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# Initiating Pancreatic Neuroendocrine Tumor (pNET) Screening in Young MEN1 Patients: Results From the DutchMEN Study Group

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**Abbreviations:** CT, computed tomography; DMSG, DutchMEN Study Group; EUS, endoscopic ultrasound; MEN1, multiple endocrine neoplasia type 1; MRI, magnetic resonance imaging; NET, neuroendocrine tumor; NF-pNET, nonfunctioning pancreatic neuroendocrine tumor; NPMLE, nonparametric maximum likelihood estimation; pNET, pancreatic neuroendocrine tumor.

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## Abstract

**Context:** Nonfunctioning pancreatic neuroendocrine tumors (NF-pNETs) are highly prevalent and constitute an important cause of mortality in patients with multiple

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endocrine neoplasia type 1 (MEN1). Still, the optimal age to initiate screening for pNETs is under debate.

**Objective:** The aim of this work is to assess the age of occurrence of clinically relevant NF-pNETs in young MEN1 patients.

**Methods:** Pancreatic imaging data of MEN1 patients were retrieved from the DutchMEN Study Group database. Interval-censored survival methods were used to describe age-related penetrance, compare survival curves, and develop a parametric model for estimating the risk of having clinically relevant NF-pNET at various ages. The primary objective was to assess age at occurrence of clinically relevant NF-pNET (size ≥ 20 mm or rapid growth); secondary objectives were the age at occurrence of NF-pNET of any size and pNET-associated metastasized disease.

**Results:** Five of 350 patients developed clinically relevant NF-pNETs before age 18 years, 2 of whom subsequently developed lymph node metastases. No differences in clinically relevant NF-pNET–free survival were found for sex, time frame, and type of MEN1 diagnosis or genotype. The estimated ages (median, 95% CI) at a 1%, 2.5%, and 5% risk of having developed a clinically relevant tumor are 9.5 (6.5-12.7), 13.5 (10.2-16.9), and 17.8 years (14.3-21.4), respectively.

**Conclusion:** Analyses from this population-based cohort indicate that start of surveillance for NF-pNETs with pancreatic imaging at age 13 to 14 years is justified. The psychological and medical burden of screening at a young age should be considered.

**Key Words:** multiple endocrine neoplasia type 1, pancreatic NET, age-related penetrance, surveillance

Multiple endocrine neoplasia type 1 (MEN1) is a rare tumor predisposition syndrome caused by an inactivating germline mutation in the *MEN1* gene (1, 2). Its 3 main clinical manifestations include pituitary tumors, parathyroid gland hyperplasia, and neuroendocrine tumors (NETs) of the gastroenteropancreatic tract (1, 2). Pancreatic NETs have a high penetrance and occur in almost all patients at age 80 years or older (3, 4). These NETs may secrete hormones, most commonly gastrin or insulin, and cause hypersecretory syndromes; however, nonfunctioning pancreatic NETs (NF-pNETs) are the most prevalent type and constitute an important cause of mortality in MEN1 patients (5, 6). NF-pNETs are typically asymptomatic and imaging modalities remain the cornerstone of surveillance programs for detection and follow-up (7, 8). The current clinical practice guideline recommends screening for MEN1-associated manifestations from age 5 years and pancreatic imaging to be commenced before age 10 years, based on reports of large NF-pNETs in young asymptomatic children (2, 9). Surgery is recommended for NF-pNETs 20 mm or larger because a larger size has been associated with increased risk of metastases, and screening programs thus aim to identify incident tumors early to prevent metastasized disease (5, 8, 10, 11).

Recommendations regarding the optimal age to initiate pancreatic screening by imaging are based on limited evidence (8). Three large studies have specifically described the penetrance of NF-pNETs in young MEN1 patients in different populations (12-14). Among 160 French patients aged 21 years or younger, 14 had NF-pNETs (8.8%), of whom 5 had an indication for surgery (3.1%); the youngest patient was age 13 years (12). Nine out of 45 Tasmanian patients aged 22 years or younger (20.0%) had NF-pNETs, 2 of which were 20 mm or larger (4.4%) (13). Of 166 German patients aged 18 years or younger, only 3 had small NF-pNETs (1.8%) (14). Whereas the French and Tasmanian studies propose regular imaging from age 10 or 12 years onward, the German study suggests that routine screening should be postponed at least to age 16 years (12-14). These conflicting conclusions illustrate the paucity of high-level evidence to substantiate recommendations for screening, while the high prevalence and malignant potential of NF-pNETs emphasize the need for an evidence-based screening program to undertake timely interventions (5, 8).

Considering that all MEN1 patients undergo extensive screening from a young age, optimizing oncological safety while considering the psychological, medical, and financial burden of screening is of great importance. No previous studies have aimed to calculate the risk of developing a clinically relevant tumor at several ages. Therefore, the primary objective of this study is to assess the age at occurrence of clinically relevant NF-pNETs (size ≥ 20 mm or rapid growth) to determine the optimal age to start surveillance by imaging. The secondary objectives are to determine the age at occurrence of NF-pNETs of any size and pNET-associated metastasized disease.

## Materials and Methods

### Study Design and Population

This study includes patients from the DutchMEN Study Group (DMSG) population, which was founded in 2008 as a retrospective database and has since been continued prospectively, including more than 95% of Dutch MEN1 patients from all Dutch university medical centers. The development of this study cohort has been described previously (15). Quarterly data from 1990 onward are available. All patients who had regular pancreatic screening using computed tomography (CT) or magnetic resonance imaging (MRI) or endoscopic ultrasound (EUS) and did not have metastasized disease at earliest documented imaging were considered eligible for inclusion; mutation-negative patients were excluded because they have a different phenotype and clinical course (3).

### Study Objectives

The primary objective is to assess the following:

I. the occurrence of a clinically relevant NF-pNET (ie, a surgical indication) by age. Clinically relevant NF-pNET is defined as (a) size 20 mm or larger or (b) documented growth 1.6 mm or greater within 1 year above a baseline size of 15 mm or larger, based on the growth rate in small progressive NF-pNETs as reported previously (16). For the growth analysis, the largest tumor in the pancreatic head and the largest tumor in the pancreatic body/tail were considered.

Secondary objectives are to assess the following:

II. the diagnosis of any NF-pNET by age. NF-pNET is defined as either a pNET visualized on consecutive CT, MRI, or EUS scans or a NF-pNET diagnosed based on pathology, in the absence of gastrinoma or insulinoma, as reported previously (16).
III. the development of metastases by age defined as metastases visualized on CT, MRI, or EUS or pathologic accumulation of activity in the liver, skeleton, or lymph nodes on a $^{68}$Ga-DOTA-TOC positron emission tomography–CT scan that is not explained by any other cause in a patient with a previous diagnosis of a pNET.

For the analysis of objective I and II, patients were excluded if they underwent pancreatic surgery (objective I) or had a registered clinical diagnosis of a pNET and/or underwent pancreatic surgery (objective II) before available data collection.

### Time-to-Event Definitions and Censoring

The outcome measures are analyzed as time-to-event data starting from birth. Because the diagnosis of a NF-pNET occurs based on periodic pancreatic screening rather than being observed directly, the true time-to-event cannot be defined exactly and is some unobserved time between 2 screening moments. These types of data are known as interval censored, for which time-to-event $t_i$ is denoted as the interval $(l_i, r_i)$ in which $l_i$ = age at last screening without a visible tumor and $r_i$ = age at first screening with a visible tumor.

The data set also includes patients who have a (clinically relevant) NF-pNET at the first screening moment, such that it is known only that the tumor developed at a younger age compared to the age at first screening (left censoring). Time to event for these patients is coded as the interval between $l_i$ = age 0 and $r_i$ = age at first imaging. Patients who do not yet have an outcome at the most recent available imaging (right censoring) are coded as $l_i$ = age at last imaging and $r_i = \infty$. Patients are right-censored when screening is terminated for any reason; for objective I and II, patients are also right-censored after any type of pancreatic surgery has been conducted or when a functional pNET is diagnosed before diagnosis of an NF-pNET.

### Statistical Analysis

All statistical analysis was conducted using R version 3.6.1 (17). Survival analysis methods equipped to deal with interval-censoring were used, as standard survival models that are equipped to handle only right-censoring may lead to an incorrect inference when different types of censoring, as described earlier, are present in the data (18).

The nonparametric maximum likelihood estimation (NPMLE) of the survival function, a generalization of the Kaplan-Meier estimator allowing for interval-censored data, was computed based on the E-M algorithm of Turnbull and 95% CIs were calculated with a modified bootstrap method as implemented in the *interval* package (19, 20). Cumulative distribution functions were plotted to show the cumulative probability of having developed a (clinically relevant) NF-pNET or pNET-associated metastases by age. Because of interval-censored data, the risk curves are not unique; the intervals in which the NPMLE is indeterminate, that is, in which each possible risk curve gives the same fit to the data, are shown as shaded boxes. All figures are capped at age 70 years because there were fewer than 10 remaining patients at risk for having any NF-pNET.

Comparison of survival curves by sex, time frame, and type of MEN1 diagnosis and genotype were conducted

using weighted log-rank tests adapted for interval-censored data as developed by Sun (20, 21). The time frame of MEN1 diagnosis is assessed to account for the influence of changes in screening over time and dichotomized as before vs after 1998, when genetic testing became available; type of MEN1 diagnosis is categorized as diagnosis based on clinical, familial, or genetic criteria (2). Genotype was categorized as nonsense and frameshift mutations vs missense mutations; it is hypothesized that nonsense and frameshift MEN1 mutations in combination with loss of the wild-type allele lead to the complete absence of the gene product and thus a more severe phenotype compared to some functional MENIN in case of missense mutations (16).

Parametric survival models were developed using the *icenReg* package for interval-censored data (22). A parametric approach is appropriate as the study objective is to estimate the baseline hazard to obtain a smooth representation of the survival function and predict survival times using interval-censored data (22). Several underlying parametric distributions were considered, including exponential, Weibull, log-logistic, log-normal, gamma, and generalized gamma γ distributions. Model selection was based on visual evaluation of fit in comparison to the NPMLE and the Akaike information criterion (22).

### Ethical Approval

The data registration for the DMSG has been approved by the ethical boards of all university medical centers in the Netherlands. Informed consent was obtained for all patients.

## Results

### Study Population

All DMSG patients with baseline data available on November 30, 2020, were considered for inclusion (n = 447), of whom 350 patients were included. Reasons for exclusion were (1) no regular follow-up, that is, data from fewer than 2 pancreatic imaging studies available in the database (n = 48), and/or (2) presence of metastasized disease at earliest pancreatic imaging study in the database (n = 32), and/or (3) mutation-negativity (n = 45). Characteristics of included patients are displayed in Table 1.

A total of 337 patients who did not undergo pancreatic surgery and 334 patients who did not have a registered clinical diagnosis of a pNET and/or pancreatic surgery before the onset of quarterly data collection were included in the subgroup analysis for objective I (clinically relevant NF-pNET) and II (any NF-pNET), respectively. All 350 patients were included in the analysis for objective III (metastasized disease).

### Occurrence of Clinically Relevant Nonfunctioning Pancreatic Neuroendocrine Tumors

A total of 127 of 337 at-risk patients developed a clinically relevant NF-pNET, that is, a surgery indication based on tumor size of 20 mm or larger or rapid growth; 64 patients were censored because of the development of a functional syndrome and/or undergoing pancreatic surgery. Five patients developed a clinically relevant NF-pNET before age 18 years, at ages 14, 15, 15, 17, and 17 years, respectively. An additional 9 patients developed a clinically relevant NF-pNET at ages 18 to 21 years. For 8 out of these 14 patients, clinically relevant NF-pNETs were identified on the first pancreatic imaging. The estimated cumulative probabilities (95% CI) for a clinically relevant NF-pNET at ages 15, 18, and 21 years are 3.6% (0.0%-7.3%), 4.7% (1.5%-9.1%), and 7.8% (4.2%-12.1%), respectively; at age 70 years, the estimated probability is 62.6% (52.2%-73.5%, Fig. 1). Weighted log-rank tests for interval-censored data did not show clear differences in tumor-free survival based on sex ($P = .59$), time frame ($P = .24$), and type ($P = .06$) of MEN1 diagnosis and genotype ($P = .52$) (22). A gamma model provided the best fit to the data (22). Cumulative distribution function estimates for clinically relevant NF-pNETs by age were calculated (Table 2). The estimated ages (median, 95% CI) at a 1%, 2.5%, and 5% risk of having developed a clinically relevant tumor are 9.5 (6.5-12.7), 13.5 (10.2-16.9), and 17.8 years (14.3-21.4), respectively.

### Occurrence of a Nonfunctioning Pancreatic Neuroendocrine Tumor of Any Size

A total of 177 of 334 at-risk patients developed an NF-pNET; 46 patients were censored because of the development of a functional syndrome and/or undergoing pancreatic surgery. Nine of 334 patients developed an NF-pNET before age 18 years, the youngest of whom was age 14 years at diagnosis. An additional 14 patients developed an NF-pNET at ages 18 to 21 years. For 16 of these 23 patients, the NF-pNET was diagnosed at the first available imaging. Seven patients developed a functional syndrome (insulinoma or gastrinoma) up to age 21 years and were censored. The cumulative probability (95% CI) of having developed an NF-pNET at age 15, 18, and 21 years is 8.6% (0.8%-15.3%), 12.0% (5.9%-17.0%), and 16.1% (11.2%-21.5%) respectively; at age 70 years, the estimated probability is 80.0% (72.2%-97.0%, Fig. 2). Out of 9 patients who were followed up to age 70 years without developing an NF-pNET, only 1 subsequently developed an NF-pNET diagnosed through radiological imaging, at age 71 years. Weighted log-rank

tests for interval-censored data did not show clear differences in NF-pNET-free survival based on sex ($P = .96$), time frame ($P = .88$), and type ($P = .35$) of MEN1 diagnosis and genotype ($P = .60$) (23).

## Development of Metastases

In 66 of 350 at-risk patients, metastases associated with any pNET were visualized over the course of follow-up. No metastases were identified in patients younger than 18 years. Three patients had evidence for pNET-associated metastases before age 30, at ages 19, 24, and 25 years. The cumulative probability of having any pNET-associated metastasized disease at age 70 years is 41.2% (31.3%-50.3%, Fig. 3A). Weighted log-rank tests for interval-censored data did not show clear differences in metastasis-free survival based on sex ($P = .29$) or time frame ($P = .13$) of MEN1 diagnosis (22). There was a difference in survival distributions depending on genotype ($P = .01$). Seven out of 73 patients with missense

**Table 1.** Characteristics of the study population (n = 350)

| Characteristics | | Study population | |
|---|---|---|---|
| Birth quarter (median, range) | | 1966 Q2 | (1921 Q4-1999 Q2) |
| Age at MEN1 diagnosis (median, range), y | | 34.0 | (4.25-71.25) |
| Age at first available imaging (median, range), y | | 37.5 | (4.50-68.75) |
| First available imaging conducted < age 18, No., % | | 37 | 10.6% |
| First available imaging conducted < age 22, No., % | | 75 | 21.4% |
| Sex, No., % | Male | 157 | 44.9% |
| | Female | 193 | 55.1% |
| Alive, No., % | Alive | 298 | 85.1% |
| | Dead | 52 | 14.8% |
| MEN1 diagnosis, No., % | Familial | 84 | 24.0% |
| | Genetic | 219 | 62.6% |
| | Clinical | 47 | 13.4% |
| Mutation type, No., % | Nonsense/frameshift | 170 | 48.6% |
| | Missense | 73 | 20.8% |
| | Other mutations | 107 | 30.5% |

Abbreviations: MEN1, multiple endocrine neoplasia type 1; Q, quarter.

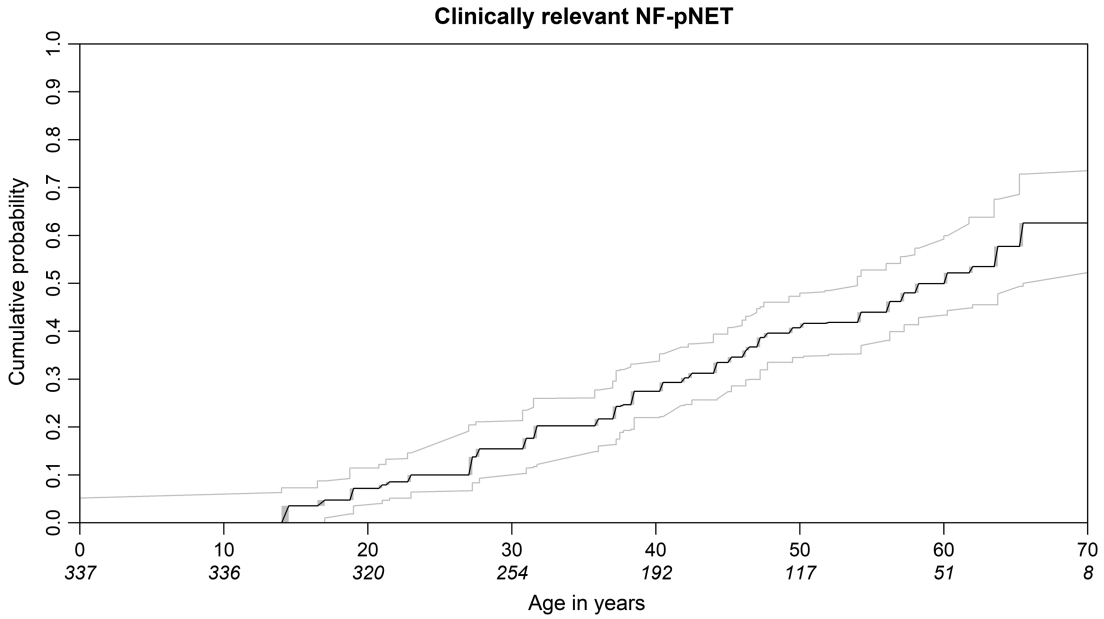


**Figure 1.** Cumulative probability of having a clinically relevant nonfunctioning pancreatic neuroendocrine tumor (NF-pNET) with 95% CI (nonparametric maximum likelihood estimation [NPMLE] of cumulative distribution functions). The intervals in which the NPMLE is indeterminate are shown as shaded boxes. Number at risk (italics) is given for right censoring.

mutations developed metastases compared to 38 out of 170 patients with nonsense/frameshift mutations; the cumulative probabilities of metastases at age 70 years were 10.0% (2.6%-82.7%) and 53.9% (37.8%-74.3%), respectively (Fig. 3B). There also was a difference by type of MEN1 diagnosis ($P = .01$). Twenty out of 47 patients with a clinical diagnosis compared to 26 out of 219 with a genetic diagnosis and 20 out of 84 with a familial diagnosis developed metastases; the cumulative probability at age 70 years was 60.7% (40.2%-87.3%) in those with a clinical diagnosis compared to 34.6% (20.0%-53.4%) and 39.8% (22.1%-79.5%) in patients with a genetic or familial diagnosis, respectively (Fig. 3B).

**Table 2.** Gamma model estimates of cumulative probability of having a clinically relevant nonfunctioning pancreatic neuroendocrine tumor

| Estimates by age (%, 95% CI), y | | Estimates by percentile (median, 95% CI), y | |
|---|---|---|---|
| 10 | 1.1% (0.4-2.4) | 1.0% | 9.5 (6.5-12.7) |
| 11 | 1.5% (0.6-3.0) | 2.5% | 13.5 (10.2-16.9) |
| 12 | 1.8% (0.8-3.5) | 5.0% | 17.8 (14.3-21.4) |
| 13 | 2.3% (1.1-4.2) | | |
| 14 | 2.7% (1.4-4.8) | | |
| 15 | 3.3% (1.7-5.5) | | |
| 16 | 3.8% (2.1-6.3) | | |
| 17 | 4.4% (2.5-7.1) | | |
| 18 | 5.1% (3.0-7.9) | | |

### Clinical Course of Nonfunctioning Pancreatic Neuroendocrine Tumors Diagnosed in Patients 18 Years or Younger

Of 37 patients who underwent imaging before age 18 years, 9 patients were diagnosed with an NF-pNET before age 18, 7 of whom at first imaging (Fig. 4). Five patients developed a clinically relevant NF-pNET, that is, tumors demonstrating a size of 20 mm or larger or rapid growth, at younger than 18 years, the youngest of whom was aged 14 years and was diagnosed at first imaging. One of these patients diagnosed at age 17 years had lymph node metastases visualized by EUS at age 19 years. Another patient with a clinically relevant tumor at age 15 years had lymph node metastases visualized by MRI at age 24 years. The remaining 3 patients did not develop metastases over the 8.25 to 9.0 years of available follow-up after tumor diagnosis. Of the 4 patients with a small NF-pNET visualized before age 18 years, 2 experienced an increase in size to 20 mm or larger at ages 19 and 23 years, whereas the other 2 patients were followed until ages 21 and 26 years without developing an indication for surgery; none developed metastases during available follow-up.

## Discussion

A recent systematic review on screening for NF-pNETs in patients with MEN1 outlined the paucity of high-level evidence to substantiate recommendations for the starting age of surveillance (8). This study aimed to fill this gap in evidence by modeling the occurrence of clinically relevant

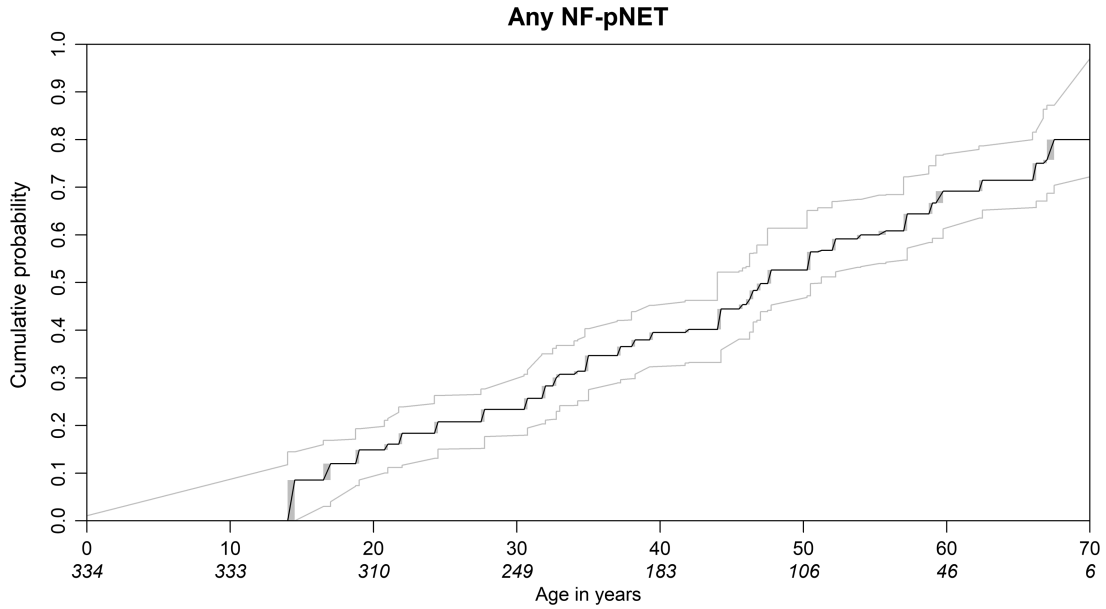


**Figure 2.** Cumulative probability of having a nonfunctioning pancreatic neuroendocrine tumor (NF-pNET) of any size with 95% CI (nonparametric maximum likelihood estimation [NPMLE] of cumulative distribution functions). The intervals in which the NPMLE is indeterminate are shown as shaded boxes. Number at risk (italics) is given for right censoring.

NF-pNETs in MEN1 patients by age. Additionally, data from the Dutch nationwide MEN1 database were used to estimate the age-related penetrance and the risk of metastasized disease to create a comprehensive overview of the course of disease in young MEN1 patients. In 5out of 354 patients a clinically relevant NF-pNET, demonstrating a size of 20 mm or larger or rapid growth of 1.6 mm/year or greater, was identified before age 18 years, 2 of whom subsequently developed lymph node metastases. According to the gamma model that provided the best fit to the data, the estimated probabilities of having developed a clinically relevant NF-pNET are 1%, 2.5%, and 5% at ages 9.0, 13.2, and 17.9 years, respectively.

The overall penetrance of NF-pNETs is high. The NPMLE cumulative probabilities of having any NF-pNET at ages 18 and 21 years are 12.0% and 16.1%; probabilities of having developed a clinically relevant NF-pNET are 4.7% and 7.8%, respectively. The reported age-related penetrance is broadly consistent with the penetrance of NF-pNETs reported among Tasmanian patients (20% of patients ≤ 22 years) but higher compared to the French and German cohorts (8.8% ≤ 21 and 1.8% ≤ 18 years, respectively) (12-14). On the other hand, these estimates are considerably lower compared to a small Brazilian study that found an NF-pNET penetrance of 42% in 19 patients aged 12 to 20 years, of which half were clinically relevant (21%) (24). The variation between these studies may be explained by variation in the use of imaging modalities and local screening protocols, patient selection, and unexplained phenotypic variation between study cohorts (8). None of these studies has developed a parametric survival model; it would be of interest to apply this survival model to data from the other cohorts to assess its external validity.

There were no associations between sex, time frame, and type of MEN1 diagnosis and genotype and survival time free of any or clinically relevant NF-pNETs, suggesting that, as of now, it is not possible to stratify screening recommendations based on any of these demographic characteristics. A significant association was found between MEN1 genotype and survival free of metastasized disease associated with any pNET, in line with the hypothesis that nonsense and frameshift mutations demonstrate a more severe phenotype compared to missense mutations that allow for some remaining functional MENIN (16). Additionally, there was a higher risk of metastasis in patients with a clinical diagnosis compared to those with a familial or genetic diagnosis, which may represent higher age at MEN1 diagnosis and later identification of pNETs in mutation-positive index patients compared to patients who undergo presymptomatic screening. However, these results should be interpreted with caution because the number of events was small and surgical and pathological characteristics such as timing, method, and radicality of surgery as well as tumor grade and local invasion were outside the scope of this study (10).

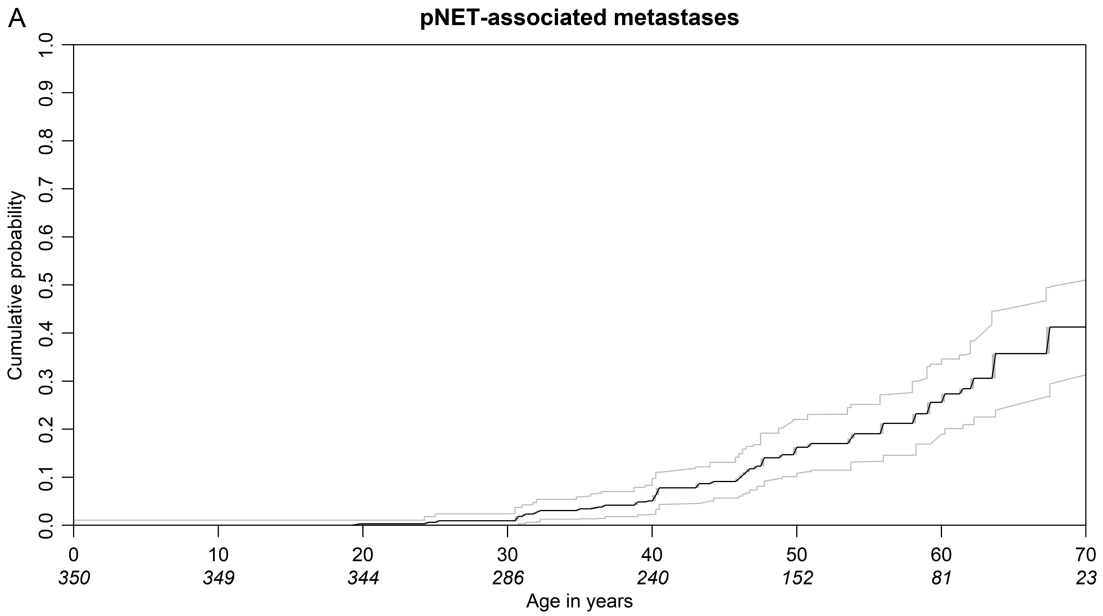


**Figure 3.** A, Cumulative probability of having pancreatic neuroendocrine tumor (pNET)-associated metastasized disease with 95% CI (nonparametric maximum likelihood estimation [NPMLE] of cumulative distribution functions). The intervals in which the NPMLE is indeterminate are shown as shaded boxes. Number at risk (italics) is given for right censoring. B, Cumulative probability of having developed pNET-associated metastasized disease stratified by multiple endocrine neoplasia type 1 (MEN1) genotype and type of MEN1 diagnosis, with numbers at risk given for missense, nonsense/frameshift, and other groups, and familial, genetic, and clinical diagnosis, respectively.

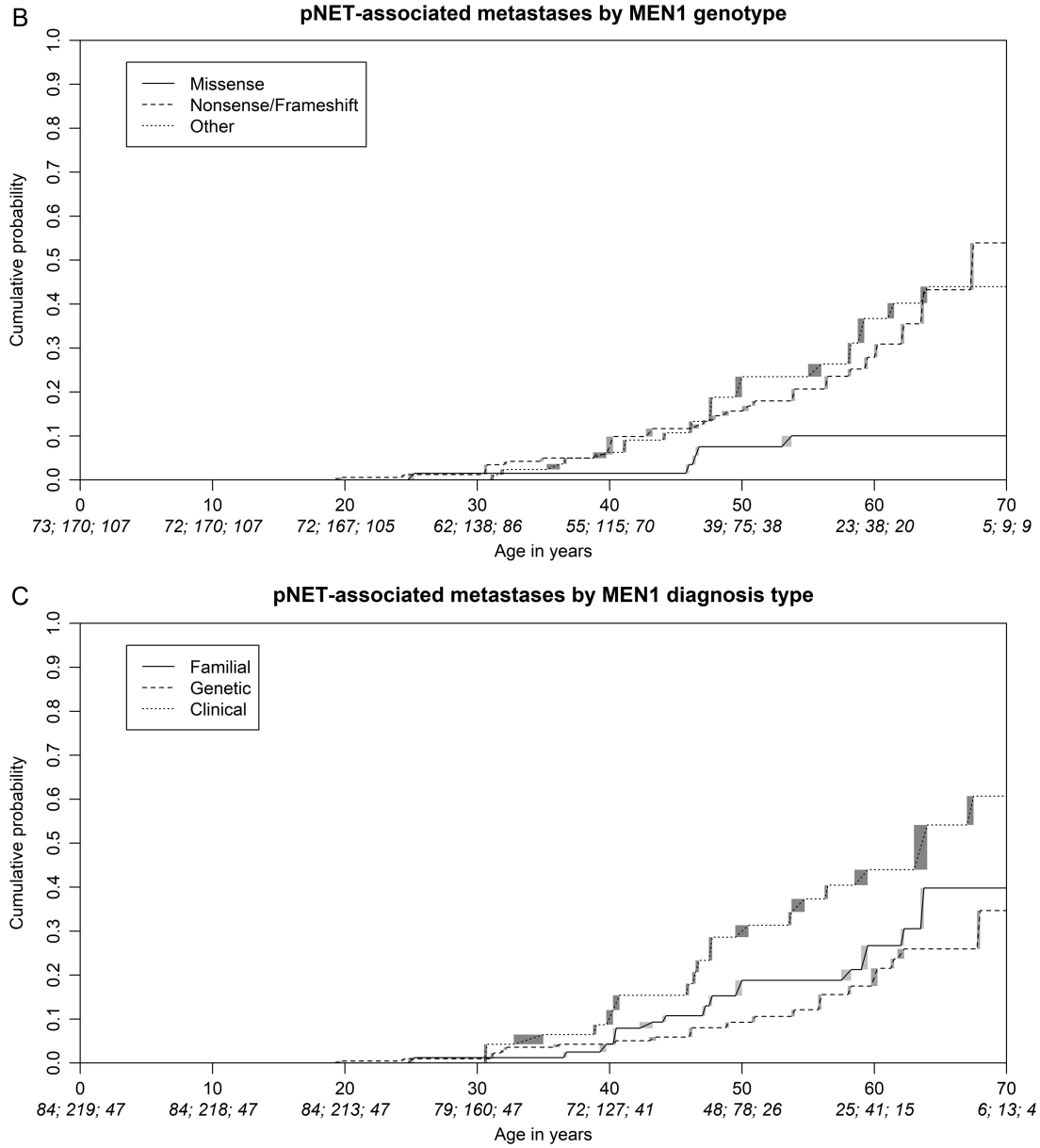


**Figure 3.** Continued.

The clinically relevant outcome measures, the representative sample of MEN1 patients for which extensive data are available, and the use of statistical methods equipped for interval-censored data are considered as major strengths. This is the first study that developed a survival model to predict the risk of clinically relevant NF-pNETs in this population. Increasingly sensitive imaging modalities in combination with early diagnosis result in a high chance of detection of small NF-pNETs, which may have a mostly indolent course, underlining the need for clinically relevant outcome measures. By reporting on the surgical indication rather than the surgery itself, the estimates are not influenced by management decisions. More than 95% of the Dutch MEN1 population participates in the DMSG database, and quarterly data collection was conducted following a predefined protocol for all patients. Statistical methods equipped for interval-censored data were used to allow for reliable inference from this data set. As NF-pNETs are diagnosed through screening, the exact time to event can be defined only up to an interval between scheduled imaging studies; for young patients with an NF-pNET on first screening, it is known only that the tumor developed at some time before that moment. Assuming that the time of diagnosis is equal to the time of occurrence results in an overestimation of the tumor-free survival time when an NF-pNET may have been present for months to years before imaging is conducted (25). The reported estimates account for this uncertainty in the data.

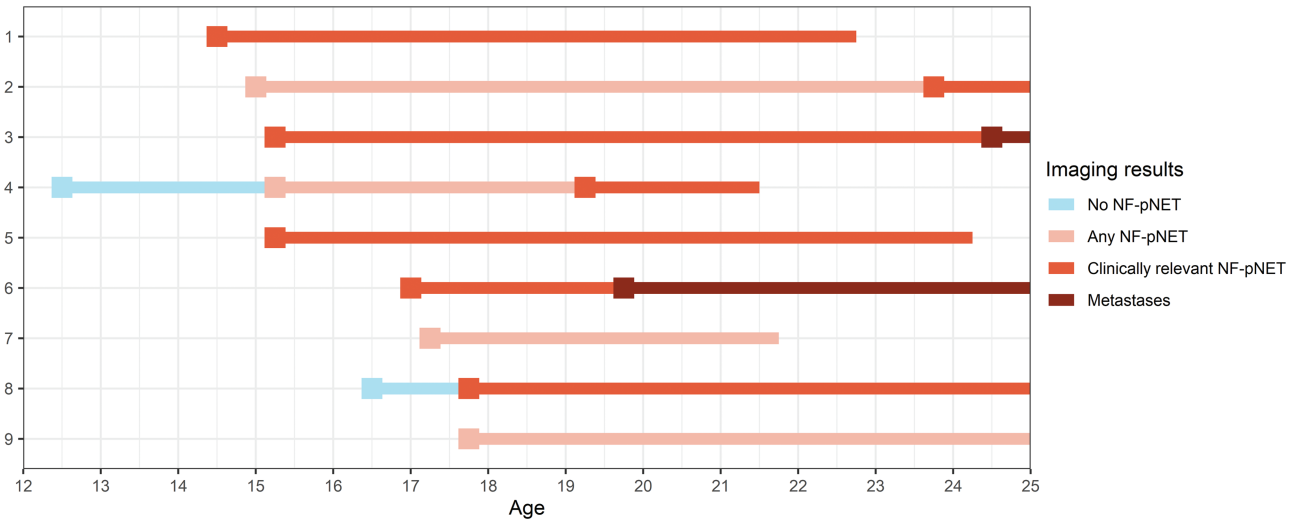


**Figure 4.** Imaging results of 9 patients with a nonfunctioning pancreatic neuroendocrine tumor (NF-pNET) of any size diagnosed before age 18 years. The bars start at age of first available follow-up and end at age of last available follow-up, limited to age 25 years for patients with longer follow-up.

The DMSG database records abstract imaging and laboratory results (eg, tumor in pancreatic head visualized on CT scan or negative fasting test) without clinical interpretation of these modalities (eg, clinical diagnosis of an NF-pNET). Uniformity within this study was guaranteed by strictly applying the definitions provided earlier to all quarterly data. A limitation of this study is that only the size of the largest tumor per localization was recorded, allowing for calculation of rapid growth only in either the largest tumor in the pancreatic head or that in the body/tail, although additional tumors may have been present. However, as only tumors 15 mm or larger demonstrating rapid growth were considered clinically relevant, in the absence of any tumors 20 mm or larger that met the definition of a clinically relevant tumor, the available data likely represent the most clinically relevant tumors.

Considering the occurrence of clinically relevant tumors in adolescent patients and the malignant potential of NF-pNETs, there is a medical indication to conduct pancreatic screening during the second decade of life. The exact age to initiate screening must be decided individually in consideration of the burden of surveillance. Repeated imaging may be experienced as frightening, invasive (in case of EUS), and/or associated with significant cumulative radiation exposure (in case of CT) (7); moreover, experiences with affected family members and fear of malignancy may play a role in MEN1 families (26). According to the Dutch medical jurisdiction, for children aged 12 to 16 years, children and parents both need to give permission for treatment (27). Considering a risk of 1 in 40 of having a clinically relevant tumor to be the maximum acceptable, the present findings demonstrate that initiating surveillance around age 13 to 14 years is justifiable. However, as the identification of an acceptable cutoff is not straightforward, risk estimates for ages 10 to 18 are provided to allow other MEN1 centers to independently assess what constitutes an acceptable risk for their population. Overall, shared decision making by the pediatrician, child, and parents should guide the start of abdominal imaging.

The psychological impact of screening for pNETs on young MEN1 patients is not known. Previous studies have described a decreased health-related quality of life and fear of disease occurrence related to pNETs in adult MEN1 patients (26, 28). In adults and children who survived cancer, surveillance imaging has been associated with distress and anxiety; a good doctor-patient relationship and adequate communication about follow-up play an important role in mediating this distress (29, 30). To our knowledge, no studies have explored these concerns within the pediatric and adolescent MEN1 population.

Of note, a recent study suggests potential genetic anticipation within MEN1 families, in which MEN1 manifestations including duodenopancreatic NETs are identified at a younger age in successive generations (31). Because this study was explorative in nature, further research is necessary to confirm whether this mechanism plays a significant role and how it can be addressed in personalized and family-based screening recommendations. Finally, it is not known if the clinical course of NF-pNETs in pediatric patients differs from that in adults. Currently, the clinical guidelines do not describe lower size thresholds to be considered clinically relevant for tumors detected in children (2); studies specifically describing growth patterns and the metastatic potential of NF-pNETs detected in young patients would be of relevance.

Based on the occurrence of clinically relevant tumors and the risk of subsequent metastasized disease, initiation of surveillance from age 13 to 14 years is justifiable. Further research should evaluate the impact of regular surveillance at the pediatric age on overall survival and quality of life. At this time, the estimated risks provided in this study may aid clinicians in informing their patients and implementing surveillance policies.

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## Additional Information

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