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REVIEW ARTICLE

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Update on the clinical management of multiple endocrine neoplasia type 1

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Abstract

This review provides an overview of novel insights in the clinical management of patients with Multiple Endocrine Neoplasia Type 1, focusing on the last decade since the last update of the MEN1 guidelines. With regard to *Diagnosis:* Mutation-negative patients with 2/3 main manifestations have a different clinical course compared to mutation-positive patients. As for *primary hyperparathyroidism:* subtotal parathyroidectomy is the initial procedure of choice. Current debate centres around the timing of initial parathyroidectomy as well as the controversial topic of unilateral clearance in young patients. For *duodenopancreatic neuroendocrine tumours* (NETs), the main challenge is accurate and individualized risk stratification to enable personalized surveillance and treatment. *Thymus NETs* remain one of the most aggressive MEN1-related tumours. *Lung NETs* are more frequent than previously thought, generally indolent, but rare aggressive cases do occur. *Pituitary adenomas* are most often prolactinomas and nonfunctioning microadenomas with an excellent prognosis and good response to therapy. *Breast cancer* is recognized as part of the MEN1 syndrome in women and periodical screening is advised. Clinically relevant manifestations are already seen at the *paediatric* age and initiating screening in the second decade is advisable. MEN1 has a significant impact on *quality of life* and US data show a significant financial burden. In conclusion, patient outcomes have improved, but much is still to be achieved. For care tailored to the needs of the individual patient and improving outcomes on an individual basis, studies are now needed to define predictors of tumour behaviour and effects of more individualized interventions.

KEYWORDS

disease management, genetic testing, multiple endocrine neoplasia type 1, neuroendocrine tumours, pituitary neoplasms, primary hyperparathyroidism, review

1 | INTRODUCTION

Multiple endocrine neoplasia type 1 (MEN1) is a rare autosomal dominantly inherited endocrine tumour predisposition syndrome, caused by germline heterozygous mutations in the *MEN1* gene, located on chromosome 11q13.[1] *MEN1* is a tumour suppressor gene encoding the menin protein, which is involved in the regulation of gene transcription.[1] MEN1 is highly penetrant as >95% of the mutation carriers will have manifestations by the age of 50.[2] The three main manifestations (Figure 1) of MEN1 (collectively known as the three Ps) are **P**arathyroid adenomas (primary hyperparathyroidism [pHPT]), duodeno**P**ancreatic neuroendocrine tumours (dpNETs) and anterior **P**ituitary adenomas (PAs) which have a lifetime prevalence of 95%, 80% and 50%, respectively.[3,4] Other endocrine tumours include thymic, lung and gastric NETs and adrenal cortical adenomas.[2] Women with MEN1 have a 2–3 fold increased risk of breast cancer compared to the general population.[5] Additional nonendocrine manifestations such as skin lesions (collagenoma, angiofibroma), lipomas and meningiomas can also be seen.[2] With regard to the individual manifestations of the syndrome among mutation carriers, one has to distinguish penetrance from point prevalence. Penetrance is the cumulative prevalence of a manifestation at a certain age, while point prevalence is the number of current cases which depends, among others, on the age distribution of the cohort. An example is the life-time prevalence of dpNETs of 80%[3,4] as discussed above, while in a published cohort the point prevalence may be 46%.[6]

Patients with MEN1 have a decreased life-expectancy compared to the general population, which is mainly due to malignant NETs in particular duodenopancreatic and thymus NETs.[3,7]

They are advised to follow a life-long surveillance program including clinic visits and biochemical and radiological screening for manifestations to enable timely treatment.[2] Due to the rarity and complexity of the syndrome, diagnosis and follow-up should, whenever possible, be done in centres of expertize with a dedicated multidisciplinary team.

The knowledge of the clinical picture and natural course of MEN1-related manifestations has vastly increased in the last decades and important developments and medical advances have changed the phenotype of the syndrome. After the discovery of the *MEN1* gene, presymptomatic diagnosis of family members of MEN1 patients has changed the phenotype because patients are diagnosed at earlier stages of the different manifestations. Subsequent development of Clinical Practice Guidelines, first in 2001[8] and updated in 2012,[2] have led to more uniform screening and surveillance and has enabled standard observations of disease course. Large multicentre (population-based) cohorts[7,9] have elucidated many aspects of the natural course of MEN1-related tumours in the past two decades, as have several large single-centre cohorts.[10–15] Improved sensitivities of conventional imaging techniques and advances in nuclear medicine imaging have led to better and earlier identification of MEN1-related NETs, adrenal and pituitary tumours. This has on the one hand led to increased identification of smaller, mostly indolent, nonfunctioning (NF) NETs in the pancreas (PanNETs) and lung, as well as NF pituitary microadenomas. On the other hand, nuclear imaging techniques have also increased the detection of very early distant metastatic disease. Presently, one of the main challenges in the care for patients with the MEN1 syndrome, is the identification of those tumours with an aggressive disease course that would necessitate and justify early intervention as opposed to cases where patients are more at risk from intervention-related complications, than tumour-related adverse outcomes.

This review provides an overview of the novel insights in the clinical management of patients with MEN1, focusing on the last decade since the publication of the most recent MEN1 guidelines.

2 | DIAGNOSING MEN1: RECOGNITION AND CLASSIFICATION

Presently MEN1 can be diagnosed genetically by identifying the mutation in the *MEN1* gene. A familial diagnosis is made if a patient has one of the main MEN1 manifestations and a first-degree family

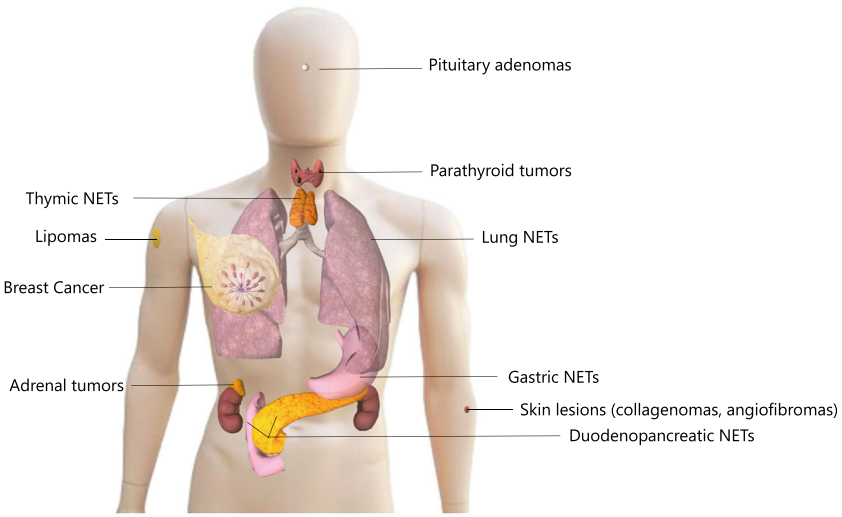

FIGURE 1 Manifestations of the MEN1 syndrome. Figure created by JM de Laat. MEN1, multiple endocrine neoplasia type 1; NET, neuroendocrine tumour

member with MEN1. Preferably, this is also confirmed genetically, as it can occur that members of an MEN1 family develop a tumour within the MEN1 spectrum without actually having MEN1 (e.g., pHPT in the absence of the familial *MEN1* germline mutation).

The final criterion for an MEN1 diagnosis as currently stated in the guidelines, is the clinical criterion of having two out of the three main MEN1 manifestations without genetic confirmation.[2] The value of this criterion is currently under debate since there is emerging evidence that these patients have a different clinical course compared to genetically confirmed MEN1 patients. At present, the percentage of a negative genetic test in clinically diagnosed MEN1 patients is around 5%–10%.[16] Possible explanations are, depending on the clinical picture, other hereditary syndromes causing an MEN1-like phenotype, 'false-negative' testing or the sporadic co-occurrence of two MEN1-related tumours.[16,17] Data from the DutchMEN Study Group (DMSG) has shown that patients with clinical MEN1 who are mutation negative develop manifestations at a higher age, do not develop a third manifestation and have a life-expectancy that is comparable to the general population.[3] Of note, most of these patients (77%) had a combination of pHPT and PA and pHPT in those patients was often uniglandular.[3,16] These results have been independently validated in the United States in a cohort from the University of Texas MD Anderson Cancer Center.[17] The family history is usually negative in these patients.[3,16,17] Based on these findings the authors of both papers have suggested a more limited follow-up for patients with a clinical diagnosis of MEN1 based on pHPT/PA and negative (comprehensive) mutation analysis, conditional on other clinical characteristics such as age, uniglandular/multiglandular pHPT, and family history.[16,17]

A timely diagnosis of MEN1 in the index case is of utmost importance to prevent morbidity and mortality both in the patient and the family. To recognize patients suspicious of MEN1 can be challenging as some tumours occurring as part of the MEN1 syndrome are also prevalent in the general population (e.g., pHPT and PA).[18,19] The current guidelines advise genetic testing in those meeting clinical or familial diagnostic criteria, first-degree family members of patients with MEN1 and those suspicious of MEN1 defined as pHPT <30 years, multiglandular pHPT, gastrinoma or multiple PanNETs at any age or two MEN1-related tumours not meeting clinical criteria.[2] There are concerns that these criteria might be too strict and should for example also include a diagnosis of PanNET before age 20, a diagnosis of PA before age 30 and consideration of family history for endocrine tumours.[16,20] Based on the Dutch MEN1 cohort, de Laat et al.[21] developed and validated a prediction rule to predict the presence of an *MEN1* mutation in patients presenting with sporadically occurring endocrine tumours. The authors developed a nomogram for clinical practice, allowing the clinician to calculate the risk of MEN1 in patients suspected of MEN1 with sporadically occurring endocrine tumours (Figure 2).[21] After the diagnosis of the index case a timely diagnosis of family members carrying the familial *MEN1* mutation is of equal importance as a delay can lead to avoidable morbidity and mortality in at risk family members.[22] Moreover, recent data from the DMSG are suggestive of genetic anticipation in MEN1, with manifestations

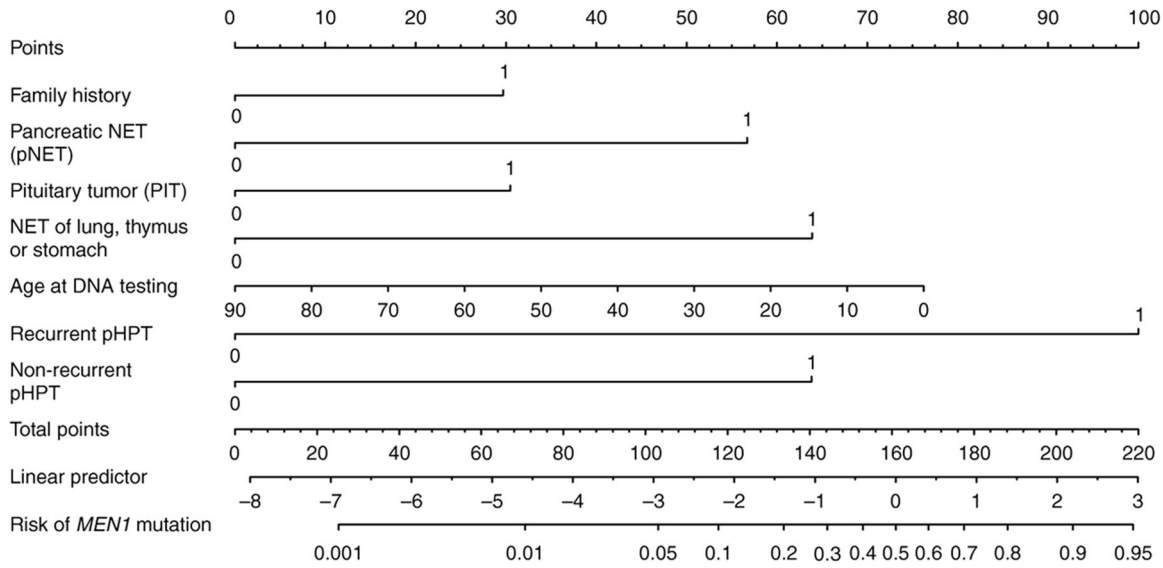

FIGURE 2 *Previously published by Bioscientifica in* 'De Laat et al. Predicting the risk of multiple endocrine neoplasia type 1 for patients with commonly occurring endocrine tumours. Eur J Endocrinol. 2012; 167: 181-7'. Nomogram. Example: a 54-year-old patient (score = 30 points) with the combination of a negative family history (score = 0 points), a nonrecurrent and nonmultiglandular pHPT (score = 63 points), and a pNET (*n* = 57 points) has a sum score of 150 points, corresponding with a linear predictor of −0.50 and a risk of 38% of having a MEN1 mutation. Example: a 41-year-old patient (score = 42 points) with a positive family history (score = 29 points) and recurrent pHPT (score = 100 points) has a sum score of 171 points, corresponding with a linear predictor of 0.50 and a risk of 63% of having a MEN1 mutation. Example: a 51-year-old patient (score = 33 points) with a negative family history (score = 0 points) of pituitary tumour (score = 31 points) and a pNET (score = 57 points) has a sum score of 121 points, corresponding with a linear predictor of −2.0 and a risk of 11% of having a MEN1 mutation. MEN1, multiple endocrine neoplasia type 1; NET, neuroendocrine tumour; pHPT, primary hyperparathyroidism

occurring at an earlier age in subsequent generations emphasizing the importance of timely cascade screening of first-degree family members.[23]

3 | PRIMARY HYPERPARATHYROIDISM

pHPT is the most frequent manifestation of MEN1 and often the first manifestation of the disease. In paediatric patients who are prospectively screened, at least half already have early signs of pHPT, which is mostly asymptomatic and rarely seen before the age of 10.[13,24–26] Symptomatic pHPT is usually not seen before the third decade of life. pHPT in MEN1 is a multiglandular disease, although glands are often affected asymmetrically and asynchronously. Patients with MEN1-related pHPT have a lower bone mineral density (BMD) than patients with sporadic pHPT.[27–32] Furthermore, urolithiasis is seen frequently and at a young age[29–31] and patients with MEN1 aged 20–59 appeared to have a higher prevalence of chronic kidney disease stage 3 compared to the general US population.[33] It is therefore important to monitor patients with MEN1-related pHPT for these complications. The treatment of pHPT is surgical, and the aim of initial parathyroidectomy is achieving eucalcemia for as long as possible, while preventing hypoparathyroidism and facilitating potential reoperative surgery. Since the publication of the guidelines and publication of additional studies, most experts agree that the preferred initial operation in MEN1 is a bilateral cervical exploration, identifying all four parathyroid glands and performing a subtotal parathyroidectomy with concomitant cervical thymectomy.[2,34–37] This provides the best balance between rates of persistent/recurrent disease and postoperative hypoparathyroidism. In recent years it has been debated if for young people with MEN1-related pHPT, a stepwise approach to parathyroid surgery should be offered in the form of unilateral clearance (resection of all parathyroids and cervical thymus on one side) as initial operation.[38–41] The rationale for considering this in those with unilateral disease on preoperative imaging, is to provide several years of eucalcemia allowing to accumulate peak bone mass, while not being subjected to the risk of hypoparathyroidism. Others are fiercely opposed such an approach, due to unacceptable failure rates.[42] As currently, no consensus exists, if such an approach is considered, the risks and benefits should be discussed with the patient and/or parents. Another topic that becomes increasingly important with more widespread use of predictive testing and prospective screening is the timing of initial parathyroidectomy when pHPT is mild and asymptomatic at diagnosis, especially in children. Arguments favouring initial observation are to avoid the risk of symptomatic hypoparathyroidism, multiple operations and making the glands more easily identifiable if the disease progressed a bit more. Others advocate early intervention based on early bone and renal complications.[37] In children, the effect of mild pHPT on peak BMD or development in general is unknown as is the effect of hypoparathyroidism. Decisions are therefore different in children compared to adults and currently no consensus exists.

4 | NEUROENDOCRINE TUMOURS

4.1 | Duodenopancreatic NETs

dpNETs are highly prevalent, and updated penetrance data from the French Groupe d'Etude des Tumeurs Endocrines (GTE) and the DMSG show that >80% of the patients with MEN1 have a dpNET by the age of 80.[3,4] Due to increasingly sensitive imaging, NF PanNETs are now the most frequently diagnosed dpNET, followed by (duodenal) gastrinomas (30%), and insulinomas (10%–15%). Other functioning PanNETs are rare. NF-PanNET cumulative probability steadily rises with age from 8.6% at age 15, 12% at age 18, 16.1% at age 21 up until 80% at age 80 (modelled data from the DMSG).[43] Insulinomas can already occur at a young age and in a large international multicenter cohort, half the patients were diagnosed before age 30.[44] Gastrinomas usually occur later in life, with age of onset in the National Institutes of Health (NIH) cohort being 30–35 years[10,45] and even 51 years in the DMSG cohort.[46]

Distant metastases are seen in 15%–30% of the patients with dpNETs,[10,47–49] mostly from NF-PanNETs and gastrinomas, and are one of the most important causes of MEN1-related death.[7] Results from the DMSG show that for patients with dpNETs without liver metastases, 5- and 10-year overall survival rates were 95% and 86%, respectively, while for patients with liver metastases rates were 65% and 50%.[49]

4.1.1 | Risk stratification

As smaller PanNETs are increasingly identified because of more sensitive imaging techniques, the main challenge is accurate risk stratification to assess which patients or which tumours are most at risk for adverse outcomes and therefore should undergo more aggressive treatment and surveillance. In the last decade, much evidence was gained regarding this topic, but true personalized risk-based treatment and surveillance is unfortunately not yet possible.

Several research groups have reported genotype–phenotype correlations with specific genotypes associated with a more aggressive dpNET-related natural course (Table S1).[43,47,50–57] However, either these results could not be validated in independent cohorts, or this has not yet been attempted, therefore these associations presently cannot guide clinical practice.

In NF-PanNETs important 'classical' risk factors for (distant) metastases are tumour size (risk increasing with increasing size) and tumour grade (higher risk in WHO grade 2 tumours).[58] Significant tumour growth while under surveillance is also considered a risk factor.[59]

In gastrinomas, which are duodenal in origin and usually small, regional lymph node metastases are found in up to 80% at diagnosis, although they do not seem to have a negative impact on overall survival.[60] In two independent studies, age, level of fasting serum gastrin (FSG), size of (coexisting) PanNETs and liver metastasis were associated with aggressive tumour growth[48] and decreased survival

of patients[46] with an MEN1-related gastrinoma. Overall 5- and 10-year survival rates of patients with a gastrinoma in the DMSG cohort were 83% and 65% respectively, significantly worse compared to age- and gender-matched MEN1 patients with MEN1 without gastrinoma.[46]

Recent data from the GTE have also provided more insight in factors associated with the development of PanNET and gastrinoma related distant metastases and death. They identified PanNET size >2 cm and age >40 as independently associated with the development of distant metastases and death. Patients with Zollinger-Ellison syndrome (ZES) had an increased risk of developing distant metastases, but when distant metastases developed an increased risk of death was not seen in this subgroup.[47]

Insulinomas generally have a good prognosis and distant metastases are rarely seen.[61]

In the last years, several new potential prognostic tissue-based biomarkers for NF-PanNETs have been identified, with some evidence regarding their use in MEN1. Mutations in alpha-thalassaemia/mental retardation X-linked (*ATRX*) and death domain-associated protein (*DAXX*), which lead to the alternative lengthening of telomeres (ALT) phenotype have found to be associated with decreased disease-free survival and higher rates of distant metastases.[58,62] Next to *DAXX/ATRX* and ALT, the differential expression of transcription factors aristaless-related homeobox gene (*ARX*) and pancreatic and duodenal homeobox 1 (*PDX1*) as assessed by immunohistochemistry was also found to be associated with risk of metastases.[63,64] In patients with MEN1-related NF-PanNETs, one study showed that liver metastases were only seen in ARX+ or ARX −/PDX1− tumours and that ALT positivity was only seen in ARX+ or ARX−/PDX1− tumours and significantly correlated with relapse rate.[63] However, since the publication of these data, it was demonstrated in a large international cohort of sporadic NETs that ATRX/DAXX and ALT, but not ARX/PDX1 were independent negative prognostic factors.[62]

As elements of tumour-specific genome, transcriptome, proteome and metabolome can be detected in blood, the concept of liquid biopsy for risk stratification in patients with MEN1 is of great interest. Fahrmann et al.[65] identified a 3-marker polyamine signature that distinguished patients with MEN1 with distant metastatic dpNETs from controls and which yielded an AUC of 0.84 (95% CI: 0.62–1.00) with 66.7% sensitivity at 95% specificity for distinguishing cases form controls in an independent test set.[65] These preliminary results form the basis for prospective testing of plasma polyamines as a prognostic factor for MEN1-related dpNETs.[65] No data are available yet in MEN1 regarding the value of the NETest, a transcriptome-based liquid biopsy approach for NETs.[66]

4.1.2 | Diagnosis and surveillance

In the diagnosis of NF-PanNETs there is no role for tumour markers chromogranin A, pancreatic polypeptide or glucagon, as shown by a systematic review.[67] Therefore imaging forms the basis for diagnosis, and patients with MEN1 without any PanNETs regularly undergo imaging studies. The same systematic review evaluated the role of imaging studies in the diagnosis of NF-PanNETs and concluded that, although endoscopic ultrasound (EUS) is the most sensitive method for detecting NF-PanNETs, it is also invasive, operator dependent and can miss clinically relevant PanNETs in the pancreatic tail. Magnetic resonance imaging (MRI) was found to be more sensitive than computed tomography (CT) and has the added advantage of no exposure to ionizing radiation, which is very relevant in a disease that needs lifelong monitoring.[67] As studies have shown that the yearly growth of small (<2 cm) NF-PanNETs is between 0.1 and 1.32 mm,[67] an interval of 2–3 years for repeat pancreatic imaging after initial negative imaging seems safe, provided there is no clinical reason for earlier imaging. Most small PanNETs have an indolent course, but progression does occur.[56] Therefore, if active surveillance is chosen for NF-PanNETs, imaging interval should be personalized according to growth. Initial repeat imaging is advised after 6–12 months, afterwards if the tumours are stable this interval may be extended to every 1–2 years. Modality can be either MRI or alternating with EUS. EUS should be combined with another imaging modality for metastases detection. Current state of evidence suggests that the optimal place for somatostatin receptor positron emission tomography (PET)-CT (SSTR-PET-CT) is when it may change management such as in prevalent NF-PanNETs > 10 mm for detection of occult metastases or as a comprehensive staging method before interventions are considered.[67,68]

Current guidelines advise initiating radiological surveillance for the pancreas at age 10, while others advocate to postpone until the age of 16 in the absence of signs and symptoms.[2,69] Modelled data form the Dutch MEN1 cohort show that the estimated age at which the chance is 1%, 2.5% and 5% of having a clinically relevant NF-PanNET (≥2 cm or documented growth of ≥1.6 mm within 1 year above a baseline size of ≥15 mm) is 9.5, 13.5 and 17.8 years, respectively and the authors conclude that screening should start in the second decade of life and a starting age of 13–14 years is justifiable.[43]

Patients with MEN1 are screened for the presence of a gastrinoma by yearly determination of FSG levels. Although classically gastrinoma/ZES is diagnosed biochemically by the combination of a FSG more than tenfold the upper limit of normal in combination with a gastric pH < 2 (without retained antrum), the biochemical diagnosis of gastrinoma/ZES has become increasingly complicated due to the widespread use of proton pump inhibitor (PPIs) (and risk of cessation in true ZES), unreliable gastrin assays and the unavailability of secretin stimulation testing.[70] Recently, experts from the NIH have suggested possible new criteria to diagnose ZES in patients with elevated FSG when gastric acidity cannot be assessed. They rank different combinations of clinical findings (symptoms, secretin test, somatostatin receptor imaging, histology/cytology and [suspected] presence of MEN1) into categories of strongly, moderately, weakly and minimally supportive of the diagnosis of ZES, with different criteria for those with and without PPI.[70] These criteria have not been clinically validated. When there is a (suspected) gastrinoma,

MRI and CT are of limited use for localization, as gastrinomas are often small, multiple and located submucosal in the duodenum. Esophagogastroduodenoscopy (EGD)/EUS should be performed both to potentially locate the gastrinomas and to assess complications from peptic ulcer disease and the presence of gastric NETs. Since most gastrinomas have regional lymph node metastases SSTR-PET-CT can also be very valuable in correct staging. As PanNETs and gastrinomas are often multiple in patients with MEN1, it may be challenging to attribute locoregional lymph node metastases to the correct primary NET. In a recent study, most patients with metastatic PanNETs and/or gastrinomas had a single NET of origin for their metastases, but multiple metastatic primaries were also seen.[71] A most clinically relevant finding was that in six patients with MEN1 and hypergastrinemia, periduodenopancreatic lymph node metastases clustered with minute duodenal gastrinomas and not with larger PanNETs. So a duodenal origin for locoregional lymph node metastases in patients with MEN1 and hypergastrinemia should always be considered.[71]

Gastric NETs are almost exclusively seen in patients with a gastrinoma,[72] and patients with hypergastrinemia are therefore advised to undergo EGD surveillance for gastric NETs at least every 3 years.[2]

Patients with MEN1 are screened for insulinoma by yearly history taking and fasting glucose. The gold standard for the biochemical diagnosis of insulinoma in patients fulfilling Whipple's triad is a supervised fast.[73] Although multiple insulinomas do occur in 8%–40% in surgical series,[44,74–76] most of the multiple PanNETs comprise a single insulinoma and multiple concomitant NF-PanNETs. For determining surgical strategy, correctly identifying the insulinoma is very important. In this respect, ^{68}Ga-Exendin-4 PET-CT is very promising.[77,78]

4.1.3 | Intervention

Presently, surgery is the only curative treatment for MEN1-related dpNETs. However duodenopancreatic surgery is associated with high short- and long-term morbidity.[79,80] Therefore careful consideration of timing and extent of surgery in multidisciplinary teams in centres of excellence is necessary. Especially since new NETs will likely develop in the remnant duodenopancreatic tissue due to the hereditary background.

Current consensus is that surgical resection in NF-PanNETs is indicated for those >2 cm or progressing during surveillance.[59] Presence of suspicious lymph nodes and—if tissue is available—a WHO grade ≥2 may also guide intervention decisions.

For MEN1-related gastrinomas, the if, when and how of a surgical intervention are still controversial and there is an excellent review on the contemporary surgical management by the Marburg team.[60] Important considerations are (1) the often excellent long-term survival of patients with gastrinomas even in the absence of surgical management (2) acid-related complications usually can be very effectively controlled with high-dose PPI (3) approximately a quarter of the patients will develop distant metastases and approximately 15% shows aggressive growth and we currently cannot adequately predict in which category an individual patient will fall (4) cure for MEN1-related gastrinoma can be achieved if the right organ (duodenum) is addressed and systematic local lymph node resection is performed and (5) such a surgery is associated with high morbidity.[60]

Localized insulinomas are an indication for surgical resection. Regarding the extent of resection (enucleation vs. resection) recent data show excellent outcomes of enucleations in patients with solitary insulinomas.[44] Therefore, given the better outcomes of pancreatic function over the long-term and young age of the patients, if surgically feasible, enucleation seems the better option for solitary insulinomas in MEN1, provided of course that concomitant PanNETs or gastrinomas do not dictate a different strategy.[44]

The option of chemoprevention for PanNETs in MEN1 is interesting and a recent small observational cohort study compared lanreotide with a standard of care active surveillance.[81] The study showed improved RECIST-defined progression-free survival (PFS) in the lanreotide group. In both groups however, one patient developed liver metastases.[81] Limitations next to the small sample size, include the nonexperimental and therefore nonrandomized design and the nonblinded outcome evaluation. In addition, improved RECIST PFS is not yet known to predict longer overall survival for MEN1 patients with small NF-PanNETs. Ideally, this is further evaluated in a randomized double-blind trial.

4.2 | Thoracic NETS

Thymic NETs (thNETs) are one of the most aggressive MEN1-related manifestations. Although their prevalence is low (2%–8%) among patients with MEN1,[82–89] they are responsible for up to one-fifth of the MEN1-related deaths.[10] More than 50% of the published cases presented with distant metastases and 10-year survival was 33%.[82] Median age at diagnosis of thNETs is in the fifth decade, and there is only one published case of an adolescent with a thNET.[82–89] thNETs predominately, but not exclusively, occur in males, although less pronounced in Asian cohorts.[82–89] Some cohorts report a familial occurrence of thNETs,[85,87,90] but this is not seen by others.[84,88] The most important challenge is the early identification of this rare MEN1-related tumour, as currently most published cases were not detected during surveillance. When more data becomes available of patients who are diagnosed early in life through predictive testing, we may get a sense if early detection of thNETs in MEN1 may improve the outcome. Prophylactic thymectomy during initial parathyroidectomy is advocated to reduce the risk of subsequent thNETs, although the risk is not abolished.[85,91]

Since the publication of the 2012 guidelines, data from several cohorts have added to knowledge of occurrence and natural history of MEN1-related lungNETs.[12,88,92–95] Histologically confirmed lungNETs are seen in approximately 5% of the patients with MEN1, however, it is now recognized that the prevalence of lesions radiologically suspect for lungNETs is much higher (22%–29%).[12,88,92–96] The originally reported female predominance, was not confirmed in later studies.[12,88,92,94,95] As with thymicNETs, lungNETs are predominantly seen in adults, with only two reported cases of lungNET in adolescents.[13,69] Most lungNETs

in MEN1 are well-differentiated typical and atypical carcinoids, with the majority being typical carcinoid.[12,88,94,95] However, in the French GTE MEN1 cohort five patients with small cell and large cell neuroendocrine carcinomas were seen, although because of the large size of the cohort, long-term follow-up (49 years), high frequency of smokers and lack of molecular analysis, the causal relationship with MEN1 was deemed unclear.[94] LungNETs are generally detected through screening in patients with MEN1 and <20% are symptomatic at diagnosis.[12,93,94] A functional syndrome is rarely seen. Overall, lungNETs do not seem to impact MEN1-related overall survival.[92,94] Small lungNETs generally are indolent, with the most recent data from the DMSG reporting a tumour doubling time of close to 12 years, compared to 4.5 years in an earlier DMSG study.[88,95] However, unexpected growth and more aggressive disease courses are also seen.[94,95] In histologically proven lungNETs (mostly histology from resection) nodal metastases were seen in 37% in the GTE cohort and in 31% in the DMSG cohort, distant metastases were seen in 16% of the GTE cohort and 3% in the DMSG cohort.[94,95] The single patient in the Dutch cohort with distant metastases demonstrated an atypical clinical course with sudden rapid growth of a previously stable lungNET and an additional somatic driver mutation in the *PIK3CA* gene was identified.[95] In the GTE cohort, male sex, atypical carcinoid, nodal involvement and distant metastases were associated with worse survival.[94]

Current guidelines recommend that patients with MEN1 are screened for thoracic NETs by thoracic imaging every 1–2 years.[2] Given the indolent course of most small lungNETs this interval can probably be safely extended on a group level, but individual cases of thNET and/or more aggressive lungNET can be missed. This should be discussed with the patient and individualized and shared decisions should be made regarding thoracic screening. For patients with small MEN1-related lungNETs, guidelines are needed when safe observation can be performed and when surgical intervention is indicated. Compared to sporadic lungNETs, patients with MEN1-related lungNET had a significantly higher disease-related survival in a recent study, although these findings need independent validation.[92]

5 | PITUITARY ADENOMAS

Since the publication of the guidelines, four cohorts of MEN1-related PAs have been published.[11,97–99] Due to guidelines for periodical screening,[2] increased sensitivity of imaging techniques and better identification of patients with MEN1 through genetic testing, the phenotype of PAs in the context of MEN1 has changed. MEN1-related PAs show a slight female predominance and mean/median age of diagnosis is in the fourth decade. Life-time prevalence of PAs in patients with MEN1 is around 50%.[4,97] PAs can often be the first manifestation of MEN1 and are also penetrant at the paediatric age but rarely before the age of 10. Prolactinomas are the most prevalent PA among patients with MEN1 (28%–45%), nowadays closely followed by nonfunctioning PAs (NFPAs).[11,97–99] Other functioning PAs are seen far less often. Multifocal PAs are rare in MEN1, but still seem to be more common compared to sporadic PAs.[100] Presently, most NFPAs in MEN1 are microadenomas detected by prospective screening. These microadenomas show indolent behaviour during follow-up.[11,97,98] Prolactinomas are also mostly microadenomas, while 30%–38% are macroadenomas. As in sporadic PAs, growth hormone-secreting tumours are more often macroadenomas and ACTH-secreting tumours are generally microadenomas.[11,97,98] Treatment in MEN1-related PAs is not different from sporadic PAs and in contrast to previous assumptions, recent data show similar treatment responses to sporadic PAs (although no new head-to-head comparisons have been performed).[11,97,98]

6 | BREAST CANCER—A NEW MEN1-RELATED TUMOUR

In 2014, it was shown in the Dutch MEN1 cohort that females with MEN1 had a 2.8 times increased risk of breast cancer compared to the general Dutch population.[5] Additionally, breast cancer in patients with MEN1 was diagnosed approximately 15 years earlier than in the general population.[5,101] This increased incidence of breast cancer was confirmed in three independent cohorts form France, Tasmania and the United States.[5] A follow-up study within the Dutch cohort showed that this increased risk was not associated with other breast cancer risk factors or familial breast cancer risk.[101] Therefore, currently Dutch females with MEN1 are recommended to undergo breast cancer screening from the age of 40, which is a decade earlier than the regular population screening program in the Netherlands.[101] Up to now, no data is available about the benefit of breast cancer screening in females with MEN1. However, Mandelblatt et al.[102] studied harms and benefits of different screening strategies by using simulation models and found that annual screening from the age of 40 years in women with a 2–4 fold increased in breast cancer risk had a similar or more favourable harm/benefit ratio as biennial screening of women with average-risk from 50 to 74 years,[102] which is applicable to the MEN1 setting.

7 | MEN1 IN CHILDREN

Current practice guidelines recommend DNA testing for the familial *MEN1* mutation in children at the earliest opportunity, but at least in the first decade, based on the earliest documented manifestations of MEN1 in the literature up until then.[2] In those who are carriers of the familiar mutation, the recommended age for initiation of biochemical and radiological screening for the different manifestations is based on the earliest reported case in the literature combined with the experience of the expert authors of the guidelines.[2] The recommendation for early DNA testing and initiation of screening has increased the knowledge of the spectrum of MEN1 in children, and since the publication of the guidelines five cohorts have been published on the clinical picture of MEN1 in childhood, which are summarized in Table 1.[13,24–26,69] In addition, a study from Brazil reported a 42% prevalence of PanNETs in 19 patients with MEN1 age 12–20[103] and a series from Italy (same centre as Vannucci et al. 26) reported on pHPT (63%) among 30 patients genetically diagnosed before age 20.[104] These combined data show that 12%–70%

TABLE 1 Paediatric cohorts in MEN1

	Goudet et al. (2015)[24]	Manoharan et al. (2017)[69]	Vannucci et al. (2018)[26]	Herath et al. (2019)[13]	Shariq et al. (2021)[25]
Setting	Retrospective multicentre cohort	Retrospective analysis of two prospective single-centre databases	Retrospective single-centre	Tasman 1 Kindred, Retrospective single-centre	Retrospective international multicenter
Definition paediatric age	<21	≤18	≤31	<22	≤18
Total cohort[a]	*N = 924*	*N = 166*	*N = 22*	*N = 84*	*N = 80*
Age MEN1 dx, mean/median, years (range)					
In entire cohort	N/A	N/A	9.4 (0–14)	N/A	11.5 (0.8–18)
Those with manifestations at paediatric age	N/A	N/A	N/A	N/A	13 (2–18)
Manifestations at paediatric age	*160 (17%)*	*20 (12%)*	*12 (55%)*	*N = 46 (55%)*	*N = 56 (70%)*
Age first manifestation mean/median (range)	N/A	17 (8–18)	16 (12–26)	N/A	14 (6–18)
pHPT	*122/160 (76%)*	*9/20 (45%)*	*11/12 (92%)*	*42/46 (91%)*	*46/56 (82%)*
Age at diagnosis, mean/median (range)	16 (SD 4) Youngest 4 years	Youngest 8 years	Youngest 12 years	17 (8–21)	15 (6–18)
Symptomatic	21/122 (17%)	0	1/11 (9%)	N/A	9/46 (20%)
Intervention	38/122 (31%)[b]	5/9 (55%)[b]	7/11 (64%)[c]	16/42 (38%)[b]	23/46 (50%)[b]
PA	*55/160 (34%)*	*6/20 (30%)*	*7/12 (58%)*	*14/46 (30%)*	*18/56 (32%)*
Age, mean/median (range)	17 (SD 4) Youngest 10 years	Youngest 16 years	N/A	Youngest 12 years	14 (9–18)
Type	PRL 34/55 (62%) NFPA 14/55 (25%) CD 1/55 (2%) GH 1/55 (2%) Multiple 4/55 (7%) Unk 1/55 (2%)	PRL 4/6 (67%) NFPA 2/6 (33%)	PRL 7/7 (100%)	PRL 9/14 (64%) NFPA 3/14 (21%) CD 2/14 (14%)	PRL 15/18 (83%) NFPA 3/18 (17%)
Symptomatic	30/55 (55%)	0	1/7 (14%)	N/A	7/18 (39%)
Intervention	9/55 (16%) Surgery[b]	0	7/7 (100%)[c]	10/14 (71%)[b]	12/18 (67%)[c]
All dpNET	*37/190 (23%)*	*8/20 (40%)*	*2/12 (17%)*	*13/46 (28%)*	*21/56 (38%)*
NF PanNET	*14/160 (9%)*	*3/20 (15%)*	*2/12 (17%)*	*9/46 (20%)*	*15/56 (27%)*
Age, mean/median (range)	16 (SD 2) Youngest >10 years	17 (16–18)	N/A	N/A	15 (10–18)
Symptomatic	0	0	0	N/A	N/A
Intervention	5/14 (36%)[b]	2/3 (67%)[b]	1/2 (50%)[c]	2/9 (22%)[b]	5/15 (33%)[c] Age 15 (12–20)
Insulinoma	*20/160 (13%)*	*5/20 (25%)*	*0*	*3/46 (7%)*	*8/56 (14%)*
Age, mean/median range)	15 (SD 4) Youngest 5 years	13 (9–18)		14 (14–18)	15.5 (6–18)
Symptomatic	20 (100%)	13 (100%)		3 (100%)	8 (100%)
Intervention	20 (100%)[d]	13 (100%)[b]		3 (100%)[b]	8 (100%)[c] Age 16 (6–19)

TABLE 1 (Continued)

	Goudet et al. (2015)[24]	Manoharan et al. (2017)[69]	Vannucci et al. (2018)[26]	Herath et al. (2019)[13]	Shariq et al. (2021)[25]
Gastrinoma	*3/160 (2%)*	*0*	*0*	*0*	*1/56 (2%)*
Age, mean/median (range)	16 (SD 8) Youngest 6 years				N/A
Symptomatic	3 (100%)				N/A
Intervention	1/3 (33%) surgery[b]				N/A
LungNET	*0*	*1/20 (5%)*	*0*	*1/46 (2%)*	*0*
Age		15		20	
Symptomatic		0		1 (100%)	
Intervention		1 (100%)[b]		1 (100%)[b]	
ThymusNET	*1/160 (<1%)*	*0*	*0*	*0*	*0*
Age	16				
Symptomatic	1 (100%)				
Intervention	1 (100%)[b]				
Adrenal	*2/160 (1%)*	*0*	*0*	*0*	*1/56 (2%)*
Age	4 and 16 years				
Malignant	2 (100%)				0
Intervention	2 (100%)[b]				1/1 (100%)[b]
Metastases at paediatric age	*2/160 (1%)*	*0*	*0*	*0*	*2/56 (4%)*
Origin	Gastrinoma—LM ThymusNET				Insulinoma-LN (18 years) NF-PanNET—LM (10 years) NF-PanNET one additional LM (20 years)

Abbreviations: CD, Cushing's disease; dx, diagnosis; GH, growth hormone; LM, liver metastases; LN, lymph node metastases; MEN1, multiple endocrine neoplasia type 1; N/A, not available; NET, neuroendocrine tumour; NFPA nonfunctioning pituitary adenoma; NF-PanNET, nonfunctioning pancreatic neuroendocrine tumour; PA, pituitary adenoma; pHPT, primary hyperparathyroidism; PRL, prolactinoma; SD, standard deviation; Unk, unknown.

[a]*Goudet* et al. GTE database formed the entire cohort; *Manoharan* et al. two prospectively kept single-centre databases formed the entire cohort; *Vannucci* et al. patients with a clinical and/or genetic diagnosis of MEN1 before the age of 16, with regular follow-up between 1998 and 2016 in a single centre; *Herath* et al. Prospectively screened members of the Tasman 1 kindred; *Shariq* et al. Patients ≤35 years at time of data collection, who were diagnosed/screened ≤18, followed and underwent screening imaging.

[b]At paediatric age.

[c]Unsure if only interventions at paediatric age were counted.

[d]*n* = 18 were operated <21 years, two patients were operated at age 21.

of children with MEN1 already have manifestations at the paediatric age (although different age cut-offs are used).[13,24–26,69,103,104] The wide range can partly be explained by different screening practices as Goudet et al.[24] found that 73% of those following a screening program <21 years had manifestations diagnosed at the paediatric age, while overall in their cohort this was only 17%.[24] Median age at first manifestation in the five cohorts was 14–17 years. pHPT is highly prevalent at the paediatric age (45%–92% in those who have manifestations), but mostly asymptomatic (80%–91%) and leading to intervention at the paediatric age only in 31%–55% of the cases.[13,24–26,69] PAs are seen in approximately one-third of the children who have manifestations, mostly prolactinomas followed by NFPAs, and lead to intervention more often.[13,24–26,69] dpNETs are seen in 17%–40% of those with manifestations, mostly insulinomas and NF-PanNETs, while gastrinomas are rare.[13,24–26,69] Insulinomas are symptomatic in all cases and were resected in all cases. NF-PanNET are asymptomatic, leading to intervention in 22%–67% of the cases. Thoracic NETs are rare at the paediatric age, as are adrenal manifestations.[13,24–26,69] Frank malignancy is reported at the paediatric age in two of the five cohorts, although it is rare with two ACCs and four malignant NETs (pancreas [2], gastrinoma and thymus).[24,25] Therefore, the most important manifestations in childhood are pHPT, prolactinomas, NFPAs, NF-PanNETs and insulinomas and parents and children should be

TABLE 2 Quality of Life data in patients with MEN1

References	Study population	Main QoL-related outcome measures	Main results
Berglund et al. (2003)[105]	*N* = 29 patients visiting a specialist ward for MEN1 at the University Hospital Uppsala, Sweden	– HADS – IES – LOT – SF-36	Psychosocial outcomes only marginally different between hospital stay and at home. Depression increased in those with higher disease burden. Compared to population-based norm-values, lower scores for General Health and Social Functioning.
Stromsvik et al. (2007)[106]	*N* = 29 patients recruited through a specialist MEN1 ward at the University Hospital Uppsala, Sweden	Qualitative research interview	Majority of patients have adjusted to their situation, describing themselves as being healthy despite physical symptoms/treatment. Greater effort should be put into patient information.
You et al. (2007)[107]	*N* = 28 patients with MEN1 after panreaticoduodenal surgery	– EORCT-QLQ-30 – 10 Disease-specific items adapted from Gastrointestinal Quality of Life Index	Global QoL scores not different from those of the general population. Symptom scores showed more diarrhoea, nausea/vomiting and appetite loss than the reference population Patients with MEN1 had more financial difficulties than the reference population.
Goswami et al. (2017)[109]	*N* = 207 MEN1 patients (US and abroad) recruited from AMENSupport website/social media	– Questionnaire on eligibility, demographics, diagnosis, presentation, treatment and financial burden – PROMIS-29	Patients with MEN1 had significantly worse anxiety, depression, fatigue, pain interference, sleep disturbance, physical function and social function compared with US normative data. Factors associated with worse HRQoL were persistent pHPT, age <45 at diagnosis, current age >45, long travel distance for doctor appointments and ≥20 doctor appointments/year.
Peipert et al. (2017)[108]	*N* = 153 US patients with MEN1 recruited from AMENSupport website/social media	– Questionnaire on eligibility, demographics, diagnosis, presentation, treatment and financial burden – PROMIS-29	84% Reported financial burden due to MEN1. Linear relation between degree of financial burden and worse health-related QoL across all PROMIS-20 domains.
Peipert et al. (2018)[110]	*N* = 153 US patients with MEN1 recruited from AMENSupport website/social media	– Questionnaire on eligibility, demographics, diagnosis, presentation, treatment and financial burden – PROMIS-29	MEN1 patients reported more anxiety, depression and fatigue compared with other chronic conditions (back pain, cancer, COPD, RA, NETs, pHPT).
Van Leeuwaarde et al. (2018)[112]	*N* = 227 patients with MEN1 recruited from the Dutch MEN1 cohort	– Cancer Worry Scale – SF-36	FDO was high and negatively associated with almost all SF-36 subscales. The diagnosis of a PA, a PanNET and unemployment were associated with FDO. Patients had higher FDO for their family members than for themselves.
Van Leeuwaarde et al. (2021)[111]	*N* = 227 patients with MEN1 recruited from the Dutch MEN1 cohort	– Cancer Worry Scale – SF-36	HRQoL scores were lower than the general Dutch population in the majority of SF-36 subscales. Unemployment status followed by the presence of a PA were the most consistent predictors of HRQoL. Patients with a PanNET or PA who were unaware of these tumours had a better QoL than patients who were aware.

TABLE 2 (Continued)

References	Study population	Main QoL-related outcome measures	Main results
Giusti et al. (2021)[113]	*N* = 76 patients with MEN1 followed at the University Hospital of Careggi, Florence	– Sociodemographic questionnaire – LOT-R – IES-R – HADS – SF-36	Patients were moderately optimistic (50%). Patients had a QoL (SF-36) in the normal range. 75% Had symptoms of posttraumatic stress. 28% Had major anxiety and 8% major depression.

Abbreviations: AMENSupport, American Multiple Endocrine Neoplasia Support US-based MEN support group; COPD, chronic obstructive pulmonary disease; EORCT-QLQ-30, European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire; FDO, Fear of Disease Occurrence; HADS, hospital anxiety and depression scale; (HR)QoL, (health-related) quality of life; IES(-R), impact event scale (Revised); LOT(-R), life-orientation test (Revised); NET, neuroendocrine tumour; PA, pituitary adenoma; PanNET, pancreatic NET; pHPT, primary hyperparathyroidism; PROMIS-29, Patient-Reported Outcomes Measurement Information System 29-item profile measure; RA, rheumatoid arthritis; SF-36, Short Form 36.

educated as to their symptoms. Initiating biochemical and radiological screening in the second decade of life seems appropriate, based on currently available evidence. To be able to formulate true evidence-based guidelines for the management of MEN1 at the paediatric age, long-term outcome data are needed for those children who underwent screening from their first decade.

8 | QUALITY OF LIFE DATA

In the last decade, there has been more attention for patient-reported outcomes and quality of life (QoL). The published data on this subject have been summarized in Table 2. The initial studies from Sweden in 2003 and 2007 showed that depression increased in patients with MEN1 with increasing disease burden, but generally the majority of patients adjusted to their situation and described themselves as healthy.[105,106] Data from US patients after pancreaticoduodenal surgery showed global QoL scores to be comparable to the general population, but they had higher symptom scores and more financial difficulties.[107] The high financial burden (in the United States) was confirmed in a study among members of the American Multiple Endocrine Neoplasia Support Group, and this financial burden was linearly related to worse health-related QoL.[108] In both the US patient support cohort and the Dutch population-based MEN1 cohort, QoL of patients with MEN1 was lower than the general population and in the US cohort also lower than patients with other chronic condition.[109–111] In the Dutch cohort fear of disease occurrence (FDO) was high among patients with MEN1 and was correlated with worse QoL. Patients expressed higher FDO for family members than for themselves.[112] In a recent Italian cohort, QoL scores were in the normal range, but 75% had symptoms of posttraumatic stress and anxiety and depression scores were high.[113]

9 | CONCLUSION

In the last two decades, we gained more insight in the natural course of manifestations of the MEN1 syndrome and the consequences for treatment and follow-up. Patient outcomes have improved, but much is still to be achieved. What seems to be appropriate for patients on a group level might not be suitable for the individual patient. For care tailored to the needs of the individual patient and improving outcomes on an individual basis, studies are now needed to define predictors of tumour behaviour and effects of more individualized interventions. Patients with MEN1 should therefore be treated in centres dedicated to care and research in MEN1. These centres can collaborate in the structured collection of uniform clinical data and biospecimen for research in patient cohorts of sufficient size to further improve care and outcomes for this rare disease.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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