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ORIGINAL ARTICLE

Multiple endocrine neoplasia type 1 (MEN1): its manifestations and effect of genetic screening on clinical outcome

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Summary

Objective Effect of genetic screening on outcome in multiple endocrine neoplasia type 1 (MEN1) remains unclear. Expression of MEN1 is described using currently available diagnostic techniques. Manifestations and outcome are compared in patients diagnosed because of clinical expression with those diagnosed by genetic screening.

Design Retrospective cohort study. Patients are divided into two groups: patients with a (i) clinical MEN1 diagnosis and (ii) MEN1 diagnosis by genetic screening.

Patients and measurements Demographic and clinical data were collected on MEN1 patients treated in the UMCU up to 1 January 2008. Results of mutation analysis were obtained from the Department of Medical Genetics.

Results A total of 74 patients was included (median follow-up 5·5 year); 78% had hyperparathyroidism, 46% a pancreatic neuro-endocrine tumour (NET), 38% a pituitary abnormality, 8% a NET of other origin and 16% an adrenal adenoma at the end of follow-up. Of the patients 18% had no manifestation. All five MEN1-related tumours were seen as first manifestation. Compared with patients identified by genetic screening, patients with a clinical MEN1 diagnosis had significantly more manifestations at diagnosis ($P < 0{\cdot}001$) and at end of follow-up ($P = 0{\cdot}002$). Eleven of 30 patients with a genetic MEN1 diagnosis (mean age at diagnosis 30·0 years) already had manifestations at diagnosis. No malignancy or death was seen in genetically diagnosed patients.

Conclusions MEN1 is a syndrome with high morbidity. Genetic diagnosis is associated with less morbidity at diagnosis and at follow-up. Early genetic diagnosis might therefore lead to improvement of long-term outcome.

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Introduction

Multiple endocrine neoplasia type 1 (MEN1) is a rare autosomal inherited disorder. Patients suffer from multiple tumours originating in different endocrine organs, sometimes even from a very young age.[1] This syndrome is characterized by the combined occurrence of (i) parathyroid hyperplasia or adenomas (ii) neuro-endocrine tumours (NETs) of the pancreas (pancreatic endocrine tumour PET) (iii) NET of the gastro-intestinal tract, thymus or bronchus (iv) pituitary abnormalities and (v) adrenal hyperplasia or adenomas. Lipomas, leimyomas and skin disorders such as angiofibromas and collagenomas are also frequently seen. The reported prevalence of the principal manifestations among MEN1 patients varies.[2–5] In the Netherlands the prevalence of MEN1 syndrome is estimated to be 2–3/100 000.[6] MEN1 is caused by a germline mutation in the *MEN1* gene on chromosome 11, which is inherited in an autosomal dominant fashion.[7] Germline mutations are mutations in the DNA of germ cells and, with embryonic development, will be found in all cells of the body. The mutation is carried on from generation to generation. The *MEN1* gene that was identified in 1997, encodes for the tumour suppressor protein menin.[7] This protein is involved in the regulation of cell proliferation. Absence of the menin protein leads to development of tumours. Almost everyone with a mutation in the *MEN1* gene will eventually develop the clinical MEN1 syndrome.[1] The clinical definition of MEN1, as is used in the Netherlands, is the combined occurrence of three out of the five manifestations mentioned above.[6] In a MEN1 family patients are considered to be affected if they have one out of five manifestations combined with MEN1 in a first degree relative. DNA-analysis is a powerful tool in the diagnosis of MEN1 syndrome. In a previously published Dutch study a *MEN1* mutation was found in all patients who fulfilled the clinical criteria for MEN1.[8] When the mutation is known in a MEN1 family, genetic (presymptomatic) screening of the family members is an option. Chances of having the MEN1 syndrome are 60% in patients from the general population if one of the following criteria is met: (i) age under 35 years and one of the five principal tumours (ii) more than one MEN1-associated lesion in one organ and (iii) two of the five principal tumours.[8] If a patient meets one of these criteria *MEN1* mutation analysis is justified.

Signs and symptoms of MEN1 occur as a consequence of overproduction of hormones, local mass effects or malignancy. Most MEN1-associated tumours are benign, but especially the NETs of the pancreas, the gastro-intestinal tract, the thymus and the bronchus might become malignant. MEN1 patients have a decreased life expectancy compared with the general population.[9–11] Today, malignancy – mostly from PETs – is the main MEN1 related cause of death.[9,10] If a familial MEN1 syndrome is present, early genetic diagnosis subsequently followed by periodical monitoring for tumour manifestations if a mutation is confirmed, might lead to a better life expectancy and a better quality of life.[11] One small study in MEN1 patients showed a tendency towards better outcome in patients diagnosed by genetic screening.[12] However, it still remains unclear whether genetic screening does lead to a better outcome.

The aim of this study is to describe the sequence of manifestations in a Dutch MEN1 cohort using currently available diagnostic techniques. Second, to compare the prevalence of MEN1 manifestations in patients diagnosed clinically with those diagnosed by genetic screening. We assessed if presymptomatic screening for a *MEN1* mutation can identify patients before manifestations have occurred and if genetic screening leads to a better outcome at follow-up. The spectrum of manifestations within each identified mutation was also studied.

Patients and measurements

The hospital diagnosis registries (using data from 1978 to 2007) of the University Medical Center Utrecht for patients with MEN1 were used to identify the patients. All patients > 16 years with a definite MEN1 diagnosis were included. Clinical and demographical information was collected from included patients and the medical records were reviewed for patient demographics, presence and timing of MEN1 related manifestations and death. The patients were divided into two groups. Group I consisted of patients with a clinical MEN1 diagnosis and group II consisted of patients diagnosed by genetic screening. Patients diagnosed by combined clinical and genetic findings were included in group I.

A clinical diagnosis of MEN1 was made when clinical criteria were met or when a patient had one of the five principal manifestations in combination with a positive family history. A genetic diagnosis was made if a patient was diagnosed by presymptomatic genetic screening. When the diagnosis of MEN1 was suspected, based on two of the five principal manifestations, in a patient with a negative family history which was subsequently genetically confirmed, it was considered to be a combined clinical and genetic diagnosis.

The protocol for periodical screening of MEN1 patients used, was based on the consensus guidelines published by Brandi *et al.* in 2001[13] (Table 1). Before 2001 the usual care for all MEN1 patients was in line with this protocol and based on the experience of the individual caregivers. Identical periodical screening was carried out in all MEN1 patients according to this protocol, regardless of the manner of diagnosis (clinical or genetic diagnosis).

Hyperparathyroidism was defined as the first reported episode of abnormal laboratory investigations (calcium, PTH).

A PET was confirmed when it was visible on imaging studies [magnetic resonance imaging (MRI) examination, CT-scan, endoscopic ultrasound (EUS) and/or somatostatin receptor scintigraphy (SRS)]. Functionality of PETs was determined by relevant laboratory investigations. Results of secretin tests were not included because reference values were lacking.

A pituitary abnormality was confirmed when this was identified on MRI-examination. Functionality was determined by laboratory investigations (PRL and IGF-1).

An adrenal tumour was identified using imaging studies (MRI-examination, CT-scan or SRS) to show an adrenal lesion. Functionality of adrenal tumours (Cushing, pheocromocytoma, Conn) was determined by relevant laboratory investigations.

A NET of the gastro-intestinal tract, thymus or bronchus was identified when laboratory investigations (5-hydroxyindoleacetic acid and/or platelet serotonin) and imaging studies (MRI, CT-scan and/or SRS) were abnormal and the diagnosis was confirmed by biopsy.

Indications for interventions and subsequent interventions (e.g. medical and/or surgical) once a manifestation was diagnosed, did not differ between the patients diagnosed clinically and genetically.

Genetic analysis for MEN1 was initially performed by linkage analysis, using highly polymorphic DNA-markers near the MEN1 locus on chromosome 11q13. Following the identification of the MEN1 gene itself in 1997, direct mutation testing by DNA sequencing has become available. With direct mutation analysis the base-sequence

Table 1. Protocol for periodical screening of MEN1 patients*

	Starting age (years)	Frequency	Content
Visit outpatients clinic	5	Biannually	History and physical examination
Laboratory investigations	5	Biannually	Ionised calcium, chloride, phosphate, PTH, fasting glucose, fasting insulin, fasting c-peptide, glucagon, fasting gastrin, pancreatic polypeptide, PRL, IGF-1, platelet serotonin, chromogranin A.
Imaging studies	15	Every 2 years	MRI of upper abdomen MRI of pituitary (iv. contrast with gadolinium) MRI of mediastinum (in males)

*MEN1 patients, *MEN1* gene germline mutation carriers and MEN1 suspected patients without a confirmed mutation are eligible for periodical clinical monitoring.
MRI, magnetic resonance imaging; iv, intravenous.

of the *MEN1* gene in a symptomatic patient is determined and compared to a normal reference sequence. In this way the presence or absence of a specific mutation can be determined. Next to sequencing, large deletions or duplications in the *MEN1* gene are also sought for by using the multiplex ligation-dependent probe amplification assay.

The follow-up of the patients included in this study was part of regular medical care. The approaches described in this paper did not involve any randomization, experimental intervention or questionnaire and the anonymity of patients was not breached. As this article meets the conditions required under Dutch Law (WGBO) for making medical and/or personal data available for statistical or other scientific research, the Medical Ethics Review Committee of the University Medical Center Utrecht concluded that the Medical Research Involving Human Subjects Act (WMO) is not applicable.

Statistical analysis

SPSS 13·0 (SPSS Inc., Chicago, IL) was used for statistical analyses. In describing the study population and outcomes the mean ± SD or median (IQR) was calculated, depending on the normal distribution. Differences between these variables were determined with, respectively, the student's *t*-test or the Mann–Whitney *U*-test. To detect significant differences in the number of manifestations between the two groups Pearson's χ^2-test was used. Differences were considered significant if $P < 0{\cdot}05$.

Results

Study population

According to the hospital registries 100 patients were initially identified. However, in 22 patients the diagnosis of MEN1 was uncertain and therefore they were excluded from the present study. These patients had attended the MEN1 screening program for several years because of a positive family history, but they neither developed any clinical manifestation nor was mutation analysis performed. On four patients insufficient information was available and therefore they were also excluded from the present study. Subsequently, 74 patients were included in whom all tests and imaging procedures were performed.

General characteristics of the patients are shown in Table 2. The study population consisted of 74 patients from 21 different MEN1 families. The median follow-up was 5·5 years (IQR 2·25–12·0; range 0–31). Forty-three (58%) patients were diagnosed clinically (including six patients with a combined clinical and genetic diagnosis) and 30 (41%) patients were diagnosed by genetic screening. Of one patient the diagnostic method could not be determined.

Clinical manifestations

There were a median of 2 (IQR 1–3; range 0–5) prevalent manifestations in the study population. The prevalence of each individual manifestation is shown in Table 3. Thirteen *MEN1* mutation carriers have not (yet) shown any clinical manifestation of the syndrome. The median duration of follow-up in this group was 2·5 years (IQR 0·5–4·75; range 0–5) and the mean age at the end of follow-up was 32 ± 13 years (range 16–66). In the 61 patients who have clinical expression of the syndrome, the first manifestation was primary hyperparathyroidism in 44 (72%) patients, a PET in 16 (26%) patients, a pituitary abnormality in 10 (16%) patients, a NET of the gastro-intestinal tract, thymus or bronchus in 2 (3%) patients and an adrenal adenoma in 2 (3%) patients. There are 11 patients in whom more than one manifestation occurred simultaneously at the time of the first manifestation. The mean age at first manifestation was 32 ± 13 years (range 11–68). In 16 (22%) patients the first manifestation occurred before MEN1 was diagnosed. The median time interval between the occurrence of the first manifestation and subsequent MEN1 diagnosis was 9·5 years (IQR 3·25–18·25; range 1–36).

Table 2. Patient characteristics

Characteristics	Group I ($n = 43$) clinical MEN1 diagnosis	Group II ($n = 30$) genetic MEN1 diagnosis	Total ($n = 74$)*
Sex M/F (%)	22/21 (51/49)	12/18 (40/60)	35/39 (47/53)
Mean age at diagnosis years ± SD (range)†	34 ± 14 (11–64)	30 ± 14 (16–67)	32 ± 13 (10–64)
Median year of diagnosis	1994	2002	1998
Mean age at end follow-up years ± SD (range)‡	47 ± 14 (26–77)	36 ± 14 (16–67)	42 ± 15 (16–77)
Median follow-up years (IQR; range)§	11 (4·0–17·0; 0–31)	3 (2·0–6·0; 0–13)	5·5 (2·25–12·0; 0–31)
Death/alive	10/33	0/30	10/64
Death MEN1 related			
Yes	5		5
No	0		0
Unknown	5		5
Mean age death ± SD (range)	52 ± 16 (26–72)	Not applicable	52 ± 16 (26–72)

*In one patient the diagnostic method could not be determined; †Age at diagnosis was not different between group I and II ($P = 0{\cdot}151$); ‡Not including diseased patients; age at the end of follow-up differed significantly between group I and II ($P < 0{\cdot}0001$); §Follow-up differed significantly between group I and II ($P = 0{\cdot}001$).

Table 3. Prevalence of manifestations in the study population

	Group I ($n = 43$) Clinical MEN1 diagnosis		Group II ($n = 30$) Genetic MEN1 diagnosis		Total ($n = 74$)*	
Manifestation	*n* (%)	Mean age at diagnosis ± SD (range)	*n* (%)	Mean age at diagnosis ± SD (range)	*n* (%)	Mean age at diagnosis ± SD (range)
HPT	41 (95)	32 ± 10 (11–61)	16 (53)	33 ± 14 (14–65)	58 (78)	32 ± 11 (11–65)
HPT first	31		13		44	
PET	28 (65)	38 ± 15 (13–68)	6 (20)	30 ± 13 (15–47)	34 (46)	37 ± 15 (13–68)
Gastrin	14		3		17	
Insulin	4		0		4	
Glucagon	7		0		7	
VIP	2		0		2	
PP	9		3		12	
GHRH	1		0		1	
NF	6		2		8	
PET first	12		4		16	
PIT	21 (49)	35 ± 14 (12–69)	7 (23)	31 ± 13 (15–52)	28 (38)	34 ± 14 (12–69)
Prolactin	10		4		14	
GH	4		0		4	
ACTH	1		0		1	
NF	8		4		13	
PIT first	6		4		10	
NET	6 (14)	40 ± 9 (29–50)	0 (0)	NA	6 (8)	40 ± 9 (29–50)
Stomach	1				1	
Bronchus	1				1	
Thymus	3				3	
Unknown	1				1	
NET first	2		0		2	
ADR	10 (23)	48 ± 11 (30–62)	1 (3)	NA	12 (16)	48 ± 11 (30–62)
NF	10		1		12	
ADR first	1		1		2	
Patients with no clinical expression	0	NA	13 (43)	NA	13 (18)	NA

*In one patient the diagnostic methods could not be determined.
ACTH, corticotrophin; ADR, adrenal adenoma; GH, growth hormone; GHRH, growth hormone releasing hormone; HPT, hyperparathyroidism; NA, not applicable; NET, neuro-endocrine tumour; NF, non functioning; PET, pancreatic endocrine tumour; PIT, pituitary abnormality; PP, pancreatic polypeptide; VIP, vasoactive intestinal peptide.

Clinical vs. *genetic diagnosis*

General characteristics of groups I and II are shown in Table 2. The mean age at MEN1 diagnosis was 34 ± 14 years for clinically diagnosed patients and 30 ± 14 for genetically diagnosed patients ($P = 0{\cdot}151$). Duration of follow-up was significantly ($P = 0{\cdot}001$) shorter in genetically diagnosed patients than in clinically diagnosed patients [median 11 years (IQR 4–17·0; range 0–31) *vs.* 3 years (IQR 2·0–6·0; range 0–13), respectively]. The prevalence of manifestations at the end of follow-up in both groups is shown in Table 3.

The prevalence of manifestations at the time of MEN1 diagnosis in both groups is shown in Table 4. When comparing the number of manifestations at diagnosis between the two groups, significantly more manifestations were observed in patients diagnosed clinically ($P < 0{\cdot}001$). One of the families in this study (previously reported by Dreijerink *et al.*) has shown a very low penetrance of the MEN1

Table 4. Prevalence of manifestations at the time of MEN1 diagnosis

Number of manifestations at the time of MEN1 diagnosis	Group I 'clinical MEN1 diagnosis' ($n = 43$) *n* (%)	Group II 'genetic MEN1 diagnosis' ($n = 30$) *n* (%)
None	0 (0)	19 (63)
1	17 (40)	6 (20)
2	11 (26)	5 (17)
3	3 (7)	0 (0)
4	2 (5)	0 (0)
5	1 (2)	0 (0)
Unknown	9 (21)	0 (0)

The number of manifestations differs significantly between both groups ($P < 0{\cdot}001$).

Table 5. Prevalence of manifestations at the end of follow-up*

Number of manifestations at the end of follow-up	Group I 'clinical MEN1 diagnosis' ($n = 18$)† *n* (%)	Group II 'genetic MEN1 diagnosis' ($n = 30$)‡ *n* (%)
None	0 (0)	13 (43)
1	2 (11)	8 (27)
2	5 (28)	5 (17)
3	6 (33)	4 (13)
4	3 (17)	0 (0)
5	1 (6)	0 (0)
Unknown	1 (6)	0 (0)

The number of manifestations differs significantly between both groups ($P = 0{\cdot}002$).
*In patients with year of diagnosis ≥ 1994; †Median follow-up: 5 years (range: 0–11); ‡Median follow-up: 3 years (range 0–13); follow-up differed significantly between the two groups ($P < 0{\cdot}0001$).

syndrome.[14] Only two of the 10 *MEN1* mutation carriers show clinical expression of the syndrome and in all cases, except the index case, the diagnosis was made genetically. Because this family could bias the results, we also made the comparison without this particular family. In that case there were also significantly more prevalent manifestations at diagnosis in patients diagnosed clinically ($P < 0{\cdot}001$).

We also calculated the number of manifestations at the end of follow-up in each group (Table 5). To create more comparable groups only those patients diagnosed clinically in or after 1994 have been included in this analysis. Patients diagnosed genetically had fewer manifestations at the end of follow-up ($P = 0{\cdot}002$). When again excluding the aforementioned family, the difference between clinically and genetically diagnosed patients was still significant ($P = 0{\cdot}036$).

Malignancy and mortality

In the study population 10 patients (14%) suffer(ed) from malignant NETs as defined by the presence of metastases. Six patients had a PET, three patients a NET of the thymus and one patient a NET of unknown origin. These patients were all diagnosed clinically.

The time of PET diagnosis ranged from 4 months before –205 months after MEN1 diagnosis. Three patients already had metastases at the time of PET diagnosis, in the other three they developed after 20, 31 and 45 months, respectively. Three patients have died because of tumour progression (FU after diagnosis of metastases ranged from 39 to 65 months). The other patients are alive with disease 4, 32 and 61 months after the diagnosis of metastases.

The diagnosis of a NET of the thymus was made at initial MEN1 diagnosis in one patient and 12 and 371 months before MEN1 diagnosis in the other two patients. One patient had already metastases at NET diagnosis, in the other two metastases developed after 51 and 239 months. All patients have died, one because of tumour progression. Of the other two the cause of death could not be determined. The follow-up after the diagnosis of metastases ranged from 28 to 115 months.

One patient had a metastasized NET of unknown origin at the time of MEN1 diagnosis. This patient died 2 months after the diagnosis from tumour progression.

Three patients without malignant disease died from unknown causes. All were diagnosed clinically.

Clinical spectrum within mutations

The clinical spectrum within each mutation is shown in Table 6. We only depict manifestations of which three or more representatives were found in our population. The results show that within each mutation there is a wide clinical spectrum. This goes for both the type of manifestations and for the number of manifestations in each

Table 6. Clinical spectrum for each mutation

	357del4	IVS3-6 (c > g)	Lys120del	Lys362Stop	IVS7+5 (g > a)	Ala390Val	1178ins8
Patients (*n*)	22	10	10	6	4	4	3
Manifestations							
HPT (*n*)	20	1	9	4	4	2	3
PET (*n*)	17	0	3	2	1	1	1
PIT (*n*)	9	1	5	0	2	1	1
ADR (*n*)	2	1	1	1	0	0	0
NET (*n*)	1	0	1	0	0	0	0
Manifestations per patient							
0 (*n*)	0	8	1	2	0	2	0
1 (*n*)	1	1	3	1	2	1	2
2 (*n*)	12	1	3	3	1	0	0
3 (*n*)	8	0	2	0	1	1	1
4 (*n*)	0	0	1	0	0	0	0
5 (*n*)	0	0	0	0	0	0	0
Unknown (*n*)	1	–	–	–	–	–	–

Only mutations with three or more representatives in our population are depicted.
ADR, adrenal adenoma; HPT, hyperparathyroidism; NET, neuro-endocrine tumour; PIT, pituitary abnormality; PET, pancreatic endocrine tumour.

individual patient. When comparing the different mutations, patients with the 357del4 mutation tend to have more PETs than patients with other mutations. In patients with the IVS3-6 (c > g) mutation, manifestations are generally few – eight patients have no clinical expression of the syndrome – and when manifestations occurred no PETs or NETs were observed.

Discussion

The prevalence of manifestations in our cohort using currently available diagnostic techniques is high. For hyperparathyroidism, PETs and pituitary adenomas, these prevalences are lower than those reported in recent literature.[2,12,15–17] This can be explained by the fact that in our population 18% of the patients have not (yet) developed any clinical manifestation of the MEN1 syndrome. When these patients are not included in the analysis we find the same prevalence as recent literature. The prevalences of other NETs and adrenal adenomas did not differ from recent literature.[2,12,15–17]

We found that by presymptomatic screening for a *MEN1* mutation patients can be identified before manifestations occur. However, in our cohort, 11 of the 30 genetically diagnosed patients already harboured manifestations at the time of diagnosis. This leads us to the conclusion that screening for a *MEN1* mutation should be done at an early age. In our cohort the mean age at diagnosis did not differ ($P = 0{\cdot}151$) between clinically diagnosed patients (34 years) and genetically diagnosed patients (30 years). Recent guidelines recommend screening for a mutation at the age of 5, because the earliest manifestation of MEN1 described in literature occurred at that age.[13,18] In our population, which consisted of patients aged 16 years and older, the earliest clinical manifestation occurred at the age of 11 years.

Patients in our study population who were diagnosed genetically had a better outcome than those diagnosed clinically. Fewer manifestations were seen at the end of follow-up in the genetically diagnosed group. Malignancy and death only occurred in the clinically diagnosed group. These results should, however, be viewed with caution. The number of patients in each group is relatively small. In addition, although we compared patients in both groups diagnosed in the same time frame, temporal influences cannot be ruled out. The results can possibly be explained by the fact that patients diagnosed genetically are diagnosed earlier (lead-time bias). However, the age at diagnosis was comparable in both groups, and at the end of follow-up, comparisons were made only in patients diagnosed from 1994 onward. Longer term follow-up is needed to see if the effects we found are sustained. Still, we observed a better outcome and this corroborates the results of Lourenco-Jr *et al.* who also found a trend towards fewer and less aggressive manifestations in a genetically diagnosed subgroup compared with subgroups of index cases and clinically diagnosed cases.[12] Viewed together one might speculate that earlier intervention in patients with a genetic MEN1 diagnosis could play a role in the observed better outcome.

Asymptomatic *MEN1* mutation carriers should be periodically screened for tumour manifestations, possibly leading to diagnosis in an early stage, which would prevent complications. The same holds true for patients with a positive family history who refuse DNA analysis. In the older studies it was recommended that screening for hyperparathyroidism was enough because in virtually all cases this was the first manifestation.[19,20] We have now shown that all manifestations can occur as the first manifestation. Hyperparathyroidism as first manifestation is still most prevalent (72%), however, a NET of the pancreas (26%) or pituitary adenoma (16%) was also frequently seen as the first manifestation. Even a NET of other origin (3%) and an adrenal adenoma (3%) occurred as first manifestation. This confirms the findings of a recent German MEN1 study, in which gastroenteropancreatic endocrine tumours and pituitary tumours were frequently seen as the first manifestation and adrenal adenomas and NETs of lung and thymus were also seen as first manifestation.[17] In genetically diagnosed patients all manifestations, with exception of NETs of thymus, bronchus or GI-tract, occurred as first manifestation.

We have also shown that the clinical spectrum within a single mutation is wide. Though we observed fewer manifestations in patients with the IVS3-6 (c > g) mutation and more PETs in patients with the 357del4 mutation, the number of patients is too small to draw conclusions from this observation. Reports regarding genotype-phenotype correlation in MEN1 vary. In contrast to specific genotype-phenotype correlations recent studies do show a relationship between type and location of mutations and clinical expression of the MEN1 syndrome.[16,17,21] How these results translate into clinical practice needs to be determined in future research.

In conclusion, multiple endocrine neoplasia type 1 (MEN1) is a syndrome with a high morbidity. Early genetic diagnosis is recommended to identify patients before manifestations occur and to improve long-term outcome. In all asymptomatic MEN1 patients, screening for manifestations should include screening for all five MEN1-related tumours. For all MEN1 patients, regardless of the manner of diagnosis, we recommend periodical screening according to protocol. Once a manifestation is identified, we advise a tighter follow-up scheme with appropriate and early interventions (medical and/or surgical) according to current standards of care.

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