1 (approximately 40–55% of patients). Conversely to the sporadic counterpart, MEN1 gastrinomas occur principally in the duodenum (more than 80% of cases) and manifest as multiple microadenomas (<0.5 cm), are diagnosed by the age of 40 years, and present lymph node metastases at the time of diagnosis in 34–85% of cases (Yates *et al*. 2015). Diagnosis of gastrinoma is made with a fasting gastrin 10 times over the gastrin normal upper limit of 100 pg/mL, in presence of hyperchloryhydria or pH < 2. If fasting gastrin levels are below the diagnostic level of 1000 pg/mL, gastrin stimulation test by 12 h-fasting intravenous injection of secretin is useful in establishing the diagnosis of gastrinoma (gastrin is dosed a baseline, then an intravenous bolus of 2–3 U of secretin per kilogram of body weight is administered over 30 s and serum gastrin levels are then measured at 2.5, 5, 7.5, 10, 15 and 30 min after infusion). A gastrin increase of 120–500 pg/mL with respect to baseline value and a gastrin rise of 110 pg/mL immediately after secretin infusion strongly suggest gastrinoma; approximately 90% of patients with gastrinoma have a positive secretin test. Imaging screening is suggested after the biochemical diagnosis to localize tumors. Majority of MEN1 gastrinomas are multiple tumors localized in the submucosa of the proximal duodenum. Given their specific localization, their commonly reduced size (less than 0.5 cm) and their multiplicity, majority of MEN1 gastrinomas are often missed by SRS or conventional imaging surveillance (CT scan, MRI and EUS). Thin-section multi-slice CT scan of the abdomen demonstrated, also in our long-term experience with MEN1 patients, a very good accuracy in the localization of duodenal gastrinomas, and it should be the initial imaging method for these tumors (Pfannenberg *et al*. 2005). Pancreatic gastrinomas are usually investigated by CT, MRI and/or EUS (Table 2) (Yates *et al*. 2015). Gastrinoma is often associated to hypergastrinemia and multiple peptic ulcers of the duodenum (ZES). Symptoms of ZES can be improved by restoring normocalcemia in MEN1 patients with concurrent PHPT, in up to 20% of cases. Indeed, PHPT and hypercalcemia both increase gastrin secretion and reduce the gastric acid anti-secretory effects of drugs. Therefore, the normalization of calcium and PTH level is recommended before starting pharmacological therapy both to ensure the real effectiveness of the treatment and the establishment of the correct dosage. Medical therapy is aimed to reduce gastric acid over-secretion. It consists principally of histamine-2 receptor antagonists (cimetidine, ranitidine, famotidine), proton pump inhibitors (PPIs; omeprazole, lansoprazole, pantoprazole) and SSAs (octreotide and lanreotide). These drugs have demonstrated a long-term effectiveness and safety in controlling hypergastrinemia



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**Table 2** Main characteristics of imaging techniques for detection of gastro-entero-pancreatic neuroendocrine tumors (GEP-NETs).

| Tumor type | Imaging technique | Advantages | Limitations |
|---|---|---|---|
| Pancreatic gastrinoma | CT scan | – High sensitivity and specificity<br>– Able to detect small lesions down to 0–3 cm<br>– Assessment of metastatic disease | – Exposure to ionizing radiations |
| | MRI | – High sensitivity and specificity<br>– Better soft tissue contrast than CT<br>– No ionizing radiations | – Long examination time<br>– High cost<br>– May miss pNETs less than 1.5–2 cm |
| | EUS | – The most sensitive modality to detect intra-pancreatic tumors<br>– Allows for tissue biopsy and offer the possibility of lesion tattooing<br>– Detection of lymph node metastases<br>– No ionizing radiations | – Invasive technique, the procedure requires use of conscious sedation<br>– Operator-dependent<br>– Low sensitivity for distal pancreas |
| | SRS with In-DPTA-octreotide (octreoscan) | – High sensitivity (overall 78%). More sensitive than cross-sectional imaging (MRI, CT)<br>– Allows a whole-body imaging at one time<br>– Detection of distant metastases (bone, distant lymph nodes, soft tissues) | – Missing the 35–50% of pNETs less than 1 cm |
| | $^{68}$Ga-DOTATATE-PET/CT | – Greater sensitivity (92–94%) (down to 2–5 mm)<br>– Excellent specificity (85%)<br>– Allows a whole-body imaging at one time<br>– Shorter imaging time<br>– Lower radiation exposure<br>– Cheaper cost<br>– Gives a panoramic view of MEN1-related lesions (not only pNETs) at one assessment with a good sensitivity/specificity (including pituitary adenomas (75/83%) and adrenal adenomas (75/83%))<br>– Beneficial for imaging of pNET metastases (liver and bone, distant lymph nodes, soft tissues) | – Exposure to ionizing radiations<br>– Vantages and positive data on its application are mostly derived from sporadic pNETs<br>– A recent study on 33 MEN1 patients reported a low lesion detection rate for small tumors (<1 cm) (Albers *et al*. 2017)<br>– The high physiological uptake of radiolabeled DOTATATE by the posterior portion of the pancreatic head can mask the real tumor uptake and can be responsible for the low detection rate of primary tumors in this region of the pancreas |
| Duodenal gastrinoma | Multi-slice CT scan | – High sensitivity and specificity<br>– Able to detect small lesions down to 0–3 cm<br>– Able to detect multiple lesions in the submucosa of the duodenum<br>– Assessment of metastatic disease | – Exposure to ionizing radiations |
| | EUS | – Allows for tissue biopsy and offer the possibility of lesion tattooing<br>– Detection of lymph node metastases<br>– No ionizing radiations | – Invasive technique, the procedure requires use of conscious sedation<br>– Operator-dependent<br>– Low sensitivity for distal pancreas |
| | SRS with In-DPTA-octreotide (octreoscan) | – High sensitivity (overall 78%). More sensitive than cross-sectional imaging (MRI, CT)<br>– Allows a whole-body imaging at one time<br>– Detection of distant metastases (bone, distant lymph nodes, soft tissues) | – Missing the 35–50% of pNETs less than 1 cm |
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*(Continued)*



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**Table 2** Continued.

| Tumor type | Imaging technique | Advantages | Limitations |
|---|---|---|---|
| Insulinoma | MRI | – It is the imaging of choice for localization of insulinoma<br>– Non-delivering ionizing radiations; possibility of frequent serial imaging assessments<br>– High sensitivity to detect insulinomas <1 cm (down to 0.5 cm) | – It is not usually for diagnosis but for the assessment of primary localization and extent of the disease after the biochemical diagnosis is established<br>– Long examination time<br>– High cost |
| | CT | – Usually used as additional imaging modality for the correct pre-operative tumor localization, for evidencing the relationship to the pancreatic duct and assessment of metastatic disease | – Exposure to ionizing radiations |
| | EUS | – Usually used as additional imaging modality for the correct pre-operative tumor localization and for evidencing the relationship to the pancreatic duct | – Invasive technique, the procedure requires use of conscious sedation<br>– Operator-dependent<br>– Low sensitivity for distal pancreas |
| Non-functioning pNETs | MRI | – Reduced radiation exposure<br>– Similar sensitivity of CT scan<br>– Non-invasive procedure | – May miss pNETs less than 1.5–2 cm<br>– Long examination time<br>– High cost |
| | CT scan | – Possibility of a cross-sectional imaging analysis | – Exposure to ionizing radiations |
| | EUS | – High sensitivity to detect pancreatic tumors <1 cm (down to 0.5 cm)<br>– Better indicated as pre-operative localization of tumors of an already identified tumor<br>– It is the most sensitive technique to detect intra-pancreatic pNETs, both for functioning and non-functioning tumors<br>– It allows accurate assessment of pNET size (can be used to monitor changes in pNET size) | – Low sensitivity to detect tumor on the tail region of the pancreas<br>– Invasive procedure, the procedure requires use of conscious sedation<br>– Operator-dependent |
| | SRS with In-DPTA-octreotide (octreoscan) | – High sensitivity (overall 78%). More sensitive than cross-sectional imaging (MRI, CT)<br>– The advantage of allowing whole-body imaging at one time<br>– Detection of distant metastases (bone, distant lymph nodes, soft tissues) | – Miss 35–50% of pNETs less than 1 cm |
| | $^{68}$Ga-DOTATATE-PET/CT | – Greater sensitivity (92–94%) (down to 2–5 mm)<br>– Excellent specificity (85%)<br>– The advantage of allowing whole-body imaging at one time<br>– Shorter imaging time<br>– Lower radiation exposure<br>– Cheaper cost<br>– Gives a panoramic view of MEN1-related lesions (not only pNETs) at one assessment with a good sensitivity/specificity (including pituitary adenomas (75/83%) and adrenal adenomas (75/83%))<br>– Beneficial for imaging of pNET metastases (liver and bone, distant lymph nodes, soft tissues) | – Exposure to ionizing radiations<br>– Vantages and positive data on its application is mostly derived from sporadic pNETs<br>– A recent study on 33 MEN1 patients reported a low lesion detection rate for small tumors (<1 cm) (Albers *et al*. 2017)<br>– The high physiological uptake of radiolabeled DOTATATE by the posterior portion of the pancreatic head can mask the real tumor uptake and can be responsible for the low detection rate of primary tumors in this region of the pancreas |

CT, Computed tomography; EUS, Endoscopic ultrasounds; $^{68}$Ga-DOTATATE-PET/CT, $^{68}$Ga-DOTATATE positron-emission tomographic/CT imaging; MRI, Magnetic resonance imaging; pNETs, pancreatic neuroendocrine tumors; SRS, Somatostatin receptor scintigraphy.

and ZES complications (Wolin 2012, Plöckinger 2012). SSAs have also demonstrated to have an anti-neoplastic effect (Wolin 2012), but no data are still available about their effectiveness in malignant and/or metastatic gastrinoma in MEN1. The use of surgery is controversial due to the multiple microadenomatose nature of these tumors that are usually microscopic and scattered over the entire neuroendocrine tissue. Surgical tumor resection is suggested, by the consensus of experts, when the concomitant non-functioning NETs double their size in a 6 month-interval, or approach or overcome 2 cm in diameter (Thakker *et al*. 2012, Falconi *et al*. 2016). Several surgical options have been proposed, varying from the Thompson's procedure (excision of the duodenal



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gastrinoma through a longitudinal duodenotomy) to duodeno-pancreatecomy or pancreas-preserving duodenectomy. At the moment, there are no controlled trials comparing the efficacy of medical treatment with respect to surgical options.

Insulinoma is the second most common functioning GEP-NET in MEN1, developing at young age (<35 years) in approximately 10–30% of cases. Insulinomas in MEN1 can manifest as single pancreatic macroadenoma (>2 cm) or, more commonly, as multiple microadenomas (<2 cm) scattered along the entire pancreas. Diagnosis is made by concomitant fasting hypoglycemia and hyperinsulinemia. Tumors are generally localized by CT scan, MRI or EUS of pancreas body and tail. MRI is the imaging of choice for periodical surveillance; CT scan and EUS are usually used as additional imaging modalities for the correct pre-operative tumor localization and for evidencing the relationship to the pancreatic duct. Main characteristics of imaging tools for the detection and localization of insulinomas and other MEN1 GEP-NETs are summarized in Table 2. In the great majority of cases, pharmaceutical therapy fails to control hormone over-production and tumor surgery removal is mandatory to prevent neurological consequences of severe hypoglycemia. Differently from sporadic counterpart, MEN1 insulinoma is rarely treated by pancreatic enucleation due to the difficulty in localize the tumor in the contest of the multiple pNETs, both at pre- or intra-operatory level. Pancreatic enucleation can be proposed only in presence of few pNETs or of a dominant lesion responsible of the hypoglemic-hypersinulinemic syndrome. This procedure allows to preserve pancreatic parenchyma, and avoid pancreatic endocrine and exocrine insufficiency, but it presents the risk of Wirsung duct damage, pancreatic fistula (40% of cases), recurrence and inadequacy for malignant pNETs (Vezzosi *et al*. 2015). The most effective approach is pancreatic resection of the most affected part of the pancreas: either by distal corporo-caudal-pancreatectomy (DP) or pancreato-duodenectomy (PD). Patients submitted to pancreatectomy are at risk to develop impaired glucose intolerance or overt diabetes mellitus (a risk significantly higher for PD or DP than for enucleation), risk that increases with the resected pancreas volume (>25%), the time elapsed from surgery and the age of patient (Kang *et al*. 2016). Splenic preservation, following DP, must be considered whenever there is no tumor infiltration of splenic vessels, since it is associated with a reduction in perioperative infectious complications compared with conventional DP with splenectomy (Shoup *et al*. 2002). PD should be preferably performed with a pylorus preserving technique instead of pylorus-antral resection (Whipple procedure) as suggested by some perioperative outcome measures (Huttner *et al*. 2016), even if QoL does not seem to be different between the two procedures. Recently, a cross-sectional survey of recurrence-free survivors of a large number of patients who had undergone pancreatic resection has been published (Cloyd *et al*. 2017); a third of patients had a pNET. Patients who underwent a prior pancreatectomy for pNET had a significantly worse QoL scores with respect to patients operated for pancreatic or periampullary carcinomas. The type of surgery also influenced the post-surgical QoL: worse for DP than for PD. However, data about post-surgical clinical complications and patient's QoL have not been specifically evaluated in MEN1 insulinoma, yet.

NFTs of the gastro-entero-pancreatic tract occur prevalently as microadenomas and they are not associated with hormonal syndromes. Although these tumors are non-functional (not secreting any hormone or releasing neuroendocrine polypeptides that are not responsible for specific syndrome), it is very important to identify them early as their size usually correlates with metastases (4% if <1.0 cm, 10% if between 1.1 and 2.0 cm, 18% if between 2.1 and 3.0 cm, and 43% if >3.0), and malignant pNET is the most common cause of death. Growing sensitivity and specificity of imaging techniques have resulted in an increased identification of NFTs in MEN1 in the last decades. A combination of MRI, CT scan and EUS of the abdomen is suggested every year. Surgery is indicated to prevent tumor growth and malignant progression and to reduce morbidity and mortality related to metastatic disease. At the moment, no specific surgery consensus is defined about what tumor size can drive the decision for the intervention. Commonly, surgery is suggested for tumors over 2 cm and/or rapidly growing, but, recently, some authors have suggested to perform serial abdominal EUS in patients with small pNETs (<1–2 cm) and operate if growth occurs, others prefer avoiding surgery if non-functioning pNETs are less than 2 cm and/or slowly growing. Biopsy could help in identifying which patients will benefits from surgery. Unfortunately, studies on application of both the Ki-67 proliferation index and the TNM tumor staging index in non-functioning pNETs are on patients with sporadic pNETs and require specific evaluation in MEN1 tumors. In case of unresectable tumors (i.e. tumors spread all over the entire pancreas) or advanced metastatic cancer some medical therapies, such as SSAs, cytotoxic chemotherapy (streptozocin and 5-fluorouracil, doxorubicin, temozolomide with capecitabine), inhibitors of thyrosin kinase receptors (sunitinib), inhibitors of mammalian target of rapamycin (mTOR; everolimus) demonstrated to increase the median progression-free survival in sporadic pNETs. No



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specific trials have been performed in MEN1 GEP-NETs, but there is reasonable assumption they would be effective also in these tumors.

## Thymic, bronchopulmonary and gastric carcinoids

In MEN1, carcinoids of the thymus have a prevalence of 28.2%, occurring predominantly in men than in women (20:1), with a significantly higher percentage in smokers. Thymic carcinoids represents the second cause of death in MEN1 patients after pNETs; mean year survival after the diagnosis is approximately 9.5 years (with 70% a patients dying as direct consequence of these tumors), and a 10-year survival is limited only to 36.1% of diagnosed cases. Indeed, they are generally asymptomatic and do not display any clinical manifestation and, unfortunately, the great majority of them are discovered only at their advanced and malignant stage, when they have already invaded adjacent tissues, often also with liver and/or bone metastases. Therefore, the early identification of these tumors when they are still completely surgically resectable is mandatory. Diagnosis is exclusively by imaging, prevalently neck and chest low-dose contrast CT scan, or MRI, to be repeated every 12 years. CT scan is more sensitive (about 95%) but it implicates the exposure to repeated doses of ionizing radiation. Therefore, it has been proposed a screening combination of CT and interim MRI, each one to be, alternatively, repeated every two years (Table 1) to grant the annual exploration of neck-chest. Preventive total thymectomy is suggested at the time of parathyroid surgery, especially in men. Since transcervical thymectomy could not remove all thymic tissue, a combined transcervical thymectomy and a video-assisted mediastinoscopic thymectomy, performed by an expert endocrinology surgeon, is indicated in high risk patients (smoker men).

Bronchopulmonary carcinoids occur in a low percentage of MEN1 patients (3.413.3% based on analyzed series). Diagnostic protocol consists of CT or MRI every 12 years for the detection of possible bronchial masses. Surgery is the therapy of choice: lobectomy with lymph node dissection; most bronchopulmonary carcinoids can be completely resected. Survival rates do not differ between operated and non-operated patients. No clear indication about timing of surgery exists.

Type 2 gastric carcinoids derive from enterochromaffin-like (ECL) cells (ECLomas), maybe as secondary to the thropic action of chronic hypergastrinemia and somatic 11q13 LOH of these cells. In MEN1, these tumors are associated with ZES and peptic ulcers and present a high rate of liver metastases (1030%) (Norton *et al.* 2015*b*). Early diagnosis is made by annual regular EUS of the stomach in MEN1 patients and *MEN1* carriers. Localized single tumors (usually >7090% of cases) are surgically removed by endoscopic guidance. When tumors are numerous and large in size, pharmacological additional treatments, with cholecystokinin B receptor antagonists or long-acting SSAs, can be necessary, in association with aggressive surgery (subtotal or total stomach resection and D-2 lymph node dissection).

## Conclusions

Main recommendations and suggestions for the best clinical and therapeutic management of MEN1, to reduce morbidity and mortality and grant a better QoL to patients and their relatives, can be resumed as it follows:

(1) MEN1 syndrome is a complex disorders involving different endocrine tissues and organs, and including also related hormone syndromes. Patients and their families should be clinically managed and life-long followed up by a multidisciplinary team of specialists able to treat all the different aspects of the disease, or by a specialist center in the area of endocrine tumors and related genetic bases, which includes and/or is in closed collaboration with endocrinologists, oncologists, gastroenterologists, specialized genetic counselors and clinical genetists, endocrine surgeons, histopathologists with expertise in NETs, radiologists with experience also in nuclear medicine, and biologists skilled in molecular genetics and genetic tests (Thakker *et al.* 2012). MEN1 patients should be controlled regularly every 36 months; asymptomatic mutation carriers have to be appropriately reviewed every year. Follow-up by a specialist center demonstrated a significant reduction in morbidity and mortality, not only because of the choice of the best diagnostic and therapeutic plan but also because patients and relatives followed up in a specialist center show a higher adherence to both the diagnostic program and recommended therapies.

(2) General clinicians should refer index cases, suspected MEN1 patients and any suspicious and atypical case of MEN1, to specialist referral centers, for genetic counseling, genetic testing, targeted clinical and therapeutic management and follow-up.

(3) Unfortunately, in MEN1, preventive surgical ablation of target organs, to prevent the development of



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tumors and their possible malignant progression, cannot be performed (as for thyroid in MEN2), except for thymus resection at the time of parathyroid surgery. Therefore, the early diagnosis is mandatory to start the specific diagnostic surveillance as soon as possible, and to precociously intervene by surgery and/or available pharmacological treatments to reduce negative effects of hormone over-secretion and related syndromes and to prevent malignant progression of tumors.

(4) Genetic testing is fundamental in MEN1 probands to confirm clinical diagnosis and to identify the specific MEN1 mutation, and in all first-degree relatives (better before the age of 5, or as soon as possible) for the early identification of asymptomatic mutation carriers. Positive tested individuals should undergo the MEN1 diagnostic protocol immediately at the time of mutation identification, as some MEN1 tumors have been described by the age of 5.

(5) Genetic counseling should be performed before and after the genetic test and it should include: (i) the presence of personnel specialized in medical genetics, (ii) reproductive counseling, (iii) psychological support, for the management of genetic test result-associate consequences involving the emotional, social, or financial aspect of life of patients and their families.

(6) Patients and their families should be given by accurate and clear information about: (i) the inheritance pattern of their disorders and the probability of inherit and/or transmit the disease to the progeny, (ii) the genetic tests that will be performed and any potential error and limitation of every analysis technique, (iii) the risk for specific tumor development, their early age of onset, multiplicity and aggressiveness, associated with the result of the genetic test, (iv) all the clinical benefits derived from the result of genetic test, (v) all the available therapeutic options, and their benefits and possible risks.

**Declaration of interest**

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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## References

Albers MB, Librizzi D, Lopez CL, Manoharan J, Apitzsch JC, Slater EP, Bollmann C, Kann PH & Bartsch DK 2017 Limited value of Ga-68-DOTATOC-PET-CT in routine screening of patients with multiple endocrine neoplasia type 1. *World Journal of Surgery* **41** 1521–1527. (doi:10.1007/s00268-017-3907-9)

Allan JM 2008 Genetic susceptibility to radiogenic cancer in humans. *Health Physics* **95** 677–686. (doi:10.1097/01.HP.0000326339.06405.ea)

Arafah BM, Prunty D, Ybarra J, Hlavin ML & Selman WR 2000 The dominant role of increased intrasellar pressure in the pathogenesis of hypopituitarism, hyperprolactinemia, and headaches in patients with pituitary adenomas. *Journal of Clinical Endocrinology and Metabolism* **85** 1789–1793. (doi:10.1210/jc.85.5.1789)

Berglund G, Lidén A, Hansson MG, Oberg K, Sjöden PO & Nordin K 2003 Quality of life in patients with multiple endocrine neoplasia type 1 (MEN 1). *Familial Cancer* **2** 27–33. (doi:10.1023/A:1023252107120)

Brandi ML, Gagel RF, Angeli A, Bilezikian JP, Beck-Peccoz P, Bordi C, Conte-Devolx B, Falchetti A, Gheri RG, Libroia A, *et al*. 2001 Guidelines for diagnosis and therapy of MEN type 1 and type 2. *Journal of Clinical Endocrinology and Metabolism* **86** 5658–5671. (doi:10.1210/jcem.86.12.8070)

Casey RT, Saunders D, Challis BG, Pitfield D, Cheow H, Shaw A & Simpson HL 2017 Radiological surveillance in multiple endocrine neoplasia type 1: a double-edged sword? *Endocrine Connections* **6** 151–158. (doi:10.1530/EC-17-0006)

Chandrasekharappa SC, Guru SC, Manickam P, Olufemi SE, Collins FS, Emmert-Buck MR, Debelenko LV, Zhuang Z, Lubensky IA, Liotta LA, *et al*. 1997 Positional cloning of the gene for multiple endocrine neoplasia-type 1. *Science* **276** 404–407. (doi:10.1126/science.276.5311.404)

Chau I, Casciano R, Willet J, Wang X & Yao JC 2013 Quality of life, resource utilisation and health economics assessment in advanced neuroendocrine tumours: a systematic review. *European Journal of Cancer Care* **22** 714–725. (doi:10.1111/ecc.12085)

Cloyd JM, Tran Cao HS, Petzel MQ, Denbo JW, Parker NH, Nogueras-González GM, Liles JS, Kim MP, Lee JE, Vauthey JN, *et al*. 2017 Impact of pancreatectomy on long-term patient-reported symptoms and quality of life in recurrence-free survivors of pancreatic and periampullary neoplasms. *Journal of Surgical Oncology* **115** 144–150. (doi:10.1002/jso.24499)

Concolino P, Costella A & Capoluongo E 2016 Multiple endcorine neoplasia type 1 (MEN1): an update of 208 new germline variants reported in the last nine years. *Cancer Genetics* **209** 36–41. (doi:10.1016/j.cancergen.2015.12.002)

Dwight T, Nelson AE, Theodosopoulos G, Richardson AL, Learoyd DL, Philips J, Delbridge L, Zedenius J, Teh BT, Larsson C, *et al*. 2002 Independent genetic events associated with the development of multiple parathyroid tumors in patients with primary hyperparathyroidism. *American Journal of Pathology* **161** 1299–1306. (doi:10.1016/S0002-9440(10)64406-9)

Etchebehere EC, de Oliveira Santos A, Gumz B, Vicente A, Hoff PG, Corradi G, Ichiki WA, de Almeida Filho JG, Cantoni S, Camargo EE, *et al*. 2014 $^{68}$Ga-DOTATATE PET/CT, 99mTc-HYNIC-octreotide SPECT/CT, and whole-body MR imaging in detection of neuroendocrine tumors: a prospective trial. *Journal of Nuclear Medicine* **55** 1598–1604. (doi:10.2967/jnumed.114.144543)

Falconi M, Eriksson B, Kaltsas G, Bartsch DK, Capdevila J, Caplin M, Kos-Kudla B, Kwekkeboom D, Rindi G & Klöppel G 2016 ENETS consensus guidelines update for the management of patients with functional pancreatic neuroendocrine tumors and non-functional pancreatic neuroendocrine tumors. *Neuroendocrinology* **103** 153–171. (doi:10.1159/000443171)







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Flasar M & Patil S 2014 Radiating disparity in IBD. *Digestive Diseases and Sciences* **59** 504–506. (doi:10.1007/s10620-013-2922-4)

Giusti F, Cianferotti L, Gronchi G, Cioppi F, Masi L, Faggiano A, Colao A, Ferolla P & Brandi ML 2016 Cinacalcet therapy in patients affected by primary hyperparathyroidism associated to Multiple Endocrine Neoplasia Syndrome type 1 (MEN1). *Endocrine* **52** 495–506. (doi:10.1007/s12020-015-0696-5)

Hüttner FJ, Fitzmaurice C, Schwarzer G, Seiler CM, Antes G, Büchler MW & Diener MK 2016 Pylorus-preserving pancreaticoduodenectomy (pp Whipple) versus pancreaticoduodenectomy (classic Whipple) for surgical treatment of periampullary and pancreatic carcinoma. *Cochrane Database of Systematic Reviews* **2** CD006053. (doi:10.1002/14651858.CD006053)

Ito T & Jensen RT 2016 Imaging in multiple endocrine neoplasia type 1: recent studies show enhanced sensitivities but increased controversies. *International Journal of Endocrine Oncology* **3** 53–66. (doi:10.2217/ije.15.29)

Khan AA, Hanley DA, Rizzoli R, Bollerslev J, Young JE, Rejnmark L, Thakker R, D'Amour P, Paul T, Van Uum S, *et al*. 2017 Primary hyperparathyroidism: review and recommendations on evaluation, diagnosis, and management. A Canadian and international consensus. *Osteoporosis International* **28** 1–19. (doi:10.1007/s00198-016-3716-2)

Kang JS, Jang JY, Kang MJ, Kim E, Jung W, Chang J, Shin Y, Han Y & Kim SW 2016 Endocrine function impairment after distal pancreatectomy: incidence and related factors. *World Journal of Surgery* **40** 440–446. (doi:10.1007/s00268-015-3228-9)

Lemos MC & Thakker RV 2008 Multiple endocrine neoplasia type 1 (MEN1): analysis of 1336 mutations reported in the first decade following identification of the gene. *Human Mutation* **29** 22–32. (doi:10.1002/humu.20605)

Livshits A, Kravarusic J, Chuang E & Molitch ME 2016 Pituitary tumors in MEN1: do not be misled by borderline elevated prolactin levels. *Pituitary* **19** 601–604. (doi:10.1007/s11102-016-0752-z)

Luzi E, Marini F, Giusti F, Galli G, Cavalli L & Brandi ML 2012 The negative feedback-loop between the oncomir Mir-24-1 and menin modulates the Men1 tumorigenesis by mimicking the 'Knudson's second hit'. *PLoS ONE* **7** e39767. (doi:10.1371/journal.pone.0039767)

Moyes VJ, Monson JP, Chew SL & Akker SA 2010 Clinical use of Cinacalcet in MEN1 hyperparathyroidism. *International Journal of Endocrinology* **2010** 906163.

Nilubol N, Weisbrod AB, Weinstein LS, Simonds WF, Jensen RT, Phan GQ, Hughes MS, Libutti SK, Marx S & Kebebew E 2013 Utility of intraoperative parathyroid hormone monitoring in patients with multiple endocrine neoplasia type 1-associated primary hyperparathyroidism undergoing initial parathyroidectomy. *World Journal of Surgery* **37** 1966–1972. (doi:10.1007/s00268-013-2054-1)

Norton JA, Krampitz G, Zemek A, Longacre T & Jensen RT 2015*a* Better survival but changing causes of death in patients with multiple endocrine neoplasia type 1. *Annals of Surgery* **261** e147–e148. (doi:10.1097/SLA.0000000000001211)

Norton JA, Krampitz G & Jensen RT 2015*b* Multiple endocrine neoplasia: genetics and clinical management. *Surgical Oncology Clinics of North America* **24** 795–832. (doi:10.1016/j.soc.2015.06.008)

Pfannenberg AC, Burkart C, Kröber SM, Eschmann SM, Horger MS & Claussen CD 2005 Dual-phase multidetector thin-section CT in detecting duodenal gastrinoma. *Abdominal Imaging* **30** 543–547. (doi:10.1007/s00261-004-0299-8)

Plöckinger U 2012 Diagnosis and treatment of gastrinomas in multiple endocrine neoplasia type 1 (MEN-1). *Cancers* **4** 39–54. (doi:10.3390/cancers4010039)

Schraml C, Schwenzer NF, Sperling O, Aschoff P, Lichy MP, Müller M, Brendle C, Werner MK, Claussen CD & Pfannenberg C 2013 Staging of neuroendocrine tumours: comparison of [Ga]DOTATOC multiphase PET/CT and whole-body MRI. *Cancer Imaging* **13** 63–72. (doi:10.1102/1470-7330.2013.0007)

Shoup M, Brennan MF, McWhite K, Leung DH, Klimstra D & Conlon KC 2002 The value of splenic preservation with distal pancreatectomy. *Archives of Surgery* **137** 164–168. (doi:10.1001/archsurg.137.2.164)

Singh Ospina N, Thompson GB, Lee RA, Reading CC & Young WF Jr 2015 Safety and efficacy of percutaneous parathyroid ethanol ablation in patients with recurrent primary hyperparathyroidism and multiple endocrine neoplasia type 1. *Journal of Clinical Endocrinology and Metabolism* **100** E87–E90. (doi:10.1210/jc.2014-3255)

Strømsvik N, Nordin K, Berglund G, Engebretsen LF, Hansson MG & Gjengedal E 2007 Living with multiple endocrine neoplasia type 1: decent care-insufficient medical and genetic information: a qualitative study of MEN 1 patients in a Swedish hospital. *Journal of Genetic Counseling* **16** 105–117. (doi:10.1007/s10897-006-9047-2)

Thakker RV, Newey PJ, Walls GV, Bilezikian J, Dralle H, Ebeling PR, Melmed S, Sakurai A, Tonelli F, Brandi ML, *et al*. 2012 Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1). *Journal of Clinical Endocrinology and Metabolism* **97** 2990–3011. (doi:10.1210/jc.2012-1230)

Tonelli F, Giudici F, Giusti F & Brandi ML 2012 Gastroenteropancreatic neuroendocrine tumors in multiple endocrine neoplasia type 1. *Cancers* **4** 504–522. (doi:10.3390/cancers4020504)

Turner JJ, Christie PT, Pearce SH, Turnpenny PD & Thakker RV 2010 Diagnostic challenges due to phenocopies: lessons from Multiple Endocrine Neoplasia type1 (MEN1). *Human Mutation* **31** E1089–E1101. (doi:10.1002/humu.21170)

van der Plas WY, Dulfer RR, Engelsman AF, Vogt L, de Borst MH, van Ginhoven TM, Kruijff S & Dutch Hyperparathryoid Study Group (DHSG) 2017 Effect of parathyroidectomy and cinacalcet on quality of life in patients with end-stage renal disease-related hyperparathyroidism: a systematic review. *Nephrology Dialysis Transplantation* gfx044. (doi:10.1093/ndt/gfx044)

Vergès B, Boureille F, Goudet P, Murat A, Beckers A, Sassolas G, Cougard P, Chambe B, Montvernay C & Calender A 2002 Pituitary disease in MEN type 1 (MEN1): data from the France-Belgium MEN1 multicenter study. *Journal of Clinical Endocrinology and Metabolism* **87** 457–465. (doi:10.1210/jc.87.2.457)

Vezzosi D, Cardot-Bauters C, Bouscaren N, Lebras M, Bertholon-Grégoire M, Niccoli P, Levy-Bohbot N, Groussin L, Bouchard P, Tabarin A, *et al*. 2015 Long-term results of the surgical management of insulinoma patients with MEN1: a Groupe d'étude des Tumeurs Endocrines (GTE) retrospective study. *European Journal of Endocrinology* **172** 309–319. (doi:10.1530/EJE-14-0878)

Wolin EM 2012 The expanding role of somatostatin analogs in the management of neuroendocrine tumors. *Gastrointestinal Cancer Research* **5** 161–168.

Yates CJ, Newey PJ & Thakker RV 2015 Challenges and controversies in management of pancreatic neuroendocrine tumours in patients with MEN1. *Lancet Diabetes & Endocrinology* **3** 895–905. (doi:10.1016/S2213-8587(15)00043-1)

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