THEMATIC REVIEW

HEREDITARY ENDOCRINE TUMOURS: CURRENT STATE-OF-THE-ART AND RESEARCH OPPORTUNITIES

MEN1-related pancreatic NETs: identification of unmet clinical needs and future directives

C R C Pieterman[1,2,*], S M Sadowski[3,*], J E Maxwell[4], M H G Katz[4], K E Lines[5], C M Heaphy[6,†], A Tirosh[7], J E Blau[8], N D Perrier[1], M A Lewis[9,10], J P Metzcar[11,12], D M Halperin[13], R V Thakker[5] and **G D Valk[2]**

[1]Section of Surgical Endocrinology, Department of Surgical Oncology, University of Texas MD Anderson Cancer Center, Houston, Texas, USA
[2]Department of Endocrine Oncology, University Medical Center Utrecht, Utrecht, The Netherlands
[3]Endocrine Surgery, Surgical Oncology Program, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, USA
[4]Department of Surgical Oncology, University of Texas MD Anderson Cancer Center, Houston, Texas, USA
[5]Academic Endocrine Unit, Radcliffe Department of Medicine, OCDEM, University of Oxford, Oxford, UK
[6]Departments of Pathology and Oncology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA
[7]Neuroendocrine Tumors Service, Division of Endocrinology, Metabolism and Diabetes, The Chaim Sheba Medical Center, and Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel
[8]Metabolic Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland, USA
[9]Gastrointestinal Oncology, Intermountain Healthcare, Murray, Utah, USA
[10]American Multiple Endocrine Neoplasia Support (AMENSupport), Maryville, Tennessee, USA
[11]Association of Multiple Endocrine Neoplasia Disorders (AMEND), Bloomington, Indiana, USA
[12]Departments of Intelligent Systems Engineering and Informatics, Indiana University, Bloomington, Indiana, USA
[13]Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

Correspondence should be addressed to D M Halperin: dmhalperin@mdanderson.org

*(C R C Pieterman and S M Sadowski contributed equally to this work)
†(C M Heaphy is now at Department of Medicine, Boston University School of Medicine, Boston, Massachusetts, USA)

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Abstract

The PanNET Working Group of the 16th International Multiple Endocrine Neoplasia Workshop (MEN2019) convened in Houston, TX, USA, 27–29 March 2019 to discuss key unmet clinical needs related to PanNET in the context of MEN1, with a special focus on non-functioning (nf)-PanNETs. The participants represented a broad range of medical scientists as well as representatives from patient organizations, pharmaceutical industry and research societies. In a case-based approach, participants addressed early detection, surveillance, prognostic factors and management of localized and advanced disease. For each topic, after a review of current evidence, key unmet clinical needs and future research directives to make meaningful progress for MEN1 patients with nf-PanNETs were identified. International multi-institutional collaboration is needed for adequately sized studies and validation of findings in independent datasets. Collaboration between basic, translational and clinical scientists is paramount to establishing a translational science approach. In addition, bringing clinicians, scientists and patients together improves the prioritization of research goals, assures a patient-centered approach

Key Words

- MEN1
- multiple endocrine neoplasia type 1
- pancreatic neuroendocrine tumor
- conference proceeding
- unmet clinical needs
- research infrastructure
- management
- risk stratification
- surveillance
- management
- treatment

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and maximizes patient involvement. It was concluded that collaboration, research infrastructure, methodologic and reporting rigor are essential to any translational science effort. The highest priority for nf-PanNETs in MEN1 syndrome are (1) the development of a data and biospecimen collection architecture that is uniform across all MEN1 centers, (2) unified strategies for diagnosis and follow-up of incident and prevalent nf-PanNETs, (3) non-invasive detection of individual nf-PanNETs that have an increased risk of metastasis, (4) chemoprevention clinical trials driven by basic research studies and (5) therapeutic targets for advanced disease based on biologically plausible mechanisms.

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Introduction

Multiple endocrine neoplasia type 1 (MEN1), caused by pathogenic variants in the *MEN1* gene on chromosome 11q13, is a rare neuroendocrine tumor (NET) susceptibility syndrome with an approximate prevalence of 1 in 30,000 (Chandrasekharappa *et al.* 1997). By the age of 80 more than 80% of the patients will have developed a duodenopancreatic NET (de Laat *et al.* 2016) and multifocality is common. Non-functional pancreatic NETs (nf-PanNETs) are the most common type of PanNET in patients with MEN1, followed by gastrinoma, insulinoma and other rarer functional tumors. Metastatic duodenopancreatic NETs are the most frequent cause of disease-related death in patients with MEN1 (hazard ratio (HR) for death = 3.43 for nf-PanNETs; 95% CI 1.71–6.88) (Goudet *et al.* 2010). Early detection or prevention are ideal, as surgery is the only curative treatment, feasible only for localized NETs. Continued systematic duodenopancreatic NET screening and follow-up are warranted, especially since MEN1 patients frequently develop additional primaries in remnant duodenopancreatic tissue (Dralle *et al.* 2004, Thakker *et al.* 2012).

The PanNET Working Group of the 16th International Multiple Endocrine Neoplasia Workshop (MEN2019) convened in Houston, TX, USA, 27–29 March 2019 to discuss key unmet clinical needs related to PanNET in the context of MEN1, with a special focus on nf-PanNETs. The participants represented a broad range of medical scientists including basic, translational and clinical scientists from the fields of Endocrinology, Medical Oncology, Surgical Oncology, Surgical Endocrinology and Genetic Counseling. Representatives from the North American and UK MEN patient advocacy groups (AMENsupport, AMEND USA and UK) were present, as were representatives from the pharmaceutical industry and the Neuroendocrine Tumor Research Foundation (NETRF). In a case-based approach, participants addressed early detection, surveillance, prognostic factors and management of localized and advanced disease. For each topic, after a review of the current clinical understanding, the key unmet clinical needs and future research directives to make meaningful progress for MEN1 patients with nf-PanNETs were identified.

Clinical case

The patient is a 42-year-old female. She has recently been diagnosed with MEN1 by genetic screening through her 46-year-old brother, the index case. She has an unremarkable medical history. She denies any symptoms of hypoglycemia (insulinoma), acid reflux, diarrhea or peptic ulcer disease (gastrinoma) or newly developed diabetes and skin rash (glucagonoma), other functional PanNETs or mechanical symptoms. Her vital signs and general physical examination are unremarkable.

Diagnosis and follow-up of nf-PanNETs in patients with MEN1

Question 1: Do we need new blood-based biomarkers for the diagnosis of nf-PanNETs in MEN1 and how should we study this?

State of evidence

Current clinical practice guidelines, published in 2012, balanced expert opinion with scarce scientific evidence to provide the framework of care for MEN1 patients. The guidelines recommended that annual screening for nf-PanNET should include fasting glucagon, chromogranin A (CgA) and pancreatic polypeptide (PP) which would expand evidence regarding their diagnostic value (Thakker *et al.* 2012). A recent systematic review on the diagnosis of nf-PanNETs in MEN1, with strict definitions of research quality and risk of bias, has summarized evidence from multiple studies (van Treijen *et al.* 2018*b*). Most studies had significant risk of bias. Two studies with the highest quality of evidence and a low

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risk of bias showed low accuracy of the tumor markers (de Laat *et al.* 2013, Qiu *et al.* 2016), and annual use of CgA, PP and glucagon for the diagnosis of nf-PanNETs in MEN1 was not recommended (van Treijen *et al.* 2018*b*). Therefore, there are currently no available biomarkers to diagnose nf-PanNETs in MEN1.

Discussion

Studies evaluating the diagnostic value of biomarkers should include detailed assay description, since reliability can differ among assays (Rehfeld *et al.* 2011), and state the population in which reference values were derived. Outcome measures should include positive (PPV) and negative predictive values (NPV), which will be prevalence-dependent and therefore age-dependent in MEN1 patients. This is even more important considering the unknown age- and comorbidity-dependent changes (if any) in circulating CgA, PP and glucagon.

The preferred diagnostic blood-based biomarkers for PanNETs in MEN1 are markers with a very high NPV, which would enable withholding imaging if markers indicate low disease risk. Suggestions were made to utilize existing biomarkers differently, for example, to determine if time-dependent markers (trend or change) would be more informative than a single value *per se*, or by identifying new stimulation tests. In the search for new biomarker classes, liquid biopsies based on tumor-specific genomic, transcriptomic, proteomic or metabolomic changes were considered promising. The recently developed NETest (Wren Laboratories, Branford, CT, USA), a multi-transcript molecular signature for PCR-based blood analysis, has been reported to show promising results in the detection of sporadic neuroendocrine tumors (Modlin *et al.* 2013, 2014). A recent independent validation confirmed its outperformance of CgA and emphasized its potential as a marker for the presence of disease in the follow-up of patients. However, the specific use of the NETest as a screening tool was not recommended (van Treijen *et al.* 2018*a*). As patients with MEN1 often have multiple concomitant NETs of different origins, separate validations of the NETest, and indeed other novel biomarkers, in the MEN1 population are necessary before any recommendation on its use can be made.

Patients' perspective

The availability of blood-based biomarkers for diagnosis may improve adherence as regular blood draws are less stressful than (invasive) imaging procedures. In addition, frequent use of ionizing radiation and contrast-enhanced imaging may increase risk of secondary malignancies and renal function impairment. Furthermore, routine blood work may already be a part of the patient's life, more accessible in terms of travel, and less costly, all of which might facilitate more consistent monitoring as warranted by disease stage and quality of life (QoL). On the other hand, withholding imaging can increase anxiety unless markers are proven to be very reliable. Patient advocate involvement will be essential to optimize this delicate risk/benefit ratio.

Unmet clinical need

Blood-based biomarkers with a high NPV for the detection of nf-PanNET in patients with MEN1.

Future directives

Current evidence is insufficient to recommend any specific blood-based test for diagnosis of nf-PanNETs in MEN1. To meet unmet clinical needs, we suggest:

- Collaboration between clinical, translational and basic scientists in order to facilitate discovery of novel blood-based biomarkers with a focus on liquid biopsies based on tumor specific genomic, transcriptomic, proteomic or metabolomic changes.
- To investigate the utility of time-dependent markers for diagnostic purposes.
- To focus on NPV and PPV (in addition to sensitivity and specificity) of candidate diagnostic tests in well-described population-based cohorts.

Clinical case continued

Fasting laboratory tests were obtained. The calcium was 2.68 mmol/L (2.20–2.60), PTH 10 pmol/L (1.0–7.0), glucose 5.8 mmol/L (4.5–6.1), gastrin 90 ng/L (0–100), glucagon 24 pmol/L (15–50), prolactin 0.23 IU/L (0.10–0.52) and IGF1 19.6 nmol/L (11.5–33). Primary hyperparathyroidism was diagnosed. There was no evidence for a functional PanNET (insulinoma or gastrinoma), nor a functional pituitary adenoma (prolactinoma or acromegaly). MRI with pancreas protocol was undertaken to screen for nf-PanNETs.

Question 2: Do we need more studies on the most suitable imaging modality to diagnose nf-PanNETs and how should we study this?

State of evidence

Consensus for the optimal radiological screening has not been established in MEN1 and current screening protocols

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depend on local resources, clinical judgment and patient preferences (Thakker *et al.* 2012). Clinical guidelines suggest an imaging protocol for duodenopancreatic visualization with MRI, CT and/or endoscopic ultrasound (EUS) with an advised frequency of every 1–3 years in patients without identified PanNETs (Thakker *et al.* 2012). With regard to anatomical imaging, a recent systematic review on the diagnostic accuracy of different imaging modalities for MEN1-related nf-PanNETs concluded that, for the detection of nf-PanNETs, MRI is preferred. CT has reduced sensitivity and greater radiation exposure, while EUS is more invasive, operator-dependent and has marked heterogeneity in sensitivity throughout the pancreas (van Treijen *et al.* 2018*b*).

PanNETs express somatostatin receptors (SSTR) that can be targeted with radiolabeled somatostatin analogues (SSA) (Haug *et al.* 2009), which is the basis for functional imaging of these tumors. ^{68}Gallium-DOTA PET/CT (with tracers such as DOTA-TATE, DOTA-TOC or DOTA-NOC) has therefore emerged as a high-sensitivity diagnostic imaging tool for PanNETs. The aforementioned systematic review summarized the available evidence on the use of ^{68}Ga-DOTA PET/CT to diagnose nf-PanNETs in patients with MEN1. The primary identified strength of this modality was in detection of metastatic disease in patients with prevalent tumors >10 mm, rather than diagnosis of incident nf-PanNETs (van Treijen *et al.* 2018*b*). ^{18}FDG PET/CT has limited diagnostic use in well-differentiated NETs due to their low proliferative and metabolic activity (Sundin *et al.* 2004, Eriksson *et al.* 2005).

Discussion

Reports of diagnostic imaging studies should include detailed information on scanning protocols (use and timing of contrast and thinness of the slices) in order to evaluate imaging strategies properly. Outcomes in diagnostic imaging studies should include PPV and NPV and age-dependent test characteristics should be reported. One important challenge in this aspect is the lack of a non-pathology gold standard for the diagnosis of nf-PanNET. It is important to determine the optimal starting age for radiological screening in children. It was reported that metastatic PanNETs have been observed in young patients, therefore most participants advised screening of their pediatric population with imaging starting from the earliest reported case (Newey *et al.* 2009, Goudet *et al.* 2015). Currently, the guidelines advise starting radiological screening for nf-PanNET at the age of 10 years (Thakker *et al.* 2012). For a lifelong screening and surveillance program, it is important that safety issues are adequately addressed and included in the evaluation of new imaging modalities. These include, but are not limited to, the effects of ionizing radiation, risks of contrast-induced kidney injury with repeated iodine-based contrasts and the recent report of gadolinium deposits in the brain, of which the clinical effects are currently unknown (Gulani *et al.* 2017). To date, only one study has assessed the amount of ionizing radiation exposure due to radiological surveillance in MEN1 and reported a mean effective radiation dose of 121 mSv in a retrospective review of 43 patients with a mean 14 year duration of MEN1 (Casey *et al.* 2017). Based on epidemiological data, radiation scientists concluded that, for protracted exposure, 50–100 mSv are the lowest doses of x-ray or gamma radiation for which good evidence exists for increased risk of tumor formation (Brenner *et al.* 2003).

When determining which imaging modality is most suited for diagnosing nf-PanNETs in MEN1, not only do diagnostic accuracy, costs, access and safety play a role, but the clinical impact of the diagnosis must also be taken into consideration. The adverse impact on survival and prognosis of nf-PanNETs <2 cm is currently not well known. Observational studies have reported that metastases can be seen in MEN1-related nf-PanNETs <2 cm, which makes diagnosing these tumors pertinent. Data from the French Groupe d'étude des Tumeurs Endocrines (GTE) showed that 1/25 tumors of 0–10 mm and 6/10 tumors of 11–20 mm developed metastases (metastases included both lymph node and distant metastases) (Triponez *et al.* 2006*a*). In addition, after a median follow-up of 10 years, data from the GTE showed that 2/46 patients with nf-PanNETs <2 cm that were followed with watchful waiting developed distant metastases leading to death in one of these patients (Triponez *et al.* 2018). Data from the DutchMEN Study Group (DMSG) showed that 1/99 patients with nf-PanNETs <2 cm developed liver metastases (Pieterman *et al.* 2017). On the other hand, as the same observational studies show that the majority of these small nf-PanNETs have an indolent course, identification may only inflict anxiety and additional surveillance (Triponez *et al.* 2006*a*, Pieterman *et al.* 2017, Triponez *et al.* 2018). It was emphasized that, to answer these questions, multi-center collaboration will be required.

Patients' perspective

Selection of the appropriate imaging modality is multifactorial and must incorporate history of contrast reaction, traumatic EUS experiences or body habitus. This need for individual decision-making emphasizes the need

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for detailed information to enable individual patients and providers to discuss and identify an optimal personalized surveillance strategy. Additionally, judicious use of ionizing radiation and contrasts, balanced with possible (long-term) adverse effects and tracking exposures across studies, may lead to increase QoL, as patients know they are being cared for both in the short and long term. Prudent and well-coordinated ordering of diagnostic imaging may decrease financial burden, time off work and chance of follow-up fatigue.

Unmet clinical need

An evidence-based protocol for radiological screening to diagnose nf-PanNETs in patients with MEN1 which addresses optimal imaging modality and frequency, starting age, and evaluates the diagnostic accuracy based on clinical decisions as a direct consequence of imaging procedures.

Future directives

As a prerequisite for research in this area, we suggest:

- Forming collaborative research networks.
- Increasing the quality of reporting in imaging studies: studies should report the contrast used, the timing and thinness of slides used in conventional imaging, and report the protocols used for nuclear imaging, including if and when SSA was withheld.

Short-term research opportunities to address some aspects of the clinical needs are:

- Utilizing existing databases to retrospectively assess adverse effects of continued radiation or contrast agents.
- Utilizing existing databases to assess age-dependency of diagnostic accuracy of anatomical and functional imaging.
- Identifying the maximum safe interval to detect clinically relevant developments in patients with negative imaging studies to optimize screening protocols.

Clinical case continued

The patient underwent an MRI pancreas protocol and two small PanNETs were identified in the pancreatic head (6 mm and 8 mm in diameter) (Fig. 1). There was no evidence of a functional tumor.

Question 3: What is the optimal follow-up protocol for pancreatic NETs and how should we study this?

State of the evidence

Surveillance should be aimed at identifying worrisome features or determining necessity of intervention. Consensus for the optimal follow-up of prevalent nf-PanNETs, in terms of imaging modality and frequency, has not been established and protocols depend on local resources, clinical judgment and patient preferences. Current guidelines recommend at least annual imaging (Thakker *et al.* 2012). If a watchful waiting approach is chosen, evaluating the growth rate of small PanNETs could provide insight into optimal intervals for imaging. A recent systematic review reported that the course of small (<2 cm) nf-PanNETs is indolent with reported growth rates of 0.1–1.32 mm/year (van Treijen *et al.* 2018*b*).

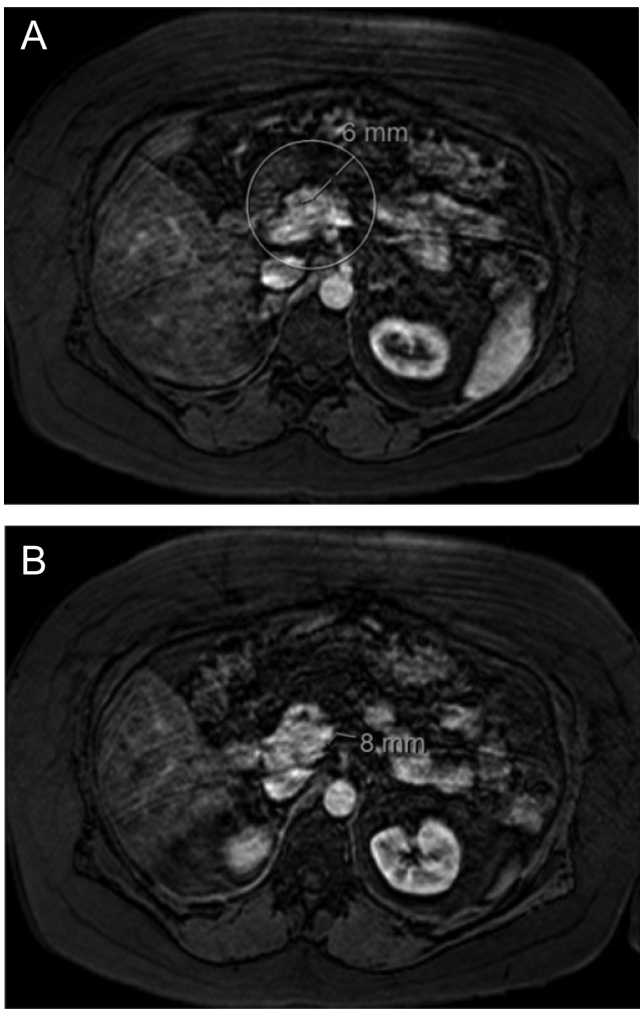

Figure 1
MRI with pancreas protocol at the time of diagnosis of the nf-PanNETs showing two PanNETs in the pancreatic head of (A) 6 and (B) 8 mm.

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Furthermore, small nf-PanNETs could be divided into groups with and without meaningful growth on subsequent follow-up. Given that tumor diameter correlates with metastatic risk (Triponez *et al.* 2006*a*), the review authors suggested using growth to individualize follow-up protocols, with surveillance extended to every 1–2 years after confirming stability, while growing tumors should be imaged at least every year (van Treijen *et al.* 2018*b*). With regard to imaging modality, the authors considered CT to be least appropriate, with rationale similar to the screening studies previously mentioned. ^{68}Ga-DOTA PET/CT was offered to potentially detect occult metastases in patients with tumors >10 mm but not as regular surveillance, in line with recommendations from other groups (Manoharan *et al.* 2017, van Treijen *et al.* 2018*b*). The exact role of the different modalities during follow-up remains to be delineated.

Discussion

Separating those tumors with and without meaningful growth was identified as a key objective, requiring a minimum of three time points. For stable tumors, there was consensus that the screening interval could be increased but the precise interval remains debatable. The role of SSTR PET/CT Imaging and PET/CT with other radionuclides remains controversial. It was agreed that SSTR PET/CT imaging to detect occult metastases and provide reference for future measurements is reasonable at some actionable point in the follow-up of nf-PanNETs.

It was felt that next to tumor diameter, other appropriate measurements (e.g. volume estimations or vascularity and perfusion characteristics by radiologists or standardized uptake values (SUV) by nuclear medicine specialists) should also be investigated to determine if these may be better predictors of clinical outcomes. To optimize follow-up schedules, further knowledge should be gained on features that characterize progressive nf-PanNETs.

Patients' perspective

Similar to screening, surveillance requires a risk/benefit balance including exposure to ionizing radiation and imaging contrasts, especially for young patients, though the balance may be distinct in established prevalent tumors. It is important to track exposures, both to guide monitoring for secondary impacts if necessary as well as to understand how those exposures might lead to secondary disease or decreased health. In addition, guidelines on screening and surveillance protocols can improve uniformity of care across disparate sites, which is a source of anxiety reported by the patient advocates in attendance. Reassurance that the entire family is receiving similar care could increase QoL.

Unmet clinical need

An evidence-based protocol for radiological follow-up of prevalent nf-PanNETs that can be tailored to individual tumor (diameter and growth) or patient (mutation type, gender and age) factors conveying increased risk of progression as well as general patient factors impacting on life expectancy is a priority requirement.

Future directives

To meet unmet clinical need, we suggest:

- Identifying the relation of nf-PanNET growth rate with distant metastases and survival, and how growth rate can be used to personalize follow-up.
- Identifying imaging features characteristic of progressive tumors.
- Clarifying the role of SSTR PET/CT imaging in follow-up of prevalent nf-PanNET.
- Including identification of novel biomarkers of progression in any future studies evaluating surveillance protocols which could, in the broadest sense, include clinical characteristics, genetics, blood-based markers or radiomics.

Clinical case continued

On follow-up imaging, there were three small PanNETs, one in the pancreatic head and two in the tail. The decision for continued surveillance was made. However, after 6 years of follow-up (annual MRI), a liver lesion was seen on MRI, while the pancreatic primaries remained small without increase in diameter. Subsequently, ^{68}Gallium- DOTATATE PET-CT revealed two liver metastases and one lymph node metastasis (Fig. 2). Due to the small size and location of the liver metastases, no histology was available.

Secondary prevention of nf-PanNETs in patients with MEN1

Question 4: Can new pancreatic NETs or growth and metastases of prevalent small pancreatic NETs be prevented?

State of evidence

Complete surgical resection remains the only curative therapy for localized nf-PanNET, and its appropriate

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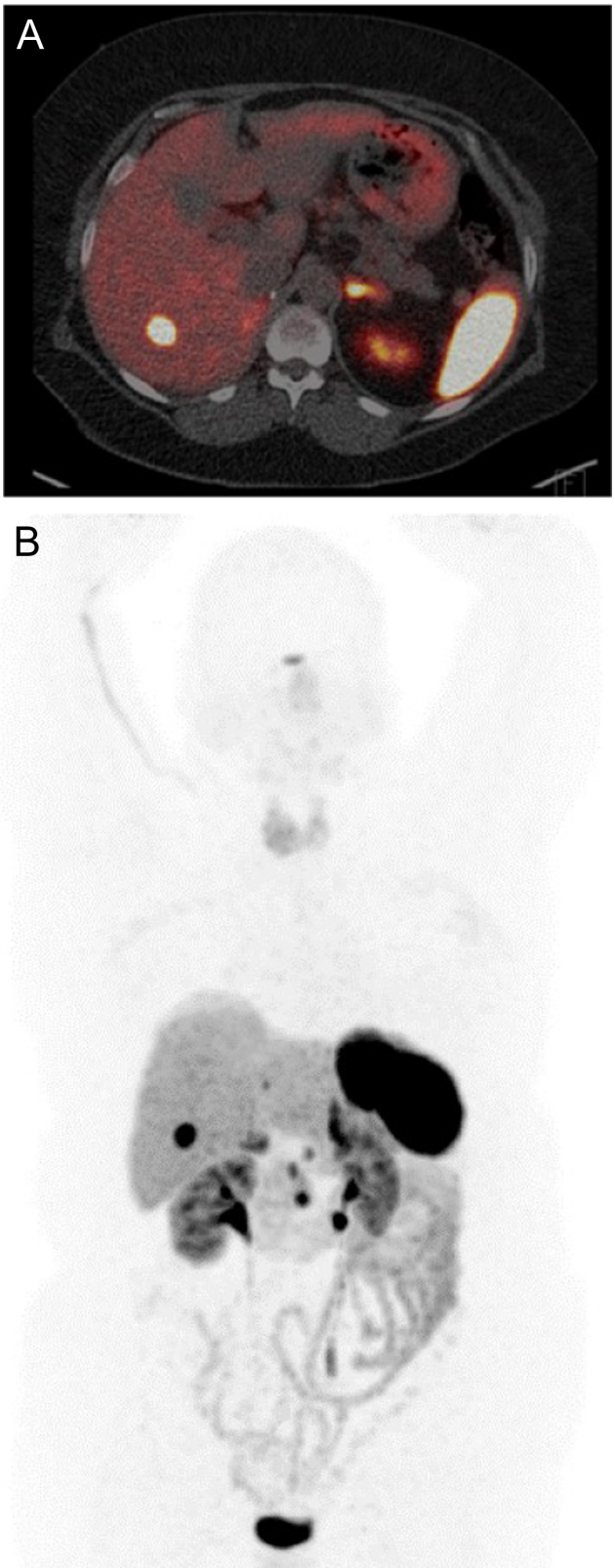

Figure 2
After 6 years of follow-up, MRI revealed a liver lesion, while the pancreatic primaries remained unchanged. Subsequent ^{68}Gallium DOTATATE PET-CT scan showed liver and lymph node metastasis (A) as well as the small pancreatic primaries (B).

implementation and timing needs to be considered. Pancreatic surgery is associated with significant short- and long-term morbidities with profound impact on QoL (Nell *et al.* 2018*a*). In addition, development of new tumors in remnant pancreatic tissue is likely. Therefore, risks and benefits of surgical intervention need to be carefully balanced. There is a higher risk of metastases in PanNET over 2–3 cm (Cadiot *et al.* 1999, Gibril *et al.* 2001, Triponez *et al.* 2006*a*, Ito *et al.* 2013, Conemans *et al.* 2017*b*, Vinault *et al.* 2018), and surgical resection of tumors smaller than 2 cm was not associated with survival benefit (Triponez *et al.* 2006*b*, 2017, Partelli *et al.* 2016, Nell *et al.* 2018*b*). Still, liver metastases from small, apparently stable nf-PanNETs can occur (Pieterman *et al.* 2017, Triponez *et al.* 2018). Extent of surgical resection is also debated, with a recent systematic review concluding that major pancreatic resections yield lower recurrence rates but more frequent postoperative endocrine insufficiency, while no difference was observed between reoperations and survival (Ratnayake *et al.* 2019). These findings need cautious interpretation as only 13/27 studies included the indications for surgery, thus confounding by indication cannot be excluded (Ratnayake *et al.* 2019). Additionally, several of the studies were heterogeneous and of low quality, as assessed by the authors' predefined criteria (Ratnayake *et al.* 2019).

Non-surgical ablative therapies are still investigational (Lee *et al.* 2013, ASGE Technology Committee *et al.* 2017, Oleinikov *et al.* 2019). Endoscopic ultrasound and percutaneous ethanol and radiofrequency ablation have been reported to be successful in sporadic insulinomas and nf-PanNETs in case-reports or small series with limited follow-up (Lakhtakia 2017, Oleinikov *et al.* 2019). These techniques were employed in patients who were not surgical candidates either because of contra-indications to surgery or patient preference. There is only one case reported in the literature where ethanol ablation was used in a patient with MEN1. In this 26-year-old woman with multiple PanNETs and biochemically proven insulinoma (positive 72 h fast), ethanol ablation of her multiple PanNETs resulted in resolution of the biochemical insulinoma for 12 months after the procedure (Lee *et al.* 2013).

Other interventions to prevent progression and development of metastases may be possible in the future and warrant study to pause progression of disease. Animal studies using lanreotide (Lopez *et al.* 2019) and pasireotide (Quinn *et al.* 2012, Walls *et al.* 2016) in mouse models of *Men1* PanNET have demonstrated their ability to decrease tumor proliferation. Recently a prospective observational

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study compared lanreotide vs active surveillance in patients with MEN1-related PanNETs <2 cm during a median follow-up of 6 years, demonstrating improved RECIST-defined progression free survival (PFS) in the lanreotide treated group (Faggiano *et al.* 2020). However, newly developed liver metastases occurred in one patient in either group. Limitations include sample size, non-randomized design and non-blinded outcome evaluation. In addition, improved RECIST PFS is not yet known to predict longer overall survival for MEN1 patients with localized PanNETs.

Discussion

Three key points emerged during the discussions for secondary prevention of nf-PanNETs. First, it should be recognized that distant metastases from small (<2 cm) nf-PanNETs may already be present at diagnosis, emphasizing the need for a sensitive baseline staging in appropriate patients. Second, mouse models for *Men1* PanNETs should be used in identifying promising strategies for secondary prevention, while remaining cognizant that the PanNETs in mouse models are in fact insulinomas and not nf-PanNETs. Third, given the results from animal experiments and data from human studies, further elucidation of the role of SSAs as chemopreventive agents in patients with MEN1-related nf-PanNETs is needed and a randomized clinical trial would be the logical next step, though endpoint selection is a critical challenge. Overall survival requires a very large sample size and follow-up length to have a sufficient event rate to detect statistically significant differences. Distant metastasis can be considered a surrogate endpoint, but has similar challenges. Therefore, validated surrogate endpoints for distant metastases and survival are urgently needed. Additionally, chemoprevention studies may necessitate a lower dose intensity of SSAs than symptom control or metastatic disease control, further complicating potential study design.

DNA hypermethylation has an important role in PanNET tumorigenesis and should be further studied to potentially identify novel therapeutic targets (Conemans *et al.* 2018, Tirosh *et al.* 2019). Additional inquiries included the exploration of possible immunotherapy-based interventions to prevent metastases or PanNET. It was concluded that we need to increase our knowledge on MEN1-related PanNET specific tumor biology at a molecular level and that, for this endeavor to succeed, prospective biobanking of highly clinically annotated MEN1-related duodenopancreatic NET tissue and blood will be vital.

Patients' perspective

Surgery is a difficult and current unfortunate necessity for most patients with MEN1, with notable impact on QoL. Prevention of growth and metastases without surgical intervention would be tremendous progress for patients, assuming that these therapies have an acceptable adverse event profile, acceptable costs and preservation of future surgical and other therapeutic options.

Employing SSAs early in the disease course may give rise to concerns about the future effectiveness of SSAs in treating subsequent advanced disease that may have developed resistance to SSAs. While clinicians note that this happened rarely in clinical practice, this key patient concern ought to be considered in future studies.

Unmet clinical need

- Validated surrogate endpoints for overall survival in MEN1-related nf-PanNETs that can be used as outcomes in studies evaluating early stage nf-PanNETs.
- Increased insight into molecular features of MEN1-related nf-PanNET development and progression to identify novel preventive strategies.
- Further elucidation of chemopreventive effects of SSAs in patients with MEN1-related nf-PanNETs.

Future directives

Prerequisites in order to facilitate multi-centered studies aimed at the secondary prevention of MEN1-related nf-PanNETs include:

- Establishing validated surrogate endpoints that can be used as outcomes in studies evaluating early stage nf-PanNETs.
- Setting up prospective biobanking at MEN1 centers worldwide, as this will enable basic and translational studies into MEN1-related tumor biology.
- Enhancing pre-clinical studies in mouse models and translating promising results into human clinical trials.
- Considering a double-blind randomized controlled chemoprevention trial with SSA in patients with small nf-PanNETs as soon as validated surrogate endpoints are available.

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Prognosis of nf-PanNETs in patients with MEN1

Question 5: Which marker or parameter is suitable for predicting the behavior of pancreatic NETs and how to predict which of the multiple tumors is the aggressive one (leading to regional and distant metastases)? How should we study this?

State of evidence

Not every patient with MEN1 and PanNETs will develop distant metastases. Similarly, the metastatic potential of various PanNETs is variable. Therefore, risk stratification is of utmost importance.

Clinical risk factors for development of distant metastases At present, the most important tumor-specific risk factor for the development of distant metastases is PanNET diameter (Cadiot *et al.* 1999, Triponez *et al.* 2006*a*, Ito *et al.* 2013, Conemans *et al.* 2017*b*, Vinault *et al.* 2018). This underlies current size-specific recommendations for surgery (Thakker *et al.* 2012). However, even small tumors have demonstrated capability of metastasizing, emphasizing the need for additional parameters for risk stratification (Triponez *et al.* 2006*a*, 2017, Pieterman *et al.* 2017). The current guidelines advise to consider both current tumor diameter and growth rate to determine when to proceed with surgical intervention (Thakker *et al.* 2012). Underlying biological factors associated with tumor growth are not well known. One study found missense mutations to be associated with faster growth of tumors that were already progressive, but it did not differentiate between stable and progressive tumors and was not externally validated (Pieterman *et al.* 2017). Data regarding whether baseline tumor size influences growth rate are conflicting, most likely caused by selection bias (D'Souza *et al.* 2014, Kappelle *et al.* 2017, Pieterman *et al.* 2017). Two small studies (Lastoria *et al.* 2016, Kornaczewski Jackson *et al.* 2017) suggest that tumor characteristics on nuclear medicine imaging, such as SUV_{max}, might have prognostic implications in MEN1, but prospective validation is still pending. Studies have identified associations between location of the *MEN1* mutations – such as exons 2, 9 and 10, the CHES1 interacting domain or the JUND-interacting domain – and aggressive duodenopancreatic disease (Bartsch *et al.* 2000, Thevenon *et al.* 2013, Bartsch *et al.* 2014, Christakis *et al.* 2018). However, these associations have either not been assessed in independent populations or could not be confirmed, thereby preventing their clinical implementation. An important reason for the lack of genotype-phenotype correlation may be found in the function of menin. Menin, through interaction with other proteins, is involved in the epigenetic regulation of gene transcription, in cell division, motility, adhesion and signaling, in cytoskeletal structure and DNA repair and in the maintenance of genomic stability, and does not have intrinsic enzymatic activity (Iyer & Agarwal 2018). Another interesting notion warranting further research is the possibility that germline mutations or polymorphisms in other genes might modify MEN1-phenotype, as recently was suggested for the V109G polymorphism in the *CDKN1B* gene (Circelli *et al.* 2015). It is interesting to note that one study observed higher estrogen exposure to be associated with smaller PanNETs (Qiu *et al.* 2017). Although this study had significant risk of bias, because only a small selected subgroup of the patients could be used in this analysis, this certainly is an area of interest, given that menin is known to interact with the estrogen receptor (Dreijerink *et al.* 2006).

Pathological and molecular risk factors for the development of distant metastases WHO grade and tumor diameter have shown to be risk factors for development of metastases in MEN1-related PanNETs (Conemans *et al.* 2017*a*) and are easily accessible and used in clinical practice. The prognostic significance of lymph node metastases is not well investigated in MEN1. Often, lymph nodes escape detection on anatomic imaging and are only identified at the time of surgical intervention. In addition, it is not clearly defined whether there are differences in the prognostic value of lymph node metastases from gastrinoma and/or nf-PanNET. It is difficult to distinguish the primary tumor of origin that is giving rise to a metastatic lymph node in patients with concomitant gastrinoma and nf-PanNET.

In sporadic PanNET, whole-exome and whole-genome sequencing studies have revealed mutually exclusive, inactivating somatic mutations in ATRX or DAXX in both primary and metastatic disease (Jiao *et al.* 2011, Scarpa *et al.* 2017). These mutations facilitate the development of the telomerase-independent alternative lengthening of telomeres (ALT) pathway (Cesare & Reddel 2010, Heaphy *et al.* 2011, Dilley *et al.* 2016). ALT-positivity has been identified as a risk factor for metastatic disease in sporadic primary PanNETs, and this association was recently also reported for MEN1-related PanNETs (Kim *et al.* 2017, Scarpa *et al.* 2017, Singhi *et al.* 2017, Cejas *et al.* 2019). Interestingly, ALT-positivity has also been associated

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with improved survival in metastatic PanNET (Jiao *et al.* 2011, Dogeas *et al.* 2014). Recently, tumor subsets among nf-PanNETs, resembling either pancreatic islet alpha or beta cells according to their transcriptomes and epigenomes, have been identified (Chan *et al.* 2018, Cejas *et al.* 2019). In one of those studies, among 103 surgical cases (stratified for MEN1-positive cases and sporadic cases), distant relapses occurred almost exclusively in patients with tumors positive for the transcription factor ARX (specifying alpha cells) and negative for PDX1 (specifying beta cells) (Cejas *et al.* 2019). Within this subtype, distant metastases were more frequent in ALT positive cases (Cejas *et al.* 2019). Before this can be translated into clinical practice, these data need additional prospective validation.

Discussion

Novel prognostic biomarkers for risk stratification are urgently needed in MEN1.

Validation in independent datasets of existing promising risk factors and development and exploration of prediction models with currently known prognostic factors were considered an important step. Additionally, exploration of clustering or other familial inherited factors as potential predictors of clinical aggressiveness was considered important, although a genotype-phenotype correlation has not yet been confirmed in MEN1. Thus, an important goal remains to identify novel prognostic biomarkers using blood-, urine-, imaging- and pathology-based approaches.

For pathology-based markers, further validation of the prognostic value of somatic mutations (e.g. *DAXX* and *ATRX*), ALT-positivity and ARX and PDX1 protein expression should be sought and their potential added value to current pathologic markers such as mitotic rate should be determined. Because DAXX, ATRX, ARX and PDX1 expression can be determined by immunohistochemistry, translation to clinical practice is easily facilitated as soon as prospective validation of their prognostic value in MEN1 is available. To identify additional pathology-based biomarkers for metastatic potential, biology-driven approaches are needed, including elucidating the mutational landscape of primary MEN1-related nf-PanNETs and paired metastases. It was considered important to also investigate stable tumors to identify factors associated with lack of progression, as this could potentially inform efforts to prevent progression in other tumors.

Additional considerations include evaluating a role for pathology-based molecular biomarkers before intervention (i.e. EUS-guided fine needle aspiration (FNA) or biopsy). Grading of nf-PanNETs by Ki-67 labeling index can be performed on cytology or biopsy specimens obtained by EUS, which can have prognostic implication and change management decisions. However, undergrading of cytology and biopsy specimen in sporadic PanNETs has been reported due to tumor heterogeneity in G2 and G3 tumors (Boutsen *et al.* 2018, Hwang *et al.* 2018). In addition, the required number of cells for a reliable count is not always available in these specimens (Boutsen *et al.* 2018). There are no data on the use of FNA-based grading in MEN1-related nf-PanNETs. Due to tumor multiplicity, sampling of all PanNETs would be required for optimal risk assessment. In addition, the vast majority of MEN1-related PanNETs are G1 (Conemans *et al.* 2017*a*). Moreover, FNA for diagnostic purposes is not a standard of care in MEN1, as imaging characteristics and pre-test probability of PanNET often establish the diagnosis. Therefore, when considering the use of EUS-guided biopsy, safety risks (such as pancreatitis) should also be addressed.

To establish imaging-based prognostic biomarkers, predictive markers of progression or aggressive behavior need to be defined, potentially including traditional imaging features such as vascularity, growth and tumor characteristics, use of specific tracers in functional imaging and newer methods such as radiomics.

Liquid biopsies are ideal for patients with MEN1, given their limited invasiveness and ability for repeated use over time. Currently no minimally invasive prognostic biomarkers for MEN1 and nf-PanNETs exist. Transcriptomic, proteomic, metabolomic and immune complex profiling of plasmas (or other bodily fluids) of patients with MEN1 may lead to identification of novel biomarkers.

To facilitate development of new relevant biomarkers, more information on nf-PanNET tumor biology in the context of germline vs somatic *MEN1* mutations are needed. To enable high-quality studies, research infrastructure has to be improved worldwide, with MEN1 centers establishing prospective biospecimen collection protocols, as well as aligning collaborative research endeavors across different centers. Complementary to prospective biospecimen collections, MEN1 centers around the globe should have high-quality prospective longitudinal research databases with a minimal common dataset to enable collaboration and quality control. It is

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critical that these serial collections of data and biospecimen begin at the presentation of disease. In addition, the availability of genetically engineered mouse models and cell lines should be leveraged as these have advantages of reducing heterogeneity. Findings from pre-clinical models could then be validated in human biospecimens.

Patients' perspective

Patients are willing to participate in research to advance medical knowledge in the field and are agreeable to additional tests and biospecimen collections. Involvement of patients in research will benefit the quality of the studies, while simultaneously increasing awareness and increasing participation. Databases of patient organizations may also help in identifying geographical regions for research studies. There is an interest from patients in understanding how genetic and epigenetic factors impact risk and how this knowledge can be harnessed for therapeutic purposes. Patients are keenly interested in identifying high-risk tumors, in the hopes of minimizing unnecessary interventions and preserving QoL.

Unmet clinical need

Novel biomarkers for risk stratification in patients with MEN1 and nf-PanNETs.

Future directives

To meet this unmet clinical need, we suggest:

- Collecting uniform and structured biospecimen and clinical data among MEN1 centers and international collaborations.
- Exploring the differences and similarities in the genetic, epigenetic and molecular landscapes between PanNETs with and without somatic and germline *MEN1* mutations.
- Validating and determining the use of those clinical, imaging, blood- and tissue-based markers that have already been identified, in prediction models.
- Identifying new prognostic biomarkers by exploring multi-omic profiling of bodily fluids, new imaging characteristics and radiomics and genetic, epigenetic and molecular characteristics of multiple tumors from the same patient, as well as paired primaries and liver metastases.
- Exploring the feasibility of a twin study with the aim of identifying genotype-phenotype correlations and/or additional (epi)genetic factors influencing the phenotype.

Treatment of advanced nf-PanNETs in the context of MEN1

Question 6: How should we treat metastasized nf-PanNETs in the context of MEN1 and how should we study this?

State of evidence

The available evidence on the treatment of metastatic PanNETs in the setting of MEN1 is extremely limited. The current MEN1 guidelines are reliant on treatments of sporadic advanced PanNETs (Thakker *et al.* 2012). The current National Comprehensive Cancer Network (NCCN), European Neuroendocrine Tumor Society (ENETS) and North American Neuroendocrine Tumors Society (NANETs) guidelines also do not provide separate recommendations for treatment of patients with MEN1-related advanced PanNETs (Kunz *et al.* 2013, Pavel *et al.* 2016, Shah *et al.* 2018). Moreover, a recent overview of treatment of advanced PanNETs in the setting of MEN1 emphasized that trials that evaluate treatments of PanNETs published after 2011 either excluded patients with MEN1 or did not provide information on MEN1 status (Frost *et al.* 2018). The CLARINET trial, demonstrating that lanreotide improved PFS among patients with metastatic enteropancreatic neuroendocrine tumors, excluded patients with MEN1 (Caplin *et al.* 2014). In the pivotal studies of everolimus and sunitinib, the number of patients with MEN1 was either minimal or unknown (Raymond *et al.* 2011, Yao *et al.* 2011).

The most recent approved therapy for patients with GEP-NETs has been peptide receptor radionuclide therapy (PRRT) using ^{177}Lu-DOTATATE. The registration for the NETTER-1 trial (Strosberg *et al.* 2017) was performed in patients with midgut NETs and therefore did not include patients with MEN1. Retrospective series have included patients with PanNETs, but did not report MEN1 status (Brabander *et al.* 2017). Studies that do report on treatment of MEN1-related advanced PanNET are small retrospective series with small sample sizes and heterogeneous treatment regimens over a long period of time, limiting the applicability of these studies. Given the lack of MEN1-specific outcome data, the current treatment for patients with MEN1 with advanced PanNET mirrors that of patients with sporadic PanNETs.

Discussion

In patients with MEN1, it can be challenging to determine the specific origin of the liver and/or lymph node metastases given the multiplicity of PanNET and the co-occurrence of other foregut NETs.

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A more aggressive approach that focused on a multimodality strategy for patients with metastatic disease was discussed. In this setting, resection of all visible disease is desirable, followed by treatment of microscopic or residual disease with new/experimental systemic treatment modalities.

The role of new and emerging anti-cancer therapies in MEN1-related metastatic PanNETs was discussed among the participants. The possible role for immunotherapy in the treatment of advanced MEN1-related PanNETs was considered, but more evidence on the immune landscape of MEN1-related PanNETs is needed in order to develop rational treatment approaches. Additionally, methods of identifying the presence of T-cells (e.g. by novel nuclear medicine tracers) would be beneficial, given the unique issues of intertumoral heterogeneity that are introduced in patients with multifocal disease. Participants highlighted the possibility of exploring novel SSTR2 directed therapy, therapies directed against epigenetic pathways, CAR-T cell therapy and identification of neo-antigens to permit vaccine development. Inclusion of MEN1 patients and reporting of mutational status should be included in advanced therapy trials as this would ideally permit subgroup analysis.

Patients' perspective

The majority of patients with MEN1 will develop PanNETs and approximately 15% will develop metastatic disease, making this topic a top priority. Management of metastatic PanNET is key to the QoL of MEN1 patients, and they are eager to participate in clinical trials. Inclusion criteria should therefore permit MEN1 patients, and knowledge of active clinical trials among MEN1 providers is critical. Social media and patient advocacy websites can play a role in this process.

Unmet clinical need

- MEN1-specific treatment outcomes in the setting of metastatic nf-PanNETs.
- Novel targeted treatments aimed at MEN1-related molecular pathways.

Future directives

As a first step to meet these clinical needs, we suggest:

- Increasing participation of patients with MEN1 in clinical trials.
- Reporting MEN1 specific results from clinical trials.
- Reporting subgroup analysis of patients with somatic *MEN1* status of sporadic PanNETs in clinical trials to further inform how molecular genetics may affect tumor functionality.

Discussion

This paper summarizes the outcomes and recommendations arising from the discussions of the PanNET Working Group of the 16th International Multiple Endocrine Neoplasia Workshop (MEN2019). It is not meant to discuss the entirety of equally important research needs for MEN1. Instead, the predefined focus was on nf-PanNETs. Recommendations aim to guide research efforts in these areas in order to make meaningful progress for MEN1 patients with nf-PanNETs.

Summary

Current evidence is insufficient to recommend any specific blood-based marker for diagnosis of nf-PanNETs in the context of MEN1. Given the lack of accurate blood-based biomarkers, imaging studies are the cornerstone of screening and surveillance for MEN1 related nf-PanNETs. While screening is aimed at identifying incident nf-PanNETs, surveillance should detect PanNETs with worrisome features that would impact surveillance or intervention.

The need for blood-based biomarkers with a high NPV for the diagnosis of nf-PanNETs in patients with MEN1 should be addressed by a biology-driven search for novel blood-based biomarkers focusing on liquid biopsies using genomic, transcriptomic, proteomic and metabolomic approaches, while investigating the utility of combined or time-dependent use of existing biomarkers. Short-term opportunities to address the need for evidence-based protocols for radiological diagnosis and surveillance include: (1) using existing databases to increase knowledge of safety issues of repeated exposure to contrast agents and ionizing radiation and identifying age-dependent performance characteristics of diagnostic imaging, (2) understanding how nf-PanNET growth rate is associated with distant metastases and survival, (3) determining if growth rate can personalize follow-up by identifying features characteristic of progressive tumors, (4) clarifying the role of SSTR PET/CT imaging in the follow-up of prevalent nf-PanNETs and (5) identifying novel biomarkers of progression in future studies designed to evaluate screening and surveillance protocols.

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Risk stratification is of paramount importance. Clinical characteristics alone, which currently comprises mainly tumor diameter, do not accurately predict behavior of all tumors. Additional parameters are based mainly on tumor sampling and presently only tumor grading based on mitotic count and Ki-67 labeling index are used in clinical practice. Sampling of nf-PanNETs in the context of MEN1 is dependent on lesion characteristics and local practice, so data always incorporate a selection bias. In addition, for a complete risk assessment, every tumor should be sampled, which increases procedural risks. Therefore, non-invasive technologies should be sought, such as imaging characteristics or circulating biomarkers.

Distant metastases are the most important determinant of overall survival. The goal of therapy is to prevent distant metastasis while minimizing treatment-related morbidity. Surgical resection of localized nf-PanNETs is curative but morbid and therefore should be pursued for patients with a supporting risk/benefit ratio. New techniques of intraoperative imaging technology to compliment minimally invasive surgical resection need to be continuously explored. Given the morbidity of surgical intervention and the likelihood of new primary nf-PanNETs in the pancreatic remnant, chemoprevention would delay and potentially prevent the need for invasive therapeutic management. In order to develop scientifically sound therapeutics, pre-clinical models are useful in order to target candidate mechanisms and approaches. Surrogate validated endpoints for localized nf-PanNETs in the context of MEN1, which currently do not exist, are a prerequisite for any chemoprevention trial and need to be established. An empiric SSA chemoprevention trial (after establishment of validated surrogate endpoints) can potentially address early pharmacological management of MEN1-associated NETs and nucleate the development of research infrastructure to support future studies based on parallel pre-clinical work.

To increase knowledge on MEN1-specific outcomes in advanced PanNETs, clinical trials should include patients with MEN1 and report germline and sporadic *MEN1* status of participants. This allows exploration of relationships between germline and sporadic *MEN1*-mutated PanNETs. In addition, novel mechanistic therapies based on specific molecular pathways of *MEN1*-mutated tumors should be sought. One such mechanistic avenue might be epigenetic pathway inhibitors (Lines *et al.* 2017).

Research infrastructure

To make meaningful progress in rare heterogeneous diseases like MEN1 and achieve research goals as outlined, collaboration is vital. International multi-institutional collaboration is needed for adequately sized studies and independent validation of findings. Collaboration between basic, translational and clinical scientists, as well as patient advocates, is paramount to establishing a translational science approach.

Validated clinical data are required for high-quality epidemiological research and to allow for accurate biospecimen annotation. Prospective, longitudinal database development is therefore a necessity at every MEN1 center. Multicenter collaboratives with experts in endocrine tumors will enhance the field. A minimal consensus dataset with associated definitions and meta-data should be developed. Uniform biospecimen collection is also a high priority. For patients undergoing PanNET surgery, tumor tissue and adjacent normal tissue should be collected (both flash frozen and formalin-fixed paraffin embedded (FFPE)) within the guidelines of a research protocol. To enable biomarker research, blood and urine samples should be collected and stored, ideally longitudinally instead of single time-point. Because pre-analytic variation can greatly affect outcome, as for data collection, a standard agreed protocol for biospecimen collection should be developed (Fisher *et al.* 2018). Web-based information dissemination structures should be in place to inform providers and scientists about ongoing or planned clinical trials and global availability of data and biospecimen for specific research questions. A cohesive research collaboration would allow for optimal design and sample size of clinical and translational studies and provide platforms for validation cohorts.

Conclusion

There is ample evidence that patients with rare diseases can derive significant benefit from focused, biologically driven interventions. Collaboration, research infrastructure, methodologic and reporting rigor are essential to any translational science effort. The highest priority for nf-PanNETs in MEN1 syndrome are (1) the development of a consolidated data and biospecimen collection architecture that is uniform across all MEN1 centers, (2) unified strategies for diagnosis and follow-up of incident and prevalent nf-PanNETs by delineating the

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appropriate type of imaging (anatomic and functional) and its starting age and scanning intervals, (3) non-invasive detection of individual nf-PanNETs that have an increased metastatic potential risk focusing discovery efforts for novel biomarkers on liquid biopsies and imaging characteristics, (4) chemoprevention clinical trials modeled on basic research studies with somatostatin analogues as a first promising candidate, and (5) therapeutic targets for advanced disease based on biologically plausible mechanisms, such as targeting epigenetic changes in MEN1-related nf-PanNETs.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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