REVIEW

'Quality in, quality out', a stepwise approach to evidence-based medicine for rare diseases promoted by multiple endocrine neoplasia type 1

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Abstract

Rare diseases pose specific challenges in the field of medical research to provide physicians with evidence-based guidelines derived from studies with sufficient quality. An example of these rare diseases is multiple endocrine neoplasia type 1 (MEN1), which is an autosomal dominant endocrine tumor syndrome with an estimated occurrence rate of 2–3 per 100,000. For this complex disease, characterized by multiple endocrine tumors, it proves difficult to perform both adequate and feasible studies. The opinion of patients themselves is of utmost importance to identify the gaps in the evidence-based medicine regarding clinical care. In the search for scientific answers to clinical research questions, the aim for best available evidence is obvious. Observational studies within patient cohorts, although prone to bias, seem the most feasible study design regarding the disease prevalence. Knowledge and adaptation to all types of bias is demanded in the strive for answers. Guided by our research on MEN1 patients, we elaborate on strategies to identify sufficient patients, to maximize and maintain patient enrolment and to standardize the data collection process. Preferably, data collection is performed prospectively, however, under certain conditions, data storage in a longitudinal retrospective database with a disease-specific framework is suitable. Considering the global challenges on observational research on rare diseases, we propose a stepwise approach from clinical research questions to scientific answers.

Key Words

- multiple endocrine neoplasia type 1
- hereditary tumor syndrome
- research strategies
- database
- observational studies

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Introduction

Rare diseases that affect less than one in 2000 people, pose challenges in supporting patients and physicians with evidence-based guidelines of sufficient quality (1). Medical decision making becomes challenging when guidelines are scarce or the underlying scientific evidence is meager.

Multiple endocrine neoplasia type 1 (MEN1) (OMIM 131100) is an autosomal dominant disease with an estimated occurrence rate of 2–3 per 100,000 (2). Due to the complexity of the disease, which is characterized by the development of multiple endocrine tumors already at an early age, developing evidence-based guidelines is a challenge (3). Most patients suffer from the classical triad of primary hyperparathyroidism (pHPT), duodenopancreatic neuroendocrine tumors (dp-NETs) and/or pituitary adenomas. The prevalence for pHPT, dp-NETs and

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pituitary tumors are 87, 56 and 44%, respectively in the Dutch population (4). Other encountered neoplasms include adrenal tumors, neuroendocrine tumors (NETs) of thymic, bronchial or gastric origin, skin and subcutaneous tumors, smooth muscle tumors and breast cancer (5, 6). Life expectancy of MEN1 patients is reduced compared to the general population (4). The prognosis of patients depends on early tumor detection and subsequent targeted interventions to prevent disease progression, making lifelong screening and intensive monitoring necessary (7).

Randomized controlled trials studying interventions and the optimal follow-up are almost impossible because of the low number of eligible patients for inclusion as well as the low yearly incidence of events in individual patients. Cohort studies are prone to various forms of bias such as selection bias, information bias and confounding by indication (8, 9).

Confronted by the principles of evidence-based medicine and need for high-quality scientific evidence regarding follow-up and interventions in MEN1, in the Netherlands in 2007, a retrospective MEN1 database was carefully designed. The aim was to answer multiple research questions that were based on the clinical dilemmas MEN1 patients and their treating physicians encountered in daily practice. The aim of this project was to provide patients and physicians with valid data. Considering the complexity of MEN1, a longitudinal database with a disease-specific framework was a necessity. Whereas strategies for conducting randomized controlled trials on rare diseases have been described, research methods for observational studies are far less developed (10). Guided by the fruitfulness of our longitudinal database and experience on this topic, this article will elaborate on our research strategy and observational study methods for rare diseases, describing the stepwise process from clinical research questions to scientific answers.

Clinical dilemma and theoretical study design

Formulating research questions and determining study design

Biomedical research consists of three main phases: formulating a research question, the collection of data based on these questions and the analysis of data. In recent years, the importance of the opinion of patients affected by the disease in this process is increasingly acknowledged. The subsequent study design is guided by a well-structured research question, addressing the study domain (patients with symptoms or a certain disease), determinant (diagnostic test, factor or therapy) and outcome of interest.

MEN1 formulated research questions

Clinical guidelines are only as good as the evidence and judgments they are based on (11). Even though there was a MEN1 consensus statement at the time, the scientific evidence underlying recommendations regarding screening and treatment of the different MEN1 manifestations was not always sufficient (12).

Our research group was confronted by a paucity of data on the natural course of the different MEN1 manifestations, prognostic factors, a genotype–phenotype relation, the timing and effect of therapy and recommendations based on strong evidence for periodical screening for these manifestations. These topics were the basis of the first set of research questions (Table 1). In addition, we consulted the patient advocacy group in this stage of the process, as to which questions they deemed important to study. The patient advocacy group considered quality of life as an important topic to study. More specifically, they considered questions regarding frequency and content of follow-up visits, effects and complications of surgery (e.g. hypoparathyroidism after (sub)total parathyroidectomy) and survival of dp-NETs as important topics since these affect quality of life. In a process of informed shared decision-making, research questions and study aims were formulated thereafter.

Study population

A single center patient population

In the University Medical Center (UMC) Utrecht, approximately 80 MEN1 patients were identified in 2007, which can be regarded as a 'large' rare disease population. However large, this study population lacked power to detect meaningful differences. In addition, we considered the population as a possible source of selection bias, since our center is a national center of expertise in MEN possibly leading to a case-mix with more advanced stages of the disease. Improper selection of patients, not being representative for the target population, leads to selection bias. In general, minimizing selection bias is attempted by including as many patients as possible in terms of percentage from similar hospitals, regarding level of patient care, during the recruitment phase.

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Table 1 DMSG MEN1 study questions.

Manifestation	MEN1 study goal	Research questions	Study objectives
pHPT			
pHPT	Timing and effect of treatment	Patient advocacy group	What is the optimal surgical strategy for multiple endocrine neoplasia type 1 (MEN1)-related primary hyperparathyroidism (pHPT)? What is the course of postoperative hypoparathyroidism? Is genotype is associated with persistent/recurrent pHPT?
NETs			
Thymus and lung NET	Natural course	DMSG Patient advocacy group	What is the prevalence, tumor growth and survival of Thymus and lung NETs in an unselected MEN1 population with long-term follow-up?
NET	Prognostic factors	Subsequent questions	Is there an association between blood type O and the occurrence of neuroendocrine tumors in the national Dutch MEN1 cohort?
pNET, tumor markers	Evidence-based screening	DMSG Patient advocacy group	What is the diagnostic accuracy of chromogranin A (CgA), pancreatic polypeptide (PP) and glucagon for pNET in MEN1?
dp-NET	Prognostic factors	DMSG	What is overall survival and what are prognostic factors for patients with liver metastases from DP-NETs?
pNET	Natural course	DMSG Patient advocacy group	What is the natural history of small (<2cm) nonfunctioning pNETs in MEN1? What are effect modifiers for tumor growth of small (<2cm) nonfunctioning pNETs in MEN1?
pNET	Timing and effect of treatment	DMSG	Is surgery for multiple endocrine neoplasia type 1 (MEN1)-related nonfunctioning pancreatic neuroendocrine tumors effective for improving overall survival and preventing liver metastasis?
pNET	Timing and effect of treatment	DMSG	What are short- and long-term morbidity after pancreatic surgery for multiple endocrine neoplasia type 1 (MEN1)-related nonfunctioning pancreatic neuroendocrine tumors?
pNET	Timing and effect of treatment	Subsequent questions	What are outcomes of robot-assisted and laparoscopic spleen-preserving pancreatic surgery in MEN1 patients?
pNET	Prognostic factors	Subsequent questions	Is there an association between WHO grade and the development of liver metastases in pNETs in MEN1 patients?
pNET	Prognostic factors	Subsequent questions	What is the role of role p27Kip1 and p18Ink4c in pancreatic neuroendocrine tumor development in MEN1 patients?
pNET	Prognostic factors	Subsequent questions	What are promoter methylation profiles in pNETs in MEN1?
Thyroid incidentalomas	Prevalence and natural course	Subsequent questions	What is the prevalence of thyroid incidentalomas in MEN1 patients compared with nonMEN1 patients? Is thyroid tumorigenesis MEN1-related?
Pituitary tumors			
Pituitary tumors	Natural course	DMSG Patient advocacy group	What are the results of systematic pre-symptomatic PIT screening in MEN1? What are the outcomes after long-term follow-up of PITs with emphasis on nonfunctioning microadenomas diagnosed by screening in MEN1?
Effect of screening			
Screening	Evidence-based screening	DMSG	What is the effect of genetic screening on outcome in multiple endocrine neoplasia type 1 (MEN1)?
Screening	Evidence-based screening	DMSG	Is there a lag time from MEN1 diagnosis of the index case to MEN1 diagnosis of family members? Is a time lag in MEN1 diagnosis associated with an increased morbidity and mortality risk?
Screening	Genotype-phenotype	DMSG	What is the clinical course of MEN1 mutation-negative patients with two out of the three main MEN1 manifestations and mutation-positive patients during long-term follow-up?
Quality of life			
Quality of life	Quality of life	Patient advocacy group	Do MEN1 patients have fear of disease for themselves of for family members? Is there an association between MEN1-related fear and health-related quality of life? What are risk factors for fear of disease occurrence in MEN1?
Other			
Breast cancer	–	Subsequent questions	What is the incidence of breast cancer in the Dutch longitudinal MEN1 database? What is the role of *MEN1* in human breast cancer?
Breast cancer	–	Subsequent questions	What are risk factors involved in early-onset elevated breast cancer in MEN1?

CgA, chromogranin A; DMSG, Dutch MEN Study Group; dp-NET, duodenopancreatic neuroendocrine tumor; MEN1, multiple endocrine neoplasia type 1; NET, neuroendocrine tumor; pHPT, primary hyperparathyroidism; PIT, pituitary; pNET, pancreatic neuroendocrine tumor; PP, pancreatic polypeptide.

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Collaboration at a national level

In the Netherlands, MEN1 patients are commonly treated in a UMC (tertiary referral center) because of the necessity of a trained and dedicated multidisciplinary team (13). To include a representative sample of MEN1 patients and to increase sample size, a nationwide collaboration, known as the DutchMEN Study Group (DMSG), was initiated in 2008 (14). The DMSG consists of endocrinologists from every Dutch UMC, a consulting endocrine surgeon and representation from the patient advocacy group. Moreover, other specialist members of the multidisciplinary team are closely involved, which is in line with MEN1 guidelines to optimize patient care (13). The DMSG program, including patients from all Dutch UMCs, has led to the inclusion of over 90% of the total Dutch MEN1 population (> 400 participants) making it a true representation of Dutch MEN1 patients (15).

Patient identification

Before enrolling patients, a consistent diagnosis in accordance with guidelines is important. In this manner, a restricted population is created and selection bias is minimized. Using a standard identification method, MEN1 patients were identified by hospital diagnosis databases review. MEN1 diagnosis was based on clinical, familial or genetic criteria, based on clinical practice guidelines (12, 13). Less than 10% of the genetically diagnosed MEN1 patients is not included in the registry and only one person refused to participate. The high participation rate (over 90%) has also been found in a survey of patients with leukodystrophies, another rare disease (16). However, for MEN1 populations, this registry participation rate is globally unique and thereby leading in the field.

Strategies to maximize patient enrolment

The urge for international data registries is expressed by The European Union Committee of Experts on Rare Diseases (17). Patients with rare diseases are generally easily accessible for participation in international data registries (16, 18). Since MEN1 is an autosomal dominant trait, patients' children have a 50% chance of inheriting the disease (2). Patients are well aware of the high disease morbidity and decreased life expectancy since the disease 'runs in the family'. Patients maximize their contribution to medical research and subsequent clinical care for their affected relatives and other MEN1 patients.

Nevertheless, before patients are willing to engage in medical research, the physician–patient interaction is important (16, 19). In addition, to enroll a maximum number of patients, the study goals should be of direct importance to patients and their families. Active involvement of the national patient advocacy group in the DMSG from the stage of designing the research questions contributed to the high participation rate of patients.

Obtaining informed consent

The study protocol for the DMSG database and subsequent studies was approved by the Medical Ethical Committees of all UMCs in the Netherlands. The requirement to obtain individual informed consent was waived because of the retrospective and observational design. However, all patients received a letter including information regarding the collection and storage of clinical data and the possibility to refuse. From 2016 onward, the clinical database was continued prospectively including the collection of biobank materials (clinical biobank). Before inclusion in the clinical biobank, patients are informed by telephone or during an outpatient clinic visit including written patient information and asked to provide written informed consent. In addition, patients are informed about the possibility to withdraw their informed consent at any given time in the future.

Strategies to maintain patient participation

Studies with a necessary long-term follow-up are vulnerable to losing patients during follow-up. This potentially leads to follow-up bias, especially when the loss to follow-up differs between groups. Since MEN1 is a chronic disease in which patients have an ongoing risk for tumor development, patients consult endocrinologists annually, reducing follow-up bias to a minimum. However, patients that move to another place might change academic treatment center, decide to transfer to a local hospital or quit the follow-up regimen altogether. With respect to the nationwide collaboration of all Dutch UMCs in the DMSG, loss to follow-up of patients is mostly prevented. Changing academic center will not end nor interrupt data collection, because registry entry will continue from the new treatment hospital. Nevertheless, effort must be made to ensure regular physician consultations. DMSG strategies to minimize loss of follow-up include the physician–patient relation, and moreover, regular physician consultation is also promoted by the patient advocacy group.

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Strategies to establish the study population of the Dutch MEN1 registry are summarized in Table 2.

From patients to data

The importance of data collection

The goal of the data collection process is to gather data which give true and objective reflections of patients' conditions. Incorrect data or inconsistent data collection leads to information bias; therefore, the process of data collection must be carefully designed, conducted and preferably secured. Before the actual collection of data, it is important to understand the nature of the data, to classify the data and to decide to which extent data are collected. The quality of data is guided by validity and precision. Systematic errors in data collection are dangerous, since these lead to irreversible damage to the study's internal validity (20).

Database design

The construction of a structured database and the valid and precise collection of data were critical research steps (Table 3). Even though some single-center MEN1 studies were conducted in the UMC Utrecht, a well-structured process of data collection was absent (21, 22). In addition to the nationwide expansion of the study population, multicenter, nationwide collaboration on data collection was essential. Considering the urge for quick answers to clinical questions and the low disease prevalence, studies with prospective data collection seemed utopia. Therefore, a retrospective database was the first step to answer multiple research questions.

After setting the basis for national multi-institutional data gathering, the actual process of data collection and storage, based on national consensus, was the next step. Since multiple research questions were formulated for different MEN1 manifestations, a database to store

Table 2 DMSG study population strategies.

Study step	Recommendation
Sample size and minimize selection bias	– Nationwide collaboration – Including comparable hospitals, e.g. tertiary referral centers – Multicenter research – Start (supra)national study group
Patient identification	– Consistent diagnosis according to guidelines – Standardized identification method in hospital diagnosis databases

Patient enrolment	– Formulate study goals that are of direct importance to patients
	– Patient advocacy group involvement from the start
	Recruitment of patients among members
	  ○ Prioritize research agenda/study questions
	  ○ Provide information among members/patients
	  ○ Familiarize medical research among members
	  ○ Yearly national and regional patient and specialist meetings
	– Disease biology
	  ○ Autosomal dominant disorder
	  ○ Families willing to help affected relatives
	  ■ Knowledge on morbidity and mortality
	– Informed consent

Patient participation	– Routine clinical care
	  ○ Trained and dedicated multidisciplinary treatment team
	  ○ One contact person for each institute
	  ○ Physician-patient relation
	  ○ Annual clinical consultation due to risk of tumor onset
	– In case of hospital change
	  – Nationwide collaboration
	  – Continue registry in new treatment center
	– International workshop on Multiple Endocrine Neoplasia (WorldMEN 2016, Utrecht, The Netherlands) including patient sessions
	– Patient advocacy group
	  ○ Promote annual clinical consultation
	  ○ Yearly national and regional patient and specialist meetings
	  ○ Distribute research findings among patients
	  ○ Formulate new patient oriented questions

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individual patient data was carefully designed according to the disease characteristics and the formulated research questions. Many research questions addressed the frequency and timing of screening, thus knowledge of the natural history was demanded. Longitudinal data provide insight in the natural disease course. Therefore, data were collected retrospectively every quarter from 1990 to 2016.

This longitudinal, retrospective design was further developed to a MEN1 disease-specific framework. MEN1 patients have a lifetime risk to develop multiple endocrine tumors in multiple organs, each with a different penetrance. Since, there is no clear age-related penetrance for every manifestation and manifestations can occur at any given age, lifelong screening for all MEN1 manifestations is required (7, 23). Consequently, the process of diagnosis, therapy and follow-up is an ongoing, repeated and simultaneous process for MEN1-related neoplasms.

Variable selection

In line with the disease's complexity, a wide range of variables needed to be included in the database. Annual consultations include clinical and biochemical screening by specialized endocrinologists. Hormonally active tumors secrete different hormones, depending on the tumor's origin. Therefore, biochemical screening ranges from 72-h fast tests for pancreatic insulinomas to serum calcium levels for primary hyperparathyroidism. Radiological screening differs both in frequency and modality for different manifestations (13). Extensive additional diagnostic procedures may be performed when patients are suspected of a manifestation. Therapeutic interventions range from medical treatment to surgical resections, guided by manifestation, patient characteristics and disease stage.

Based on these factors and the formulated research questions a dataset was developed for each specific MEN1 manifestation (pHPT, dp-NETs, pituitary tumors, NETs (of stomach, bronchus and thymus) and adrenal lesions) including biochemical, radiological, surgical and pathology data (Table 4). Besides, datasets for general data on patient characteristics, medication use and previous medical history were designed. Multiple versions of these datasets were discussed among the study group participants and thereafter the final, total dataset was agreed upon.

Ahead of the collection of biochemical data from multiple hospitals, the planning on 'how to' collect these variables is essential, since clinical laboratories often harbor different measurement methods, leading to different units of measurement and reference values. Therefore, involvement of clinical chemistry laboratories of all participating centers is important during the design of the database. In addition, to compare these values during data analysis, a useful strategy is to express the values as upper level of the normal of the reference value, which is widely used in medical research.

Data collection

Variations during the data collection process, also known as observer bias, are remarkably reduced by securing the data collection process, minimizing the number of data collectors and collecting only uninterpreted or 'raw' data to prevent interpretation before statistical analysis. For example, there was no variable 'primary hyperparathyroidism' but, to define this variable, the outcomes of serum calcium and parathyroid hormone levels were used, so data were collected without knowledge of the outcomes. In addition, outcomes had to be subsequently found in individual patients during data analysis, hereby including the repetitive identification of a tumor over time as the reference standard for the diagnosis of a tumor (24). A central protocol was developed, which described per variable how it should be collected, so data collectors would gain familiarity with the appropriate gathering of data and interobserver variations were reduced. In the database, constraints were implemented for the range of outcomes that could be collected, preventing mistakes in data collection because of typing errors. Although the data collection in multicenter studies is commonly performed by researchers from every institution, only one or two centrally appointed data collectors were operating at a time. This minimized differences in data collection and enabled the collectors to gain vast experience in this large dataset, reducing intraobserver variability. The ideal geography of the Netherlands and centralizing the DMSG from Utrecht, optimized this way of data collection. All uncertainties during data collection and data capture were discussed with one principal investigator, which minimized defaults in these areas. These uncertainties were stored and are assessable at the present and in the future for the data collectors and researchers. The importance of protocolized data collection is the gathering of complete data, structurally the same in every center and for every patient, irrespective of disease severity.

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Table 3 DMSG recommendations for data storage and data collection.

Study step	Recommendation

Data storage	– Web-based database
	  ○ Easily accessible from every hospital during data collection
	– Confidentiality
	  ○ Pseudo-anonymize patients
	  ○ E.g. convert dates to quarters (e.g. 1 Q 2010 for all dates from January 1st up to and including March 31st 2010)

Database design	– Urge for relatively quick answers
	  ○ Retrospective database design
	– Study group consensus on database design
	– Research questions on natural course of disease
	  ○ Longitudinal database design
	  ○ Quarterly collection of data
	– Develop a disease-specific framework
	– Epidemiological background: diagnostic, etiologic, prognostic and/or therapeutic aims
	– Longitudinal design
	  ○ Repetitive collection of the same variables

Variable selection	– General data and considerations
	  ○ General patient data or demographics
	  ○ Raw or primary data
	  ○ Complex diseases and multiple research questions: more variables demanded
	– Select disease-related variables
	  ○ Screening programs
	  ○ Different disease manifestations
	  ○ Biochemical, radiological, surgical and pathology data
	– Study group consensus on variables
	– Plan on how variables, such as laboratory values, should be collected in different hospitals
	– Plan on how the 'raw' data can potentially be analyzed

Data collection	– General steps
	  ○ Collect raw data
	  ○ Compulsory variables
	  ○ Implement constraints in the database
	  ○ Data capture control among data collectors
	  ○ One principal investigator
	  ■ Discuss uncertainties
	  ■ Document and store these decisions
	– Develop a central protocol to facilitate standardized data collection
	  ○ Data are consistently captured appropriately
	– Minimize number of data collectors at a time
	  ○ Data collectors will gain familiarity with the database
	  ○ Select data collectors with affinity for the project, e.g. PhD students using the data for their thesis
	  ○ Provide data collectors with enough time to collect data

Data storage

Nowadays, the use of an easily accessible electronic, web-based application facilitates the collection of data in multicenter studies. However, security issues regarding patient data are of utmost importance. Concerning confidentiality, patients were pseudo-anonymized upon inclusion in the database, where every patient received a unique identification code, which is available for future data collection at the participating hospital. Regarding the low disease prevalence, all dates were converted into a quarter of a year (e.g. 1 Q 2010 for all dates from January 1 up to and including March 31, 2010). In addition to the simplification of data collection, electronic registries offer the opportunity of direct data output for all involved researchers.

Missing data

Retrospective studies are vulnerable for missing data, which lead to bias if the missing data are related to the outcome or exposure of interest. By securing the data collection, the quarterly collection of data and the available data from annual consultations, missing data

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Table 4 Database variables for each MEN1 manifestation. *General data*: patient identification number, date of birth, gender, family identification number, date of death, cause of death. *MEN1 data*: date MEN1 diagnosis, basis MEN1 diagnosis, MEN1genetic analysis, MEN1 mutation.

	Biochemical[a]	Imaging[a]	Surgery[a]	Pathology[a]	Medication[a]
pHPT	Calcium (ionized/total) PTH Albumin 25-OH vitamin D	Conventional imaging: Neck ultrasound/CT/MRI (number of abnormalities) Functional imaging: Scintigraphy	Surgery Type of surgery Parathyroid autotransplant Thymectomy Complications	Number of parathyroids Histopathology	1,25 vitamin D Calcium suppletion Cinacalcet
NETs (pancreas, duodenum, stomach, lung, thymus)	Gastrin Glucose Insulin Pro-insulin C-peptide Glucagon Pancreas polypeptide GHRH VIP Serotonin in thrombocytes 24-h urinary 5-HIAA Chromogranin A NSE 72-h fasting test	Conventional: *Abdominal:* MRI/CT/gastroduodenoscopy/EUS (number, size and location of NETs, metastases) *Thoracic:* MRI/CT (number, size and location of NETs, metastases) Functional: Somatostatin receptor scintigraphy PET/CT (number, size and location of NETs, metastases)	Surgery Organ Type of surgery Lymph node dissection Metastasectomy Complications	Number of NETs per organ/part of organ Size of the largest NET Immunohistochemistry: • Gastrin • Insuline • Glucagon • Pancreas polypeptide • Chromogranin A • Synaptophysin • OtherMitosis per 10 HPF Ki-67 Lymph node metastases Other metastases R-status	PPI Insulin SU-derivatives Other oral antidiabetics Somatostatin analogs Chemotherapy
Pituitary	Prolactin IGF-1 TSH FT4 Cortisol (basal/midnight) ACTH LH FSH Testosterone SHBG Estradiol Dexamethason suppression test	Conventional imaging: MRI/CT (number, size and consistency of abnormalities)	Surgery Type of surgery Complications	Number of adenomas Size adenomas Type of adenoma (solitary/cystic) Immunohistochemistry: • Prolactin • GH • FSH • LH • TSH • ACTH • OtherProliferation R-status	Somatostatin analogs Pegivsomant Dopamine agonist Vasopressin analog Glucocorticoid Hormone replacement therapy Somatropin Testosterone Thyreomimetic agents Ketoconazol Metyrapon

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Adrenal	Dexamethason suppression test	Conventional imaging: MRI/CT (hyperplasia, number and size of adenomas, metastases)	Surgery Type of surgery	Number of adenomas/ carcinomas	Glucocorticoid
	24-h urinary (nor) metanephrines		Endoscopic resection	Size adenomas	Mineralcorticoid
	24-h urinary cortisol		Complications	R-status	DHEA
	Cortisol (basal, midnight)				Ketoconazol
	Plasma (nor) metanephrines				Metyrapon
	Plasma renin activity				
	Aldosterone				
	ACTH				
	DHEA				
	Androstenedione				

[a]These data are captured every quarter from 1990 to 2014.
24-h, 24-hours; 25-OH, 25-hydroxyvitamin; 5-HIAA, 5-hydroxyindoleacetic acid; ACTH, adrenocorticotropic hormone; CT, computed tomography; DHEA, dehydroepiandrosterone; EUS, endoscopic ultrasonography; FSH, follicle-stimulating hormone; FT4, free thyroxine; GH, growth hormone; GHRH, growth hormone releasing hormone; HPF, high power fields; IGF-1, insulin-like growth factor 1; LH, luteinizing hormone; MEN1, multiple endocrine neoplasia type 1; MRI, magnetic resonance imaging; NET, neuroendocrine tumor; NSE, neuron-specific enolase; PET/CT, positron emission tomography/computed tomography; pHPT, primary hyperparathyroidism; PIT, pituitary; PPI, proton-pump inhibitor; PTH, parathyroid hormone; R-status, resection margin status; SHBG, sex hormone-binding globulin; SU, sulphonylurea; TSH, thyroid stimulating hormone; VIP, vasoactive intestinal peptide.

were minimized. Nevertheless, prospective data collection will further reduce missing data.

Time aspects

Longitudinal studies covering a long time span, might encounter changes in care due to increased technology and medical knowledge. In case variations in care or measurement of determinants or outcomes lead to systematic differences between patients over time, detection bias exists. Considering the numerous manifestations and the longitudinal study design, detection bias is lurking for all MEN1 manifestations, since biochemical and radiological diagnostics have gained increased sensitivity and specificity over the years. With an increase in frequency and quality of screening, manifestations are detected in earlier disease stages. Stratifying patients into birth cohorts, to minimize the effects of detection bias, has been previously performed in a longitudinal study (23). Nevertheless, by including patients from 1990 onward, differences in diagnostic opportunities and therapies are reduced, compared to studies including patients over a longer time span.

The DMSG contributions to patient care

Up till now, publications from the retrospective database have already answered many of our research questions and clinical management has changed Table 5 (4, 6, 7, 14, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39). Moreover, the retrospective study design proved to be suitable, since a long latency between exposure and outcome exists. Most important findings from the DMSG research include the decreased life expectancy, the natural course of NETs (lung, thymus and pancreas) and pituitary adenomas, the effect of periodical screening and the surgical outcomes including complications of nonfunctioning pancreatic NETs (4, 14, 24, 26, 30, 33, 35). Another example from our database is the increased breast cancer risk for women with MEN1 compared to the general population (Risk Ratio of 2.8) (6).

Current state and future perspectives

Designing a prospective database

Prospective data collection will further reduce the number of missing data, increase the quality of data, enable the collection of baseline characteristics and unknown

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Table 5 DMSG contributions to clinical care.

Title	Study objectives	Outcomes/new insights
Multiple endocrine neoplasia type 1 (MEN1): its manifestations and effect of genetic screening on clinical outcome (7)	To determine the effect of genetic screening on outcome in multiple endocrine neoplasia type 1 (MEN1)	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
Primary hyperparathyroidism in MEN1 patients: a cohort study with long-term follow-up on preferred surgical procedure and the relation with genotype (25)	To identify the optimal surgical strategy for multiple endocrine neoplasia type 1 (MEN1)-related primary hyperparathyroidism (pHPT) To describe the course of postoperative hypoparathyroidism and to assess whether genotype is associated with persistent/recurrent pHPT	SPTX with bilateral transcervical thymectomy is the procedure of choice for MEN1-related pHPT. Genotype seems to affect the chance of recurrence. Postoperative hypoparathyroidism lasting 6 months or more should not be considered permanent in MEN1
Low accuracy of tumor markers for diagnosing pancreatic neuroendocrine tumors in multiple endocrine neoplasia type 1 patients (14)	To assess the diagnostic accuracy of chromogranin A (CgA), pancreatic polypeptide (PP), and glucagon for pNET in MEN1	The diagnostic accuracy of the tumor markers CgA, PP, and glucagon for pNET in MEN1 is low
Natural course and survival of neuroendocrine tumors of thymus and lung in MEN1 patients (26)	To assess prevalence, tumor growth, and survival of Thymus and lung NETs in an unselected MEN1 population with long-term follow-up	In MEN1 patients, Thymus NETs almost exclusively occurred in males and had a very low prevalence and a high mortality. Lung NETs occurred more often than previously thought, had an indolent course, and occurred equally in both sexes. Tumor growth in males was double compared with female patients
Breast cancer predisposition in multiple endocrine neoplasia type 1 (6)	To clarify the role of *MEN1* in human breast cancer To assess the incidence of breast cancer in the Dutch longitudinal MEN1 database	Female patients with MEN1 are at increased risk for breast cancer Our observations indicate that *MEN1* mutations are involved in human breast carcinogenesis Intensified breast cancer screening at a relatively young age should be considered in female patients with MEN1
Thyroid incidentalomas in patients with multiple endocrine neoplasia type 1 (28)	To assess the prevalence of thyroid incidentalomas in MEN1 patients compared with nonMEN1 patients To verify whether thyroid tumorigenesis is MEN1-related	MEN1 patients do not have a higher prevalence of thyroid incidentalomas compared with primary hyperparathyroidism patients without the diagnosis of MEN1. Menin was expressed in the thyroid tumors of MEN1 patients
No association of blood type O with neuroendocrine tumors in multiple endocrine neoplasia type 1 (29)	To assess the association between blood type O and the occurrence of neuroendocrine tumors in the national Dutch MEN1 cohort	An association between blood type O and the occurrence of neuroendocrine tumors in MEN1 patients was not confirmed. For this reason, the addition of the blood type to screening and surveillance practice seems not to be of additional value for identifying MEN1 patients at risk for the development of neuroendocrine tumors, metastatic disease, or a shortened survival
Long-term natural course of pituitary tumors in patients with MEN1: results from the DutchMEN1 Study Group (DMSG) (30)	To assess the results of systematic pre-symptomatic PIT screening and subsequent long-term follow-up of PITs with emphasis on nonfunctioning microadenomas diagnosed by screening	Systematic pre-symptomatic screening for PIT in patients with MEN1 predominantly results in detection of nonfunctioning microadenomas. Prolactinoma in patients with MEN1 responded well to medical treatment. Microadenomas grew only occasionally and after many years without clinical consequences. Frequent magnetic resonance imaging follow-up of nonfunctioning microadenomas in the context of MEN1 and sporadically occurring PITs therefore seems debatable
Impact of delay in diagnosis in outcomes in MEN1: results from the Dutch MEN1 Study Group (31)	To assess whether there is a lag time from MEN1 diagnosis of the index case to MEN1 diagnosis of family members To determine whether this lag time was associated with an increased morbidity and mortality risk	There is a clinically relevant delay in MEN1 diagnosis in families because of a lag time between the diagnosis of an index case and the rest of the family. More emphasis should be placed on the conduct of proper counseling and genetic testing in all eligible family members
Robot-assisted spleen preserving pancreatic surgery in MEN1 patients (32)	To describe robot-assisted and laparoscopic spleen-preserving pancreatic surgery in MEN1 patients, and to compare both techniques	Minimally invasive spleen-preserving surgery in MEN1 patients is safe and feasible. Patients who underwent robot-assisted surgery did not require conversion to open surgery

(*Continued*)

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Table 5 Continued.

Title	Study objectives	Outcomes/new insights
Early and late complications after surgery for MEN1-related nonfunctioning pancreatic neuroendocrine tumors (33)	To estimate short and long-term morbidity after pancreatic surgery for multiple endocrine neoplasia type 1 (MEN1)-related nonfunctioning pancreatic neuroendocrine tumors (NF-pNETs)	MEN1 NF-pNET surgery is associated with high rates of major short and long-term complications. Current findings should be taken into account in the shared decision-making process when MEN1 NF-pNET surgery is considered
MEN1 redefined, a clinical comparison of mutation-positive and mutation-negative patients (4)	To describe and compare the clinical course of MEN1 mutation-negative patients with two out of the three main MEN1 manifestations and mutation-positive patients during long-term follow-up	Mutation-positive and mutation-negative MEN1 patients have a different phenotype and clinical course. Mutation-negative patients develop MEN1 manifestations at higher age and have a life expectancy comparable with the general population. The apparent differences in clinical course suggest that MEN1 mutation-negative patients do not have true MEN1, but another MEN1-like syndrome or sporadic co-incidence of two neuro-endocrine tumors
Prognostic factors for survival of MEN1 patients with duodenopancreatic tumors metastatic to the liver: results from the DMSG (34)	To determine overall survival and prognostic factors for patients with liver metastases from DP-NETs	Despite the fairly indolent course of DP-NET liver metastases in MEN1 patients, half of the population was deceased after 10 years. Sex and tumor load at diagnosis of liver metastases are possible prognostic factors for worse survival
Management of MEN1 related nonfunctioning pancreatic NETs: a shifting paradigm: results from the DutchMEN1 Study Group (35)	To assess if surgery for multiple endocrine neoplasia type 1 (MEN1) related nonfunctioning pancreatic neuroendocrine tumors (NF-pNETs) is effective for improving overall survival and preventing liver metastasis	MEN1 patients with NF-pNETs <2 cm can be managed by watchful waiting, hereby avoiding major surgery without loss of oncological safety. The beneficial effect of a surgery in NF-pNETs 2 to 3 cm requires further research. In patients with NF-pNETs >3 cm, watchful waiting seems not advisable
MEN1-dependent breast cancer: indication for early screening? Results from the Dutch MEN1 Study Group (36)	To assess whether other risk factors are involved to identify MEN1 at greatest risk for early-onset elevated breast cancer	The increased breast cancer risk in MEN1 carriers was not related to other known breast cancer risk factors or familial cancer history, and therefore breast cancer surveillance from the age of 40 years for all women with MEN1 is justifiable
Prognostic value of WHO grade in pancreatic neuro-endocrine tumors in multiple endocrine neoplasia type 1: results from the DutchMEN1 Study Group (38)	To assess the prognostic value of WHO grade in MEN1-related pancreatic neuroendocrine tumors	High mitotic count is correlated with poor prognosis in MEN1 patients with large nonfunctioning pNETs
Long-term natural course of small nonfunctional pancreatic neuroendocrine tumors in MEN1-results from the Dutch MEN1 Study Group (24)	To assess long-term natural history of small NF-pNETs and its modifiers in the Dutch MEN1 population	The majority of small NF-pNETs are stable at long-term follow-up, irrespective of the underlying MEN1 genotype. A subgroup of tumors is slowly growing but cannot be identified on clinical grounds. In this subgroup, tumors with missense mutations exhibited faster growth. Additional events appear necessary for pNETs to progress. Future studies should be aimed at identifying these molecular driving events, which could be used as potential biomarkers
Expression of p27Kip1 and p18Ink4c in human multiple endocrine neoplasia type 1-related pancreatic neuroendocrine tumors (39)	To assess the role of role p27Kip1 and p18Ink4c in MEN1-related pancreatic neuroendocrine tumor development	These findings indicate that loss of p18Ink4c, but not p27Kip1, is a common event in the development of MEN1-related pNETs. Restoration of p18Ink4c function through CDK4/6 inhibitors could be a therapeutic option for MEN1-related pNETs
High fear of disease occurrence is associated with low quality of life in patients with multiple endocrine neoplasia type 1: results from the Dutch MEN1 Study Group (41)	To assess whether MEN1 leads to psychological distress because of fear of disease occurrence (FDO), and affects quality of life	The majority of patients with MEN1 have FDO for themselves and even more for their relatives. This psychological distress is associated with a lower health-related quality of life. Therefore, in the medical care for MEN1, emphasis should also be placed on FDO and quality of life
DNA methylation profiling in MEN1-related pancreatic neuroendocrine tumors reveals a potential epigenetic target for treatment (42)	To determine promoter methylation profiles in MEN1-related pNETs	Promoter hypermethylation is a frequent event in MEN1-related and sporadic pNETs. Targeting DNA methylation could be of therapeutic value in MEN1 patients with advanced pNETs

CgA, chromogranin A; DMSG, Dutch MEN Study Group; DP-NET, duodenopancreatic neuroendocrine tumor; FDO, fear of disease occurrence; MEN1, multiple endocrine neoplasia type 1; NET, neuroendocrine tumor; NF-pNETs, nonfunctioning pancreatic neuroendocrine tumor; pHPT, primary hyperparathyroidism; PIT, pituitary; pNET, pancreatic neuroendocrine tumor; PP, pancreatic polypeptide; SPTX, subtotal parathyroidectomy.

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Table 6 DMSG overview of study phases and recommendations.

Study phase	Recommendation
1. Formulating research questions	
Formulate research questions	Involvement of patient advocacy group
2. Patient inclusion	
a. Increase sample size	National multicenter collaboration and study group
b. Identify patients	• Diagnosis according to clinical practice guidelines • Standardized identification method in participating centers
c. Maximize patient enrolment	• Formulate patient relevant study aims • Involvement of patient advocacy group Recruitment of patients among members 1. Familiarize medical research among members
d. Maintain patient participation	• Continue registry entry in new treatment center • Optimize physician-patient relation in routine clinical care • Patient advocacy group Distribute research findings among patients 2. Yearly patient and specialist meetings
3. Data storage and data collection	
a. Data storage	• Web-based database • Maintain confidentiality in accordance with local legislation
b. Database design	• Consider study design • Consider epidemiologic type of research questions • Develop a disease-specific framework
c. Variable selection	• Raw data • Select disease-related variables • Reach consensus on data in study group • Plan how variables, such as laboratory values, should be collected in different hospitals
d. Data collection	• Develop a central protocol to facilitate standardized data collection • Minimize number of data collectors at a time
4. Designing a prospective database based on outcomes of the retrospective database	
a. User-friendliness b. Supranational collaboration c. Continuously update database	• Automatic data capture from hospital records • Add indicator variables of manifestations for cross-sectional identification of patients to plan supranational studies • Include new variables based on new research questions or advances in care
5. Biobanking	
a. National collaboration	• Establish central organization/collaboration between UMCs • Create centralized biobanking protocol including all phases: collection, pre-analysis, registration, processing and storage of the samples • Sites of tissue collection and storage E.g. in individual UMC biobanks
b. Decide on materials	• Choices on which patient materials to collect Blood, tissue, feces, urine and others • Plan on how to collect materials Routine patient care or in research setting
c. Link to clinical data	• Preferably implement link to clinical data

confounders. Therefore, the database is continued prospectively to enhance future MEN1 research based on the outcomes of the retrospective database. The design of the prospective database focuses on user-friendliness by using a new Web-based platform, which offers the opportunity to physicians to enter data during routine care and to automatically capture laboratory values from patient hospital records. Consequently, according to research findings, new research questions and advances in diagnostic and therapeutic regimen, several variables are added such as the breast cancer screening, bone density measurements, nuclear imaging and therapy and

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surgical techniques. In addition, some indicator variables are added for the manifestations, so cross-sectional prevalence estimates can easily be obtained, which are useful for planning supranational research projects and imaginably a global RCT in the future. In addition to clinical data collection, patient material is obtained and stored in the biobanks of all UMCs to enable future basal and translational research. Assembled MEN1 patient materials include blood (serum, EDTA and citrate plasma and DNA) and tissue (formalin-fixed paraffin-embedded and fresh frozen) of biopsies and resected specimen (40). Materials are preferably obtained during routine patient care.

The Parelsnoer Institute

This clinical database and biobank initiative is now part of the Parelsnoer Institute (PSI) (http://www.parelsnoer.org/page/en/Home), which is part of the Netherlands Federation of UMCs (40). Within the framework of PSI, individual UMC clinical biobanks store patient materials according to a standardized national biobanking protocol, covering all phases of biobanking: collection, pre-analysis, registration, processing and storage of the samples (40). These data are centrally stored and linked to the clinical patient data. Clinical data are either manually captured, however, automatic data capture options are available for certain variables, such as laboratory tests (40). The connection between clinical and biobank data offers the unique opportunity to study genetic and epigenetic factors driving hereditary NETs. Identification of these factors in familial tumors, could in the future be extrapolated to sporadic NETs to identify NETs with an unfavorable prognosis and offer specific new targets for therapeutic opportunities.

Conclusion

Guided by our MEN1 experiences, we propose a stepwise approach from clinical research questions to scientific answers (Table 6). This experience can guide others planning to start a database for rare diseases. Involvement of the patients themselves from the beginning leads to meaningful research questions guiding clinical care and, in addition, increases the participation rate, thereby minimizing selection bias. Thereafter, the protocolized and standardized process of data collection and data storage into a disease-specific database enables the collection of homogeneous data and reducing information bias. Ongoing prospective clinical data collection and the collection of biobank materials has commenced in 2016, which will further increase the quality of the data and enables clinical epidemiological and translational research in the near future. This will directly impact patient care and provide new insights into MEN1 in the future.

Declaration of interest
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Author contribution statement
D-J v B: Study design, drafting the manuscript and final approval of the manuscript. R S v L: Study design, drafting the manuscript and final approval of the manuscript. C R C P: Database design, critical revision and final approval of the manuscript. M R V: Study design, critical revision and final approval of the manuscript. G D V: Study design, database design, critical revision and final approval of the manuscript. All authors read and approved the final manuscript.

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