Review Article

# Multiple Endocrine Neoplasia Type 1

## The Current Status of Disease Management

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### Summary

**Background:** Multiple endocrine neoplasia type 1 (MEN1) is a rare genetic disease of autosomal dominant inheritance, with an estimated prevalence of 3–20/100 000. Its main feature is neuroendocrine neoplasia in the parathyroid glands, the endocrine pancreas, the duodenum, and the pituitary gland. In this article, we review the diagnostic and therapeutic options for MEN1-associated tumors.

**Methods:** We present an analysis and evaluation of retrospective case studies retrieved from PubMed, guidelines from Germany and abroad, and our own experience.

**Results:** The disease is caused by mutations in the MEN1 gene. Mutation carriers should participate in a regular, specialized screening program from their twenties onward. The early diagnosis and individualized treatment of MEN1-associated tumors can prevent the development of life-threatening hormonal syndromes and prolong the expected life span of MEN1 patients from 55 to 70 years, as well as improving their quality of life. Surgical treatment is based on the location, size, growth dynamics, and functional activity of the tumors. The evidence for treatment strategies is derived from retrospective studies only (level III evidence) and the optimal treatment is often a matter of debate. This is a further reason for treatment in specialized centers.

**Conclusion:** MEN1 is a rare disease, and, consequently, the evidence base for its treatment is limited. Carriers of disease-causing mutations in the MEN1 gene should be cared for in specialized interdisciplinary centers, so that any appreciable tumor growth or hormonal activity can be detected early and organ-sparing treatment can be provided.

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Multiple endocrine neoplasia type 1 (MEN1) is a genetic disease of autosomal dominant inheritance characterized by the synchronous or metachronous occurrence of neuroendocrine neoplasms (NENs). Being a rare disease, the actual prevalence and incidence rates of MEN1 are still unknown. For the general population, the estimated prevalence is 3–20 cases per 100 000 population (1, 2). The classical locations of tumor manifestation in MEN1 patients include pituitary gland, parathyroid glands and pancreas, and, less commonly, adrenal cortex, thymus, bronchi, and stomach *(Table 1)* (1, e1–e10). In addition, MEN1 patients frequently develop non-neuroendocrine cutaneous tumors *(Table 1)* (1, e10).

The disease is caused by the *MEN1* gene which was discovered in 1997. Since then, many new insights have been gained into this rare disease (3). Above all, using a predictive genetic test, affected individuals, having received genetic counseling, can now be diagnosed early and included in a regular screening program. Furthermore, a deeper understanding of the pathogenesis of the disease has helped to improve the diagnosis and treatment of MEN1-associated tumors. In particular, rapid advances in imaging technologies now allow the early visualization of very small lesions (4). Besides thymic NENs, duodenopancreatic neuroendocrine tumors are the most common cause of MEN1-associated mortality (5).

According to retrospective data of patients diagnosed with MEN1 in the 1990s and followed up over a period of more than 30 years, the mean expected life span of MEN1 patients was about 55 years (6–8). More recent data show that predictive screening and early treatment in interdisciplinary expert centers have helped to increase the life expectancy of patients with MEN1 to the age of at least 70 years (5, 6, 9).

**Table 1**

**MEN1 tumor manifestations up to the age of 70**

| Manifestation | Pene-trance (%) | Main age of onset (age in years) | Earliest age of onset (reference) |
|---|---|---|---|
| Primary hyperparathyroidism | > 90 | from age 20 | < 10 (e2) |
| Anterior pituitary adenomas | 30–40 | from age 20 | 5 (e3) |
| Duodenopancreatic NENs | 70–100 | from age 20 | 6–12 (e4, e5) |
| Adrenal lesions | 30–40 | from age 20 | 3 (e6) |
| Bronchopulmonary NENs | 5–10 | from age 30 | 15 (13) |
| Thymic NENs | < 5 | from age 30 | 16 (e5) |
| Gastric NENs | 10 | from age 30 | 25 (e7) |
| Breast cancer | 5 | from age 40 | 30 (e8) |
| Meningiomas | 8 | from age 40 | 29 (e9) |
| Cutaneous lesions (angiofibromas, lipomas, collagenomas) | 40–80 | from age 40 | 18 (e10) |

Classically, tumor manifestations in MEN1 are found in the pituitary gland, parathyroid gland and pancreas, less frequently in the adrenal cortex, thymus, bronchi or stomach. Sporadic case reports (e2–e10, 13) have shown that a small number of MEN1-associated neoplasms can already occur in early childhood. However, the majority of retrospective analyzes have confirmed that more than 85% of treatment-relevant tumor manifestations do not appear until as late as the 3rd decade of life.
MEN1, multiple endocrine neoplasia type 1; NEN, neuroendocrine neoplasia; pNENs, pancreatic neuroendocrine neoplasms

Despite our better understanding of the pathogenesis of the disease and the many diagnostic and therapeutic advances, the evidence on what could be the optimum diagnosis and treatment strategy is still scarce due to the rarity of the disease and the limited data available for certain tumor manifestations (e11). Given that the care and treatment of MEN1 patients is particularly challenging, it should be provided in specialized centers.

## Methods

This review is based on a selective search for pertinent literature in the PubMed database up to and including March 2024. Studies with the best available evidence (level III), retrospective case studies, German and international guidelines and our own experiences were analyzed and rated.

## Genetics

MEN1 is caused by a germline mutation of the *MEN1* gene on chromosome 11q13 which codes for the protein menin. Menin is considered to be a tumor suppressor. It has an effect on various signaling pathways related to the cell cycle; however, the exact function is still not fully understood (1). To date, more than 1300 distinct mutations have been described in the literature (10). Genetic testing is an important component of the diagnostic work-up of affected patients and their families. In the first instance, it confirms the diagnosis of MEN1 syndrome in index patients. Once the diagnosis is confirmed, MEN1 patients require a life-long structured follow-up for disease surveillance. In addition, all first-degree relatives of MEN1 patients and of persons who are carriers of the *MEN1* gene should undergo genetic testing for the *MEN1* gene. With this approach, carriers of the mutation can be identified (1). Genetic testing should also be initiated in cases presenting with two tumors with MEN1 characteristics, especially if these occur at a younger age. Up until now, a genotype-phenotype correlation could not be confirmed (e1, e11–e13).

Currently, no mutation can be detected in 5–10% of cases presenting with the clinical picture of MEN1 syndrome. A very rare finding in these cases is the presence of a germline mutation of the CDKN1B gene (11). This is a recently described subtype of the MEN1 disease, also referred to as MEN type 4. In addition to MEN type 4, a further subtype, MEN type 5, has also recently been described which is associated with mutations in the MAX *(MYC-associated factor X)* gene (e14, e15). While the phenotypes of MEN type 4 and 5 resemble that of MEN1, there are significant differences in the prevalence of some specific manifestations (11, e14 and e15).

Prenatal tests are also technically feasible. In Germany, however, such testing requires prior approval by an ethics committee.

## Diagnostic testing as part of a structured screening program

After clinical and genetic confirmation of the diagnosis, participation in a screening program is recommended to all patients with MEN1. There is currently no consensus on the age at which to start the screening and the intervals at which screening should be performed (12, 13). Sporadic case reports have shown that a small number of MEN1-associated neoplasms (especially insulinomas) can already occur in early childhood. However, the majority of analyzes have confirmed that more than 85% of treatment-relevant tumor manifestations do not appear until as late as the 3rd decade of life. (13–15).

No clear sex-specific difference has been found so far, except for thymic carcinoids which have been observed almost exclusively in men (estimated ratio of 20 : 1) (e1)

Given the complexity of the disease, specific diagnosis and treatment should be the responsibility of a multidisciplinary team (covering endocrinology, gastroenterology, surgery, radiology, nuclear medicine, and pathology) (16, 17).

At present, no recommendations regarding the examinations which should be performed as part of the screening program have been fully approved by consensus. At the Philipps University Marburg, a screening program, administered by an interdisciplinary team, is offered to asymptomatic MEN1 patients aged 16 years and over. The screening protocol was developed based on own experiences (13, e16) as well as international guidelines and recommendations (1, 12, 15, 18) *(eTable 1)*. There is no consensus among experts regarding which laboratory tests and imaging modalities should be used (e11). A detailed discussion of the diagnostic work-up is not part of this article.

**Table 2**

**Overview of retrospective studies (evidence level III) on surgical procedures for the main tumor manifestations of MEN1-associated neoplasms**

| Neoplasia | First author (reference) | Surgical procedure (n) | Recurrence or persistence | Other/outcome | | Conclusion |
|---|---|---|---|---|---|---|
| pHPT | Fyrsten (e20) | Total PTX (8) vs. subtotal PTX (30) vs. selective PTX (31) | 2/8 (25%) vs. 8/30 (27%) vs. 10/31 (32.3%) | Permanent postoperative hypoparathyroidism | 5/8 (62.5%) vs. 0/30 (0%) vs. 0/31 (0%) | Selective PTX resection possible, with low risk of hypoparathyroidism, but higher risk of recurrence |
| | Manoharan (22) | Total PTX (38) vs. subtotal PTX (23) vs. selective PTX (28) | 4/38 (10.5%) vs. 9/23 (39.1%) vs. 19/28 (68%) | | 12/38 (32%) vs. 4/23 (17%) vs. 0/28 (0%) | |
| | Santucci (e21) | Subtotal PTX (339) vs. selective PTX (178) | 152 (45%) vs. 121 (68.5%) | | ND | |
| Gastrinoma, ZES | Kong (34) | PD (11) vs. non-PD (24) | 1/11 (9%) vs. 8/24 (33.3%) | Normal gastrin levels | 9/11 (82%) vs. 5/24 (20.8%) | Long-term biochemical cure after PD possible |
| | | | | Disease-free survival | Median 134 vs. 44–70 months | |
| | | | | Liver metastases | 1/11 (9%) vs. 5/24 (20.8%) | |
| | Santucci (e25) | PD (18) | 4/18 (22.2%) | Normal gastrin levels | 11/18 (61%) | |
| | | | | Disease-free survival | 151 months | |
| | | | | Liver metastases | 3/18 (16.7%) | |
| Insulinoma | Van Beek (31) | Singular Parenchyma-sparing resection*1 (63) vs. Multifocal Extended pancreatic resection*2 (33) | 2/63 (3.2%) vs. 5/33 (15.2%) | 10-year disease-free survival | 96% vs. 81% | Parenchyma-sparing resection to be preferred |
| | | | | Liver metastases | 3/63 (4.8%) vs. 5/33 (15.2%) | |
| NF-pNEN | Partelli (28) | No surgery (33) vs. surgery (27) | 9/33 *3 (27.3%) 4/27 *3 (15%) | NF-pNEN-associated death | 0/33 vs. 0/27 | Active surveillance of NF-pNEN possible |
| | | | | Liver metastases | 1/33 (3%) vs. 3/27 (11.1%) | |
| | Nell (27) | No surgery (99) vs. surgery (53) | ND | NF-pNEN-associated death | 1/99 (1%) vs. 3/53 (5.7%) | |
| | | | | Liver metastases | 4/99 (4%) vs. 9/53 (17%) | |
| | | | | 10-year disease-free survival | 72% vs. 67% | |

*1 Enucleation, left-sided pancreatic resection
*2 Pancreaticoduodenectomy with or without enucleation/left-sided pancreatic resection
*3 Surgical intervention in case of tumor progression
ND, no data; MEN1, multiple endocrine neoplasia type 1; NF-pNEN, nonfunctioning duodenopancreatic neuroendocrine neoplasms;
Non-PD, left-sided pancreatic resection/duodenotomy /duodenotomy + left-sided pancreatic resection + enucleation at pancreatic head; PD, pancreaticoduodenectomy; pHPT, primary hyperparathyroidism; PTX, parathyroidectomy; vs., versus; ZES, Zollinger-Ellison syndrome

## Treatment strategy

It remains a challenge for physicians treating these patients to decide on the best possible treatment of MEN1-associated neoplasms. While surgical management is generally considered the primary treatment option, there is currently no consensus for all manifestations on the indication and timing of surgery and the surgical strategy *(eTable 2)*. There is a lack of prospective randomized trials to evaluate and determine optimum treatment strategies, and, given the rarity of the disease, it is unlikely that such studies will become available in the foreseeable future (evidence levels III–V) *(Table 2, Table 3)*.

The treatment of MEN1-associated pituitary adenoma is similar to that of sporadic pituitary adenoma. It is determined based on the size of the tumor and its functional activity. Most cases of nonfunctioning pituitary microadenomas (< 1 cm) that do not cause symptoms can be monitored over time, using imaging modalities such as MRI. According to retrospective data, two thirds of the patients had microadenomas which did not change in size over decades (19). Surgery is generally indicated in all cases of hormonally active pituitary adenomas (Cushing's disease) or macroadenomas which can cause, for example, visual impairment as the result of optic nerve

**Table 3**

**References with recommendations for MEN1-associated neoplasms**

| Reference | Year of publication |
|---|---|
| ENETS guidance paper for nonfunctioning pancreatic neuroendocrine neoplasms (29) | 2023 |
| ENETS guidance paper for functioning pancreatic neuroendocrine neoplasms (17) | 2023 |
| International consensus statement regarding MEN1-associated dpNENs (18) | 2021 |
| German S2k practice guideline neuroendocrine tumors (16) | 2018 |
| MEN-1 expert guideline (12) | 2012 |

ENETS, The European Neuroendocrine Tumor Society; dpNENs, duodenopancreatic neuroendocrine neoplasms; MEN1, multiple endocrine neoplasia type 1

compression due to their size (19). Prolactinomas are an exemption as they can usually be treated with dopamine agonists. In patients with prolactinoma, surgery is only performed in cases of insufficient response to drug treatment, drug intolerance and/or at the patient's request. The remission rate (50–90%) and the frequency of severe complications (5%), such as epistaxis, meningitis and visual deterioration, is similar to that for sporadic variants ([e17–e19]; evidence level III).

MEN1-associated primary hyperparathyroidism (pHPT) is diagnosed based on laboratory tests showing hypercalcemia (calcium >2.65 mmol/L) and elevated parathyroid hormone levels (parathyroid hormone >65 ng/L). Surgery is always indicated, given that long-term hypercalcemia can result in secondary damage such as osteoporosis, depression, kidney stones or gastric ulcers (20).

The extent to which the parathyroid gland tissue should be removed is subject to ongoing controversy. Given the fact that all parathyroid glands are affected due to the underlying genetic predisposition, bilateral neck exploration with subtotal (3.5 parathyroid gland resection) or total parathyroidectomy with autotransplantation of parathyroid tissue (12) was performed in the past (evidence level III). In order to prevent permanent hypoparathyroidism after surgery, subtotal parathyroid resection is performed, sparing 50 mg of parathyroid tissue with the most normal macroscopic aspect. After total parathyroidectomy, a simultaneous autotransplantation of the least hyperplastic parathyroid gland to the brachioradialis muscle of the non-dominant arm is performed (21) (evidence level III). In addition, concomitant cervical thymectomy is recommended to be performed along with both surgical procedures to eliminate ectopic parathyroid cells as a source of recurrence and to reduce the risk of thymic carcinoids. Between the studies, the recurrence rate after these surgical procedures varies between 0% and 70% and the risk of permanent hypoparathyroidism ranges between 0% and 60% (21). For this reason, selective parathyroid resection of the enlarged glands has recently been discussed as an alternative approach, as asymmetric parathyroid hyperplasia is common (21, 22, e20, e21) (evidence level III). With this focused surgical technique, the risk of postoperative permanent hypoparathyroidism is almost completely eliminated. Thus, it helps to prevent long-term effects of hypocalcemia, such as extrapyramidal abnormalities and cardiac arrhythmias as well as lifelong calcium and vitamin D supplementation. This in turn has a positive impact on quality of life (e21–e24). However, the high risk of recurrence associated with this selective procedure (up to 100%) is deliberately accepted, as patients often only develop a recurrence after several years which then again can be treated using a limited approach (22).

In the case of resectable neuroendocrine neoplasms (NEN) of the thymus, complete thymic resection is indicated, typically with lymphadenectomy. This is because thymic carcinoids metastasize early, are fast growing and therefore, despite their rarity, one of the main causes of MEN1-associated mortality (5) (evidence level III).

In patients with MEN1-associated bronchial NENs, segmental lung resection or lobectomy with lymphadenectomy is indicated in the following cases: functioning tumors, symptomatic tumors (e.g. with bleeding) and tumor size >2 cm. In the case of well-differentiated asymptomatic tumors <2 cm, annual follow-up seems to be sufficient (23) (evidence level III–V).

Regarding nonfunctioning adrenal lesions, there is discussion whether the indication for surgery should be the same as for sporadic adrenal adenomas: a tumor size of 4 cm or larger or native Hounsfield units (HU) >20, measured by native computed tomography (CT) (24, 25). Rare functioning adrenal tumors, such as pheochromocytoma and aldosterone-producing tumors, but also adrenocortical carcinomas, are always an indication for surgery. Up to a tumor size of 6 cm, all of these surgical procedures should be performed using a minimally invasive approach (25) (evidence level I).

Adequate treatment of duodenopancreatic neuroendocrine neoplasms (dpNENs) is also based on tumor size (>2 cm), observed growth dynamics and functional activity. Surgical treatment does not aim at resecting all dpNENs, but focusses on correcting any hormonal syndrome which may be present and on preventing metastatic spread and local complications. In addition, the preservation of organ function and thus quality of life should be given high priority. We strongly advise against performing prophylactic pancreatic resection, a surgical management strategy that was sometimes used in the past, as it is likely that after total pancreatectomy, the patient will develop diabetes which is difficult to control.

Nonfunctioning (NF) pancreatic neuroendocrine neoplasms (pNENs) are with 70–80% the most common manifestation of dpNENs. The malignancy rate of NF-pNENs is associated with tumor size. According to retrospective data, the risks of aggressive tumor progression and

metastatic spread (>30%) are significantly increased from a tumor size of 2 cm. Systematic reviews and prospective data have shown that active surveillance of small NF-pNENs <2 cm is acceptable (26–28). Thus, current guidelines (16–18, 29) (evidence level II–III) recommend the following indications for surgery:

- NF-pNENs >2 cm
- NF-pNENs between 1 and 2 cm, in case of rapid tumor growth (>20%/year or >5 mm/year) or high Ki67 index (>10%)
- Lymph node or distant metastases
- Imaging evidence of a dilated pancreatic duct.

For nonmalignant small NF-pNENs, a pancreatic parenchyma-sparing resection with lymph node sampling is recommended (18) *(eFigure)*. After parenchyma-sparing and also after extensive duodenopancreatic resections, occurrence of new pNENS in the residual pancreas is to be expected in 63% of cases, and almost 40% of patients with MEN1 will require further surgery at some point in their lives (18, 30). As an alternative to surgery for small NF-pNENs, radiofrequency ablation has recently been declared a successful treatment, especially for elderly patients (18). Larger (>2–3 cm) NF-pNENs require formal oncologic pancreatic resection with lymphadenectomy (evidence level III).

Functioning dpNENs include gastrinomas, insulinomas, vasoactive intestinal peptide (VIP)-secreting tumors (VIPomas), and glucagonomas. In the absence of diffuse metastasis, insulinomas should always be treated surgically in line with current guidelines (17). The aim is to use a parenchyma-sparing and, if possible, minimally invasive approach (31) *(eFigure)*. Endoscopic radiofrequency ablation is a new, but not yet sufficiently evaluated treatment option (17) (evidence level III).

Rare functioning dpNENs, such as VIPomas and glucagonomas, are often only diagnosed at an advanced stage, thus requiring oncologic pancreatic resection in the absence of diffuse metastasis or other contraindications. In patients with diffuse metastatic tumors, tumor debulking may also be attempted in order to reduce the effects of the hormonal syndrome (evidence level IV–V).

The effectiveness of somatostatin analogues (SSAs) with regard to the disease course in patients with MEN1-associated pNENs has been evaluated in a limited number of studies. For advanced metastatic disease, the same treatment options are essentially considered as for sporadic metastatic pNENs, i.e., in addition to SSA chemotherapy, targeted therapy with e.g. everolimus, sunitinib or a peptide receptor radionuclide therapy (16, 32) (evidence level III–V).

In contrast to the tumors discussed above, the optimum treatment for gastrinomas associated with MEN1, almost all of which are located in the duodenum and not in the pancreas, is still being discussed controversially (18). If a gastrinoma is confirmed by clinical and biochemical findings, some experts recommend drug therapy with proton pump inhibitors (PPIs) alone. This recommendation is based on retrospective data which showed that, despite lymphatic metastatic spread, a stable disease course was observed in 80% of cases (evidence level III). As a compromise, the indication for surgery is often established for MEN1-associated Zollinger-Ellison syndrome (ZES) if imaging demonstrates a pNEN with a tumor size >2 cm, even though virtually always a NF-pNEN as a surrogate marker is found and not duodenal gastrinomas. Furthermore, some experts, including the authors of this article, favor surgical treatment even when the diagnosis of ZES is based on biochemical findings alone. This is because it is possible today to achieve long- term biochemical cure with surgical treatment (34).

Another subject of controversy is the surgical strategy for MEN1-associated gastrinomas. There is a consensus that the surgical strategy must at least include duodenotomy with excision of duodenal wall gastrinomas as well as systematic lymphadenectomy if a biochemical cure is to be achieved and the risk of distant metastases reduced. However, the latest data show that long-term biochemical cure rates of 77 to 100% can only be achieved with partial pancreaticoduodenectomy (34) (evidence level IIa–III).

When deciding on a treatment, the preference of the fully informed patient should always be taken into account.

Breast cancers and meningiomas associated with MEN1 are treated according to stage in the same way as sporadic tumors (e8, e9).

## Prognosis and quality of life

With regular screening examinations and early treatment, an improvement in the mean life expectancy of patients with MEN1 compared to historic cohorts before 1990 (1964–1989) is noted (5–7, 9). And yet, their life expectancy still remains at least ten years lower than that of the general European population. The data show that advances in medical care are associated with an improved prognosis of MEN1 patients. Nevertheless, there is a need to further optimize the diagnosis and treatment strategies (7, 8).

Despite the increase in life expectancy, the health-related quality of life of patients with MEN1 is found reduced compared to the normal population (35, 36). Persistent hypercalcemia as well as frequent visits to the doctor, but also first diagnosis of the disease before age 45 years were associated with lower health-related quality of life (36–38). The data highlight the great importance of maintaining the patients‘ quality of life. This goal should be a key consideration in treatment decisions. While psycho-oncological support is not yet an integral part of the MEN1 screening program, it should be taken into account to optimize the management of these patients.

## Conclusion

The identification of the gene that causes MEN1 has deepened our understanding of the disease and led to advances in the diagnosis and treatment of the condition. Screening programs in specialized centers can help to detect tumor manifestations in time and provide organ-sparing treatment. With this approach, it has been possible to improve both life expectancy and quality of life. Nevertheless, some questions still remain as to how best to diagnose the disease and optimize the treatment strategy. The answers to these questions can only be found by conducting multicenter long-term studies in the future.

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**Supplementary material**
**eReferences, eTables, eFigure:**
**www.aerzteblatt-international.de/m2024.0094**

## CLINICAL SNAPSHOT

# Orbital Floor Involvement in Granulomatosis With Polyangiitis

A 35-year-old woman presented to our Rheumatology Department. She complained of bloody nasal discharge, hemoptysis and mild dyspnea, as well as myalgia and arthralgia. She had been treated for this condition in Ukraine and only recently immigrated to Germany. No previous medical findings were available. On clinical examination, the patient had a saddle nose *(Figure a, arrow)* and enophthalmos *(Figure b, line)*. A computed tomography scan of the paranasal sinuses *(Figure b)* showed extensive bony destruction, including the basal and medial orbital walls (*) as well as all turbinates (x) and the nasal septum (#). She had no history of visual impairments. Given the obvious and typical clinical findings, granulomatosis with polyangiitis was suspected. The diagnosis was confirmed by further diagnostic evaluation, showing pulmonary and renal involvement as well as positive PR3-ANCA findings. Treatment with rituximab was initiated. Although the condition is rare, granulomatosis with polyangiitis should be considered a possible cause of persistent bloody rhinitis and/or hemoptysis in order to halt the immune-mediated osseous destruction.

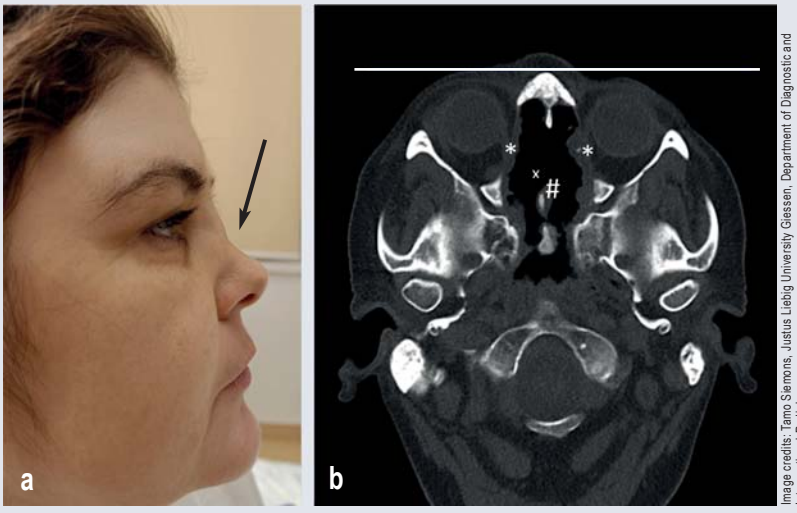


**Figure:**
a) Clinical presentation, "arrow" saddle nose; b) CT of the paranasal sinuses
*bony destruction of both medial orbital walls; # bony destruction of the nasal septum, x bony destruction of all turbinates; line: enophthalmos of the right eye

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**Conflict of interest statement:** The authors declare no conflict of interest.

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**Supplementary material** to accompany the article:

# Multiple Endocrine Neoplasia Type 1

## The Current Status of Disease Management

by Jerena Manoharan, Max B. Albers, Anja Rinke, Jan Adelmeyer, Jannis Görlach, and Detlef K. Bartsch

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**eTable 1**

**MEN1-associated NENs – Screening Program– Marburg Protocol**

| Organ manifestation | Signs & symptoms | Laboratory testing | Diagnostic imaging |
|---|---|---|---|
| **Anterior pituitary gland (micro- /macroadenomas)** | | | |
| Prolactinoma | Amenorrhea, hypogonadism, galactorrhea, infertility, loss of libido | Prolactin, prolactin diluted | MRI (in case of normal findings, follow-up scan every 3 years) |
| Somatotropinoma | Acromegaly | IGF-1, hGH | |
| Corticotropinoma | Cushing's disease | ACTH, cortisol, 24-hour cortisol urine test, dexamethasone suppression test | |
| Nonfunctioning adenomas | Hypopituitarism, visual field defects, expansile growth | Basal pituitary blood tests | |
| **Parathyroid glands** | | | |
| Primary hyperparathyroidism | Kidney stones<br>Bone and joint pain<br>Depression<br>Tiredness and fatigue<br>Gastritis<br>Gastric or duodenal ulcers<br>Osteoporosis | Calcium<br>Parathyroid hormone<br>25-OH vitamin D<br>24-hour urine testing for calcium and creatinine | In case of confirmation by lab tests:<br>– Cervical ultrasound<br>– 99mTc-MIBI scintigraphy<br><br>In case of a recurrence: if negative ultrasound and 99mTc-MIBI scintigraphy findings: MRI and/or fluorocholine PET/CT |
| **Duodenopancreatic neoplasms** | | | |
| NF-pNENs | Usually asymptomatic<br>With large tumors, pain on palpation, icterus, etc. | Chromogranin A*<br>Pancreatic polypeptide* | Annual EUS and MRI<br>$^{68}$Ga-DOTATOC PET/CT if metastases are suspected<br><br>Possibly $^{18}$F-FDG PET/CT<br>– in case of G2/G3 tumors |
| Gastrinomas | Gastric ulcers<br>Abdominal symptoms<br>Diarrhea | Serum gastrin<br>Gastric pH | EUS and esophagogastroduodenoscopy + pH measurement + FNA<br>$^{68}$Ga-DOTATOC PET/CT every 2–3 years or in case of suspected metastases |
| Insulinoma | Whipple's triad: hypoglycemia+ associated neurological/autonomous symptoms (e.g., sweating, tremor, tachycardia, dizziness, confusion) + symptoms improve after raising blood glucose levels | Insulin<br>Fasting glucose<br>C-peptide<br>72-hour fasting test | EUS with FNA and MRI<br>$^{68}$Ga PET/CT<br><br>if negative or in case of multiple pNENs, possibly GLP-1 PET/CT |
| VIPoma/glucagonoma | VIPoma:<br>Verner-Morrison syndrome with marked watery diarrhea<br>+ electrolyte imbalances<br><br>Glucagonoma:<br>Erythema necrolyticum migrans<br>Cheilitis<br>Glossitis, nail dystrophy, diarrhea<br>Abnormal blood glucose metabolism | Vasoactive polypeptide,<br>Chromogranin A<br><br>Glucagon<br>Chromogranin A | EUS and MRI/CT<br>In addition $^{68}$Ga-DOTATOC PET/CT, possibly supplemented by $^{18}$F-FDG PET/CT in case of G2/G3 tumors |
| **Adrenal glands** | | | |
| Adrenal adenomas<br>Adrenocortical carcinomas<br>Pheochromocytomas | Frequently nonfunctioning,<br>Cushing's syndrome<br>Invasive growth,<br>abdominal symptoms,<br>arterial hypertension, profuse sweating, headaches | In case of lesions >1 cm or functioning neoplasms:<br><br>Plasma renin<br>Plasma aldosterone<br>Overnight dexamethasone inhibition test<br>24-hour urine test, cortisol, catecholamines and/or metanephrines in urine | EUS and MRI,<br>possibly MIBG scintigraphy or $^{18}$F-Fluorodihydroxyphenylalanine (DOPA) PET/CT for pheochromocytoma<br>possibly $^{11}$C-metomidate PET/CT for Conn's adenoma |
| **Thymus and lungs** | | | |
| Bronchial NEN | – | – | Chest CT (every 2 years)<br>In case of lesions >1 cm:<br>In addition $^{68}$Ga-DOTATOC PET/CT, possibly supplemented by $^{18}$F FDG PET/CT for G2/G3 tumors |
| Thymic carcinoids | – | – | |

| Breast | | | |
|---|---|---|---|
| Breast cancer | As for sporadic breast cancer | – | Annual gynecological examination<br>Mammography every 2 years |

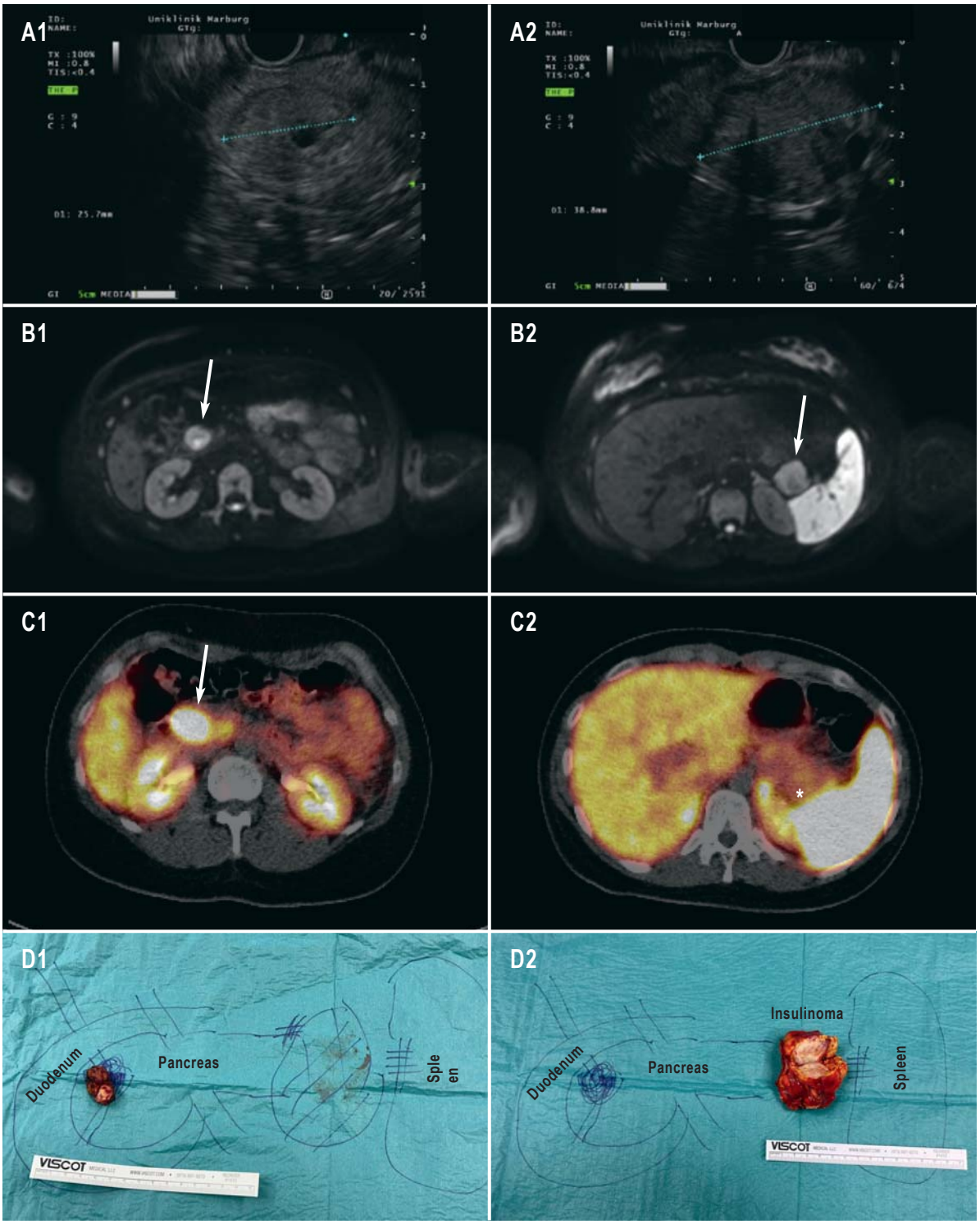
All mutation carriers over the age of 16 are recommended to participate in the regular screening program. In symptomatic patients, symptom-oriented screening is already indicated prior to age 16 years.
*Diagnostic value disputed
ACTH, adrenocorticotrophic hormone; BG, blood glucose level; EUS, endoscopic ultrasound ; CT, computed tomography, FNA, fine-needle aspiration; hGH, human growth hormone; IGF-1, insulin-like growth factor 1; MRI, magnetic resonance imaging; NENs, neuroendocrine neoplasms; NF-pNENs; nonfunctioning pancreatic neuroendocrine neoplasms; PET/CT, positron emission tomography; VIP, vasoactive intestinal peptide

**eTable 2**

**Surgical indication for MEN1-associated neuroendocrine tumor manifestations**

| Manifestation | Surgical indication |
|---|---|
| Primary hyperparathyroidism | • Laboratory findings (calcium >2.65 mmol/L and parathyroid hormone > 65 ng/L) + symptoms (bone pain, stomach pain, difficulty concentrating, fatigue, depression, etc.)<br>• Relative surgical indication: laboratory findings in asymptomatic pts |
| Pituitary adenomas | • Macroadenomas with/without compression syndrome (usually visual field defects)<br>• Functioning adenoma that cannot be controlled with medication |
| dpNENs | • Tumor size >2 cm<br>• Functional activity*<br>• Tumor size 1–2 cm, in case of G2/G3 or growth > 20% per year<br>• Tumor-related obstruction of the pancreatic duct<br>• In case of suspected lymph node or distant metastases in imaging studies |
| Adrenal adenomas | • Tumor size >4 cm<br>• Tumor growth 20% within the follow-up interval of 6–12 months (at least 5 mm)<br>• Functional activity |
| Bronchopulmonary NENs | • Tumor size >2 cm or symptoms (e.g. hemorrhage)<br>• Functional activity |
| Thymic NENs | • Detection based on imaging morphology |

*The surgical indication and surgical strategy for MEN1-associated Zollinger-Ellison syndrome is the subject of controversy
dpNEN, duodenopancreatic neoplasms; NENs, neuroendocrine neoplasms; pts, patients




**eFigure: Organ-sparing surgical treatment of MEN1 patient with multiple pNENs** A young female patient (in her twenties) presented with abdominal complaints. Initial imaging revealed two masses, one located in the head and one in the tail of the pancreas (marked with → in B1, B2 and C1). Further diagnostic testing confirmed organic hyperinsulinism. Moreover, the young patient had been diagnosed with a macroprolactinoma two years earlier. Genetic testing confirmed the diagnosis of MEN1. Endoscopic ultrasound revealed multiple (> 5) pNENs <1 cm in addition to the two known masses (A1, pancreatic head mass with a tumor diameter of 25.7 mm; A2, pancreatic tail mass with a tumor diameter of 38.8 mm). A supplementary MRI examination was also obtained (B1, pancreatic head mass; B2, pancreatic tail mass) as well as a $^{68}$Ga-DOTATOC PET/CT (C1, pancreatic head mass; C2, pancreatic tail mass). The mass in the pancreatic tail (C2) showed no tracer enhancement (*) in the $^{68}$Ga-DOTATOC PET/CT scan. The two masses, measuring >2 cm in diameter, in the head and tail of the pancreas were only treated with an organ-sparing pancreatic tail resection and an enucleation of the pancreatic head lesion, while the remaining NF-pNENs <1 cm were left in place. Image series D shows the surgical specimens (D1, enucleation pNEN from the pancreatic head; D2, organ-sparing pancreatic tail resection of an insulinoma). Histopathology confirmed that the pancreatic head lesion was a well- differentiated neuroendocrine tumor (G1) and the pancreatic tail lesion an insulinoma G1 pT2 pN1 (2/16) L0 V0 Pn0 R0. In the peripancreatic adipose tissue that was also removed during the organ-sparing pancreatic tail resection, two microscopically small lymph node metastases were identified. (Photos A1 and A2: Prof. Denzer, Philipps University, Marburg, Germany)

**Questions** on the article in issue 16/2024:

CME plus+

# Multiple Endocrine Neoplasia Type 1

The submission deadline is 8 August 2025. Only one answer is possible per question.
Please select the answer that is most appropriate.

### Question 1

**According to the article, what is the inheritance pattern of the predisposition to develop multiple endocrine neoplasia type 1 (MEN1)?**

a) Autosomal recessive inheritance
b) X-chromosomal inheritance
c) Y-chromosomal inheritance
d) Autosomal dominant inheritance
e) Intermediate inheritance

### Question 2

**In which year was the gene that causes multiple endocrine neoplasia type 1 (MEN1) identified?**

a) 1967
b) 1986
c) 1997
d) 2011
e) 2020

### Question 3

**According to the article, which of the following MEN1-associated neoplasms have so far been observed almost exclusively in men (male-to-female ratio of occurrence: approx. 20 : 1)?**

a) Thymic carcinoids
b) Thyroid carcinoids
c) Adrenal carcinoids
d) Gastric carcinoids
e) Bronchopulmonary carcinoids

### Question 4

**Which of the following statements about duodenopancreatic neuroendocrine neoplasms (dpNENs) is most likely to be true, according to the article?**

a) Surgical management strategies are not recommended for dpNENs.
b) Duodenopancreatic neoplasms generally do not appear before the 7th decade of life.
c) One should refrain from performing prophylactic total pancreatectomy.
d) The aim of surgical treatment of duodenopancreatic endocrine neoplasms should be the complete resection of all neoplastic areas.
e) Duodenopancreatic neoplasms can only be surgically removed up to a tumor size of <1 cm.

### Question 5

**According to the article, which of the following tumor entities is, despite its rare occurrence, one of the main causes of MEN1-associated mortality due to its rapid growth and early metastasis?**

a) Angiofibroma
b) Breast cancer
c) Meningioma
d) Primary hyperparathyroidism
e) Thymic carcinoid

### Question 6

**Which of the following tumors is not one of the functioning duodenopancreatic neoplasms mentioned in the text?**

a) Gastrinoma
b) Insulinoma
c) VIPoma
d) Proteasoma
e) Glucagonoma

### Question 7

**As per the article, how many different mutations have been described in the literature so far?**

a) < 10
b) Approx. 20
c) Approx. 130
d) >1300
e) > 3000

### Question 8

**For what proportion of cases with a clinical picture of MEN1 is it currently not possible to identify mutations, according to the article?**

a) 0.5–1%
b) 5–10%
c) 15–20%
d) 35–45%
e) 60–75%

### Question 9

**Which of the following diagnostic tools is not listed in the article as part of the Marburg protocol for the screening of MEN1-associated neuroendocrine neoplasms under the laboratory tests for insulinoma diagnosis?**

a) Insulin testing
b) Fasting blood glucose
c) C-peptide
d) 72-hour fasting test
e) Oral glucose tolerance test

### Question 10

**Which of the following clinical manifestations is not listed as a symptom of primary hyperparathyroidism in the article when describing the Marburg protocol for the screening of MEN1-associated neuroendocrine neoplasms?**

a) Kidney stones
b) Diplopia
c) Depression
d) Gastritis
e) Osteoporosis