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CONTROVERSY

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Controversies in NEN: An ENETS position statement on nutritional support in neuroendocrine neoplasms

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Abstract

Neuroendocrine neoplasms (NEN) themselves and also their treatment may cause malnutrition, inducing changes in physiological behaviour and eventually leading to increased rates of morbidity and mortality. Malnutrition is a common, under-recognised and under-treated condition in patients with NEN, and there are limited data available on the role of optimising nutrition in this setting. There are no formal evidence-based *European Neuroendocrine Tumor Society* (ENETS) guidelines on nutrition evaluation and management in patients with NEN to date. This manuscript was initiated during the 2024 ENETS Advisory Board meeting by using an expert panel consensus methodology and specific structured questions, which were identified and addressed through a structured review of the literature. The manuscript aims to identify the presence of specific nutrient deficits and define unmet needs and controversies regarding nutrition and NEN in a succinct manner, to promote collaborative and multidisciplinary research in the field, and to offer practical guidance in terms of how to assess malnutrition and dietary interventions by means of formulating a structured questionnaire.

KEYWORDS

diet, guidelines, neuroendocrine neoplasms, nutrition, vitamin

1 | INTRODUCTION: GENERAL BACKGROUND

The *World Health Organization* (WHO) defines malnutrition as the condition associated with deficiencies or excesses in nutrient intake, imbalance of essential nutrients, or impaired nutrient utilisation by not achieving enough calories or the correct amount of key nutrients, such as vitamins and minerals, that are needed for health.[1] Malnutrition can mean undernutrition in the case of a lack of nutrients in the diet or when the body cannot absorb nutrients from food. Conversely,

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overnutrition refers to excessive intake of energy and/or nutrients, leading to overweight, obesity, and diet-related non-communicable diseases. Furthermore, neuroendocrine neoplasms (NEN) as well as their treatment may cause malnutrition, inducing changes in physiological function (including loss of fat, muscle, and visceral mass, reduced basal metabolic rate, reduced total energy expenditure), eventually leading to increased rates of morbidity and mortality. Another related terminology used in the setting of malnutrition is *sarcopenia*, defined as a condition characterised by excess muscle wasting and muscle strength loss due to disrupted muscle homeostasis. Sarcopenia is also one of the most common adverse effects of cancer and its treatment, and can have a significant impact on patient-related quality of life.[2]

The reported prevalence of malnutrition among patients with NEN varies significantly across studies, primarily due to the use of diverse assessment tools and varying definitions, highlighting the need for standardised evaluation methods. Malnutrition is a common, under-recognised and under-treated condition in patients with NEN, and there are limited data available on the role of optimising nutrition in this setting. In other cancers, such as pancreatic adenocarcinoma and lung cancer, there is evidence that malnutrition is associated with worse outcomes.[3] However, our knowledge regarding the role of nutrition in outcomes and survival specifically for patients with NEN is strikingly limited.

Currently, the *European Neuroendocrine Tumor Society* (ENETS) has not established formal guidelines for the nutritional assessment and management of patients with NEN, underscoring a significant gap in standardised care protocols. The existing literature includes mainly recommendations in terms of foods to avoid in specific circumstances, such as the carcinoid syndrome. Some of the most frequent questions from patients in routine clinical practice are regarding dietary advice. Therefore, this manuscript endeavours to identify and define the current unmet needs and controversies regarding nutrition and NEN in a succinct manner, to promote collaborative and multidisciplinary research in the field, and to offer practical guidance in terms of how to assess malnutrition and the dietary interventions that can be undertaken by using structured questions, as detailed below (Data S2).

2 | SPECIFIC QUESTIONS ON NUTRITIONAL SUPPORT IN NEN

2.1 | Question 1. What is the prevalence of malnutrition in NEN?

Nutrition, a fundamental pillar of overall health, significantly affects the development and progression of many diseases, including cancers. Although the influence of dietary patterns and nutrient intake on cancer risk and prognosis is well documented, the specific effects on NEN require further exploration.[4] In the limited research performed so far, malnutrition in patients with NEN often leads to a worse functional status, increased treatment-related complications, and a decline in overall prognosis (Table 1).

In concordance with other patients with cancer,[5] Maasberg et al.[6] observed that around 21%–25% of patients with NEN were at risk of malnutrition. Malnutrition in this cohort was associated with longer hospital stays, decreased survival, and an adverse impact on healthcare costs with significant increase in the economic burden attributable to hospital malnutrition, especially in those with neuroendocrine carcinomas (NEC). Similarly, Barrea et al.[7] linked poor nutritional status to tumour aggressiveness and found better outcomes (e.g., lower proliferative rate tumours) in patients with well-differentiated gastro-enteropancreatic (GEP-)NEN adhering to a Mediterranean diet. Borre et al.[8] reported that 38% of NEN outpatients were at nutritional risk, although only 12% had a low body mass index (BMI) (<20.5 kg/m^2; normal BMI range 18.5–22.9 kg/m^2). Furthermore, over 40% of these patients experienced significant weight loss and changes in performance status, with 25% showing low handgrip strength (HGS).

Whyand et al.[9] noted that most patients with NEN had a normal BMI at their first clinic visit. However, 39% of patients reported weight loss prior to diagnosis, with more than half showing reduced muscle function measured by HGS. Qureshi et al.[10] highlighted that 14% of patients with GEP-NEN had a Malnutrition Universal Screening Tool (MUST) score of >1, indicating a significant positive link between malnutrition risk and treatment with long-acting somatostatin analogues (SSA).

Furthermore, the study by Clement et al.[11] revealed a high prevalence of sarcopenia in 61% of patients with newly diagnosed GEP-NEN. Sarcopenia did not significantly influence the risk of surgical complications, indicating that while sarcopenia is common, it does not necessarily affect surgical outcomes in these patients.

Finally, sarcopenia was found in up to two-thirds of cases in a recent small series of 30 patients with NEN at the time of initial diagnosis, before starting treatment with SSA.[12]

Based on these figures, it is evident that the prevalence of malnutrition and sarcopenia in patients with NEN is significant, affecting 38% to 61% of patients, underscoring the critical need for integrated nutritional support to enhance clinical outcomes.

Key points:

TABLE 1 List of specific questions on nutritional support in NEN used in the manuscript.

Question number	Question topic
Question 1.	What is the prevalence of malnutrition in NEN?
Question 2.	What are the main reasons for under-nutrition?
Question 3.	Are there specific micronutrient deficiencies in NEN?
Question 4.	Which and when nutrition assessment is required in NEN?
Question 5.	How do we personalize nutrition in NEN patients?
Question 6.	How do we address obesity in NEN?
Question 7.	How to promote research in Nutrition in NEN?

- Malnutrition is a common, under-recognised and poorly addressed condition in patients with NEN. Variation in incidence, in part, can be related to the tools used to screen/assess for malnutrition.
- As result of malnutrition, wide-ranging physiological adjustments usually occur in patients with NEN with poorer metabolic parameters, leading to worse NEN-related outcomes and increased rates of morbidity and mortality.
- An awareness of the possible insidious development of malnutrition must be increased and promoted by NEN specialized centers and related primary-care medical teams.
- Healthcare expenditures are significantly increased in malnourished patients with a NEN diagnosis.

2.2 | Question 2. What are the main reasons for under-nutrition?

The aetiology of malnutrition in patients with NEN is multifactorial. There are several scenarios in which malnutrition can occur, depending on tumour biology, rate of progression and spread, secretory status, and on the impact of treatments, including past surgical interventions.

Firstly, it is crucial to distinguish between subsets of NEN, such as neuroendocrine tumours (NET) and NEC. NET represent approximately 90% of cases, with slow proliferation rates and prolonged survival, but with the frequent development of liver metastases and hormonal secretory syndromes.[13] NET can lead to significant nutritional deficiencies due to metabolic disorders associated with hormonal hypersecretion and the impact of tumour burden. NEC, on the other hand, are more aggressive, with a rapid disease course, and often cause a hypermetabolic state that leads to cachexia. In a study of 203 patients with NEN, high-grade (G3) neoplasms as well as progressive disease and the use of chemotherapy were independent predictors of malnutrition.[14] The stage of the disease additionally influences nutritional status, as advanced NEN are associated with a more significant tumour load, metastases, and complications such as intestinal obstruction and liver dysfunction, all of which exacerbate malnutrition.

Malnutrition can be associated with local tumour mass-related effects. For example, in the case of pancreatic NEN, the presence of the tumour itself may impact pancreatic exocrine secretion due to compression of the pancreatic duct, causing pancreatic atrophy and hence steatorrhoea, with the subsequent development of malnutrition. This is commonly seen in pancreatic NEN affecting the head or neck of the pancreas or compressing the pancreatic duct. In the case of small bowel NEN, the primary tumour, and particularly its mesenteric metastases, may induce a desmoplastic reaction with fibrosis and mesenteric ischaemia leading to abdominal pain post meals, reduced nutrient absorption, and associated weight loss. Primary tumours and mesenteric ischaemia can also induce episodes of subacute bowel obstruction, which in turn lead to weight loss and in rare cases obviate the need for enteral or parenteral feeding. Peritoneal carcinomatosis of NEN metastases can also interfere with normal bowel function and be associated with malnutrition.

A variety of NEN-associated hormonal hypersecretion syndromes such as carcinoid syndrome, Zollinger-Ellison syndrome, watery diarrhoea syndrome related to VIPoma, and the syndrome associated to somatostatinoma may lead to malnutrition due to secretory diarrhoea with severe dehydration and an impact on appetite and nutrient absorption. Glucagonoma is particularly associated with cachexia and weight loss due to the occurrence of severe hypo-aminoacidaemia, glossitis and stomatitis.[15] Conversely, insulinomas may lead to weight gain due to the increase in carbohydrate intake to prevent or oppose hypoglycaemia-related symptoms, as well as the anabolic effect of insulin.

Hormonally inactive tumours can still contribute to malnutrition because of tumour mass effects and generalised symptoms of malignancy.[16] A link between inflammation and neuroendocrine carcinogenesis has also been suggested. NEN development and its response to therapy can induce an inflammatory process, which either promotes or suppresses tumour progression, potentially displaying opposing effects on therapeutic outcomes and the patient's nutritional status. Moreover, alteration of the gut microbiota has been shown for small intestinal NET and can also contribute to carcinogenesis and malnutrition.[14]

Treatment-related side effects can lead to weight loss. This is commonly seen with SSA, which can induce pancreatic exocrine insufficiency in approximately 20% of patients. This is secondary to SSAs' capacity to markedly reduce the secretion of pancreatic enzymes and curb the release of hormones such as secretin, cholecystokinin, and motilin.[17,18] SSA has also been found to reduce fasting plasma insulin, though the impact on glycaemic control and the development of diabetes is variable.[19,20]

Other systemic therapies such as everolimus and chemotherapy can lead to stomatitis, nausea, vomiting and reduced appetite, all of which can contribute to weight loss. Peptide receptor radionuclide therapy (PRRT), an effective treatment for NEN, can also cause nausea and vomiting in the weeks following each cycle, leading to a transient reduction in food intake and subsequent weight loss. Fatigue following PRRT can also impact on the ability to prepare and access food. Finally, surgical procedures such as pancreatic or extensive small bowel resections can lead to long-term complications including exocrine pancreatic insufficiency, "short-bowel syndrome" and/or bacterial overgrowth, with malabsorption and malnutrition. Bile-acid malabsorption is frequently encountered in patients with NEN, particularly after right-sided hemicolectomy and cholecystectomy.[21]

The patient's individual background also plays a significant role in the development and severity of malnutrition.[16] Age is a key factor, as older patients are more susceptible to the toxic effects of treatment, which increases the risk of malnutrition. Comorbidities, such as diabetes mellitus, gastrointestinal disorders, or previous surgery, can further complicate nutritional management. Socio-economic conditions are also important, as patients with limited access to healthcare resources, dietary support, social networks, and financial stability may find it challenging to maintain a proper diet throughout treatment.

Commonly, patients with NEN may be affected by more than one of these different aetiologies of weight loss, and hence a multi-

modality approach to malnutrition is required and awareness of the insidious development of malnutrition must be highlighted.

Key points:

- The reasons for NEN-related malnutrition are multi-factorial, including tumour related (functional vs. non-functional; NET vs. NEC; local vs. advanced/metastatic), treatment related (surgery; SSA; PRRT; biological (mTORi, TKI); loco-regional; chemotherapy) and individual patient characteristics related (age, sex, health background, socio-economic state), all of them resulting in reduced dietary intake, malabsorption, increased nutrient losses, and/or altered metabolic demands.
- Long-term complications such as exocrine pancreatic insufficiency, "short-bowel syndrome" and/or bacterial overgrowth, and bile-acid malabsorption, are frequently encountered in patients with NEN after surgical procedures and should be promptly recognized and addressed.
- A multi-disciplinary specialised approach is required for patients with NEN with under-nutrition.

2.3 | Question 3. Are there specific micronutrient deficiencies in NEN?

Micronutrient deficiencies (including vitamins) represent an important challenge in the treatment of patients with GEP-NEN.

2.3.1 | Water-soluble vitamins

Niacin (vitamin B3)

The biosynthesis of serotonin from tryptophan interferes with that of niacin. Tryptophan is the precursor for both serotonin and niacin, and under normal conditions, only a small fraction of tryptophan (about 1%) is used for serotonin biosynthesis, whereas a larger fraction of tryptophan is converted to niacin.[22] In the case of excessive serotonin synthesis that is characteristic of carcinoid syndrome (CS), both tryptophan and niacin deficiency might develop.[23,24] Severe niacin deficiency can lead to pellagra that is characterized by the 4D-s (dermatitis, dementia, diarrhoea and death)[25] and is otherwise very rare in the developed world nowadays. Niacin deficiency can complicate the clinical picture of CS by skin changes (scaly skin), glossitis, and aggravating the already present diarrhoea. Moreover, psychiatric changes, such as problems with speech and violent behaviour, can also develop in severe cases.[26] Pellagra is usually only diagnosed in advanced-stage CS, and patients often die shortly after diagnosis.[27]

NAD+ and NADP+ as biologically active forms can be used to assess niacin status,[23] but 24 h urinary N1-methylnicotinamide measurement appears to be more reliable.[24] Plasma tryptophan levels are not accurate markers of niacin status.[24] There are few studies assessing niacin deficiency in patients with NET, and there are no prospective studies available. The prevalence of biochemical or "subclinical" niacin deficiency could be as high as 30%–45%,[23,24] whereas pellagra is rare. The addition of N1-methylnicotinamide to the regular measurements of urinary or blood 5-hydroxyindolacetic acid (5-HIAA), a marker of carcinoid syndrome, might be warranted.[24]

The dose for niacin supplementation is an issue of controversy. The proposed daily dose for healthy adult individuals is 14–16 mg niacin equivalent (NE, 1 NE corresponds to 1 mg niacin or 60 mg tryptophan).[28] For patients with CS, it has been proposed to administer at least 40 mg daily niacin or nicotinamide,[16] but the average dose applied in Bouma's study was 144 mg/day (though doses ranged between 5 and 300 mg daily).[24] A daily dose of 200–250 mg (alone or as a component of "vitamin B complex" tablet) is recommended to patients with confirmed niacin deficiency and/or pellagra.[29] A vitamin B complex maybe used to supplement niacin, and this may be easier to obtain, also noting that conversion of tryptophan to niacin requires sufficient riboflavin and pyridoxine. Niacin in the form of nicotinamide is preferrable over nicotinic acid (which can cause skin flushing). Prospective trials would be warranted to confirm the ideal supplementation method and dose in patients with NET.

Vitamin B12

Hypochlorhydria induced by corpus chronic autoimmune atrophic gastritis is well known to be associated with B12 deficiency and type 1 gastric NET.[30] Vitamin B12 deficiency has been described also as a consequence of long-term treatment of gastrinoma-associated Zollinger-Ellison syndrome[31] and might be related to SSA-induced exocrine pancreatic insufficiency.[32]

Vitamin B12 levels were subnormal in about half of patients with disseminated small intestinal NET.[33] Gastric and ileal resection interferes with B12 vitamin absorption, and it is therefore suggested to supplement affected patients with deficiencies.[34] It has to be mentioned, however, that the topic of vitamin B12 supplementation in patients with cancer is controversial. There are even reports of an increased cancer prevalence in individuals with vitamin B12 supplementation, for example, in colorectal cancer.[35] Total serum cobalamin is a less accurate measure of B12 status than active B12 (serum holotranscobalamin). Oral B12 supplements may increase total B12 levels without treating deficiency, while the combined oral contraceptive pill can lower B12 levels without causing deficiency, so some interpretation of readings is needed when testing.[36]

In patients with NEN at risk of vitamin B12 deficiency, such as patients having chronic autoimmune atrophic gastritis, chronic SSA use, or stomach or ileal resection, serum vitamin B12 levels should be measured. Only patients with subnormal values should be supplemented, especially if megaloblastic anemia is also present.

Fat-soluble vitamins

Deficiency in fat-soluble vitamins in patients with NEN can develop due to diarrhoea and steatorrhoea (caused by SSA or disease or surgery of the pancreas), but surgical interventions to the bowel are also an important factor.[16]

Vitamin D

Vitamin D deficiency is frequent in patients with GEP-NEN, with rates reported in 46% to 81% of patients.[33,37–41] A study including 138 patients with GEP-NEN showed a high prevalence of vitamin D deficiency (68%) and found a correlation between low vitamin D levels and poor overall survival (OS) and progression-free survival (PFS). Vitamin D supplementation in these patients was found to improve OS.[40] Another study reported that vitamin D deficiency is frequent among patients with NEN and is associated with a higher Ki-67 proliferation index and disease progression.[41]

Over-the-counter vitamin D supplementation increases vitamin D levels in most patients with GEP-NEN. Robbins et al.[37] reported a reduction in the prevalence of vitamin D deficiency in patients after 1 year of supplementation. Another study demonstrated that only 28% of patients receiving oral vitamin D therapy had vitamin D deficiency, in contrast to 46% of patients not receiving supplementation. Moreover, vitamin D administration seems to improve bone mineral density in patients with small intestinal NEN.[33]

These studies highlight the necessity of routine vitamin D level assessments (25-OH-vitamin D levels) in patients with NEN, and indicate that vitamin D supplementation strategies may be essential in reducing the negative consequences of this deficiency.

Vitamin A, E, and K

Long-term treatment with SSA was reported to result in deficiencies of vitamins A, E, and K in 9%, 14%, and 69% of both NET and acromegaly treated patients.[38] In a feasibility trial including 15 patients with NET treated with SSA for at least 6 months, 9 had deficiencies in fat-soluble vitamins.[42]

Trace elements

There is limited information on trace element deficiencies in patients with NEN. One study assessed the selenium levels in patients with NENs undergoing (PPRT). Patients showed an important reduction in selenium levels 4 weeks after PRRT.[43]

Key points:

- There are specific micronutrient deficiencies in patients with NEN.
- Deficiencies for water- and fat-soluble vitamins and some trace elements should be considered in patients with NEN. Specifically, in patients after bowel resections and/or under chronic treatment with SSA, vitamin B12 and vitamin D should be evaluated and supplemented (if low), at baseline and routinely throughout follow-up visits by the NEN specialist/nurse and the NEN-dedicated nutritionist. Levels of other fat-soluble vitamins, like vitamin A, E, and K, should be measured when patients experience symptoms compatible with deficiencies.
- Niacin (vitamin B3) evaluation (when available) and supplementation should be considered in patients with CS, but the optimal dose needs to be defined.

2.4 | Question 4. Which and when nutrition assessment is required in NEN patients?

The diagnostic process for malnutrition involves two critical steps: screening and assessment.

Several tools (Table 2) have been developed and validated to evaluate the risk of malnutrition in both patients and the general population. These tools meet essential criteria for screening, requiring no specific training and utilizing easily accessible markers. The *European Society for Clinical Nutrition and Metabolism* (ESPEN) recommends the use of the *Malnutrition Universal Screening Tool* (MUST) in community settings, the *Nutrition Risk Screening-2002* (NRS-2002) in hospitalized patients, and the *Mini Nutritional Assessment* (MNA) for older adults.[44] The MUST incorporates two readily available markers—current BMI and involuntary weight loss—and includes a general evaluation of the impact of the patient's current clinical status on their ability to meet energy and protein requirements. Each marker is assigned a score, and the composite score categorizes the patient into low, medium, or high risk of malnutrition.

The NRS-2002 follows a two-step process. The first step consists of four questions related to nutritional and clinical aspects of the patient. If at least one question is answered affirmatively, the screening proceeds to the second step, which evaluates the underlying disease and the patient's nutritional status, classified by progressive severity scores. The cumulative score is then adjusted for the patient's age, with a final score equal to or greater than three identifying the patient at risk of malnutrition and necessitating a nutritional care plan.

In contrast to the previous tools, the MNA not only identifies older patients at risk of malnutrition but also allows for the diagnosis of malnutrition in non-frail patients. The MNA screening comprises six items, each with multiple answering options, anchored to a specific score. A score of 11 or below indicates that the patient is at risk of malnutrition.

Beyond the recommendations by ESPEN, it should be highlighted that nutritional risk screening can be performed routinely by any validated tool, based on the familiarity of the personnel with them.

When patients are identified as at risk of malnutrition, the assessment of nutritional status should lead to a diagnosis of malnutrition. In contrast with risk screening, nutritional assessment requires competencies and training by specialised healthcare professionals. According to a consensus involving the nutrition societies of Europe, North America, South America, and Asia, a set of criteria has been selected that are instrumental to the diagnosis of malnutrition. The *Global Leadership Initiative on Malnutrition* (GLIM) criteria identify phenotypic and etiologic criteria.[45] The phenotypic criteria include non-volitional weight loss, low body mass index, and reduced muscle mass, whereas aetiologic criteria are reduced food intake or assimilation and inflammation or disease burden. Patients reporting at least one phenotypic and one aetiologic criterion meet the diagnosis of malnutrition.

Despite the convergence of international societies on the GLIM criteria to identify malnourished patients, there is still debate whether only nutritional markers should be considered to assess nutritional

TABLE 2 Examples of nutritional assessment and malnutrition risk screening tools that have been developed and validated to evaluate and address the risk of malnutrition in both patients and the general population.

Examples of tools for nutrition screening & evaluation in NEN		Setting/age-population	Description	Markers/scores	Outcomes
Screening for risk of malnutrition	Malnutrition Universal Screening Tool (MUST)[44,87]	Community and in hospital setting; adult and geriatric population	A five-step screening tool to identify adults, who are malnourished, at risk of malnutrition (undernutrition), or obese. It includes management guidelines which can be used to develop a care plan.	• BMI (score 0 to 2). • Unexplained weight loss in past 3-6 months (score 0–2). • Acute effects disease score (if patient is acutely ill and there has been/it is likely to be no nutritional intake for >5 days) (score 2).	• Each marker is assigned a score. • The composite score categorizes the patient into low (0), medium (1), or high risk (≥2) of malnutrition.
	Nutrition Risk Screening-2002 (NRS-2002)[44,88]	In hospital setting; adult population	A two-step process based on impaired nutritional status and severity of disease (stress metabolism) scores.	• 1st step: four questions related to nutritional and clinical aspects of the patient. • 2nd step: evaluates the underlying disease and the patient's nutritional status, classified by progressive severity scores (absent 0 → mild 1 → moderate 2 → severe 3).	• A cumulative score adjusted for the patient's age. • If the final score ≥ 3, the patient is at risk of malnutrition.
	Mini Nutritional Assessment (MNA)[44,88]	Residential care setting; elderly population	Identifies older patients at risk of malnutrition & allows for the diagnosis of malnutrition in non-frail patients.	• Six items (food intake issues, weight loss, mobility, the existence of acute disease, neuropsychological stress, and BMI), each with multiple answering options, anchored to a specific score.	• A score of ≤11 indicates that the patient is at risk of malnutrition.
Nutritional assessment	Global Leadership Initiative on Malnutrition (GLIM)[45,88]	In hospital setting; all ages	A two-step process using three phenotypic and two etiologic criteria.	• The phenotypic criteria: non-volitional weight loss, low body mass index, reduced muscle mass • The etiologic criteria: reduced food intake or assimilation, inflammation, disease burden.	• Patients reporting at least one phenotypic & one etiologic criterion meet the diagnosis of malnutrition.

status, or whether functional assessment (i.e., HGS, gait speed, 6 min walking test, etc.) should also be considered. Indeed, these markers could be useful in estimating the efficacy of the nutritional care plan, since function appears to recover more quickly than body composition. A study by Clement et al. including 118 patients with GEP-NET on SSA, evaluated the presence of malnutrition using GLIM criteria. They indicated that overall malnutrition was present in 88 patients (75%), based on low BMI in 26 (22%) patients, based on weight loss in 35 (30%) patients, and based on sarcopenia in 83 (70%) patients. The presence of malnutrition was significantly associated with a worse OS, whereas in multivariate analysis meeting 2 or 3 GLIM criteria was significantly associated with worse OS.[3] The recently published NUTRIGETNE study by del Olmo-Garcia et al.,[46] including a large cohort of 399 patients with advanced intestinal and pancreatic NEN, confirmed previous reports and indicated a 61.9% of malnutrition prevalence according to the GLIM tool, with low muscle mass being the more prevalent criterion (50.9%).

Biochemical markers have been proposed as useful tools for identifying patients with malnutrition. However, most of the commonly suggested markers, such as albumin, transferrin, and retinol-binding protein, have significant limitations. These include being heavily influenced by inflammation (e.g., albumin), slow recovery post-nutritional intervention (e.g., albumin), or limited accessibility in clinical settings (e.g., retinol-binding protein, transferrin). Conversely, markers of inflammation, including C-reactive protein, neutrophil-to-lymphocyte ratio, and interleukin-6, may serve as effective tools due to their impact on body composition wasting. Moreover, sarcopenia can be objectively evaluated using cross-sectional imaging techniques, particularly computed tomography (CT) and magnetic resonance imaging (MRI).[12,13] These modalities provide precise and reproducible measures of muscle mass and composition. On CT images, sarcopenia is commonly assessed by quantifying the skeletal muscle index (SMI) at the lumbar (L3) vertebral level, using threshold-based segmentation to calculate muscle cross-sectional area normalized to patient height. MRI techniques such as chemical shift imaging and proton-density fat fraction (PDFF) further refine the assessment of muscle quality by detecting intramuscular fat accumulation.

As defined for solid tumors, all patients with NEN should be screened for malnutrition at their first medical visit, with subsequent regular re-screenings, before and after scheduled treatments. Healthcare professionals should remain vigilant and promptly identify nutrition alert symptoms, including changes in taste and smell,

development of early satiety, nausea and vomiting, involuntary weight loss, significant unintentional weight gains (e.g., in insulinomas), diarrhea and/or concerning changes in bowel habits. Considering that patients may not report these symptoms, clinicians should proactively search for them at each visit.

Key points:

- Several tools have been developed and validated to evaluate the risk of malnutrition and to assess malnutrition in both patients and the general population, and include *Malnutrition Universal Screening Tool* (MUST), the *Nutrition Risk Screening-2002 (NRS-2002), the Mini Nutritional Assessment* (MNA) and *The Global Leadership Initiative on Malnutrition* (GLIM).
- Routine nutritional risk screening is of major importance. Based on available data, we suggest the MUST tool for ***malnutrition screening*** for outpatient clinic assessment of all patients with NEN with either metastatic disease, locally advanced disease, or those who have undergone previous surgery at their first medical visit and regularly on a 6–12 month basis, and the GLIM tool for ***malnutrition assessment*** for those patients that trigger on MUST.

2.5 | Question 5. How do we personalise nutrition in patients with NEN?

Nutritional planning should be an integral part of patient management and be individualised to the personal needs of the patient with a NEN. This should take into account the patient's symptoms, the disease stage, the type of therapeutic intervention, comorbidities and the current nutritional status. Malnutrition is associated with worse clinical course, quality of life and survival.[3] As such, nutritional goals in all patients with NEN should include maintaining or reaching a healthy weight through a tailored approach based on nutritional needs and nutritional manageable signs and/or symptoms related to pharmacological treatment.[13] To accomplish this, it can be helpful to instruct patients to keep a diary of dietary intake and symptoms to study any aggravating nutrients that can subsequently be removed from the patient's diet. General cancer nutrition guidelines may provide adequate information for the management of nutrition issues common to a range of patients with cancer such as malnutrition and post-surgery management, but lack issues specific to patients diagnosed with a NEN including hormonal syndromes, NET-associated diarrhoea management, malabsorption and vitamin deficiencies.[47] Integrating impact of symptoms and quality of life may support assessments. QLQ-GINET21 showed good validity among patients with gastrointestinal NETs, except in the context of weight gain.[48]

Research into the *type* of diet in NEN is limited, and most recommendations are extrapolated from research in other cancer types. In general, a diet that is rich in proteins and energy through the preferred intake of fruits, vegetables, legumes and whole grains while limited in fat content, red and processed meats and sugar-sweetened beverages will be beneficial. Given the association with the deficiencies described above, dietary planning should incorporate sufficient intake of foods rich in macro- and micronutrients. Intake of daily-recommended allowances of micronutrients should be pursued, obviating the need of high-dose micronutrients unless specific deficiencies are detected.

As no interventional diet studies have been performed in patients with NEN, tailoring the dietary advice to the individual patient's needs and lifestyle is essential, as compliance is key to long-term success. Regarding specific diets, a single study showed that adherence to the Mediterranean diet was associated with less aggressive disease in NET, but this study could be biased by worse dietary intake in patients with more aggressive disease.[7] Nonetheless, the Mediterranean diet has been associated with protective effects in patients with other cancers, through, amongst other benefits, reduction of obesity, anti-oxidant and anti-inflammatory effects. Alternatively, a high-fat Western diet has been associated with negative effects on weight and cancer progression.[49] A ketogenic diet and intermittent fasting have been investigated as anti-neoplastic interventions in other types of cancer, but their effects in patients with NEN are unknown. Importantly, these diets could potentially lead to insufficient energy intake and cannot therefore be recommended at this stage.

In patients with severe malnutrition, sarcopenia or cachexia an increased oral intake of protein- and energy-rich nutrients is even more important. The use of oral nutritional supplements should be considered in these cases if normal dietary intake is insufficient. When symptoms preclude sufficient oral intake and in cases of unsuccessful oral interventions, the option of enteral nutrition through a nasogastric feeding tube should be discussed with the patient. In selected cases where oral or enteral feeding is not possible, for instance in patients with NEN with severe mesenteric fibrosis, peritoneal carcinomatosis or short-bowel syndrome, the use of parenteral nutrition can be discussed in a multidisciplinary setting.[50]

One of the major concerns regarding nutrition in patients with NEN is the presence of diarrhoea leading to malabsorption. Diarrhoea in NEN can be multifactorial and dedicated history taking, physical and biochemical evaluation, is crucial for finding the underlying causes in individual patients. For the management of patients suffering from hormone-induced diarrhoea, such as in carcinoid syndrome, gastrinoma and VIPoma, the reader is referred to the ENETS guidance papers on carcinoid syndrome and on functioning pancreatic NET syndromes.[29,51] Steatorrhoea is commonly observed in patients with pancreas NEN or in patients on SSA therapy and symptoms can be alleviated by reducing the oral intake of fat. Alternatively, patients with NEN and fatty stool can be offered a trial a pancreatic enzyme replacement therapy during meals, snacks and milk-based drinks. Patients that have undergone small bowel resection or right-sided hemicolectomy can suffer from bile acid malabsorption. In suspected cases, a trial of bile acid sequestrants can be considered. Delayed intestinal transport in the small bowel, as in the case of blind loop syndromes, causes bowel stasis that promotes bacterial overgrowth, and appropriate antibiotic supplements are required.[52] Further supportive therapies for refractory diarrhoea include the use of a low-fibre/low-residue diet, loperamide or even opiates.

Supportive therapies, such as nutritional care, are a type of comprehensive treatment addressing the patient as a whole person throughout the process of NEN treatment. Therefore, supportive therapy also encompasses psychosocial support, expert nursing, and management of cancer-related pain.[53] Nutritional management of patients with NEN should be viewed through an integrated perspective. Improvements should be made from four angles: patient, family, healthcare provider, and hospital environment, by establishing a multidisciplinary nutritional management team, preferably supervised by a nutritionist with expertise in NEN.[54] Given the lack of literature in the NEN field, lessons can be learned from other solid tumours, such as head and neck cancer, patients with incurable disease, and cachectic patients, where the recommendation of an MDT as nutritional counselling is advised as well.[55–57]

Key points:

- The precise relationship between specific dietary patterns (e.g., high-fat Western diet, Mediterranean diet, ketogenic diet and intermittent fasting) and the risk or progression of NEN is yet to be defined.
- The use of oral, enteral or parenteral nutritional supplements should be considered in patients with NEN when normal dietary intake is insufficient.
- Diarrhoea in NEN is usually multifactorial, and a thorough differential diagnosis with dedicated history taking, physical, and biochemical evaluation is crucial for identifying and treating the underlying causes in individual patients with NEN.
- The approach should be personalized, integrative, and holistic, and should be made at four angles level: the patient, the patient's family, the healthcare provider, and the hospital environment, by establishing a multidisciplinary nutritional management team, preferably supervised by a nutritionist with expertise in NEN (including NET dietitian, NET specialist, dedicated nurse, patient-advocacy group, psychologist, social-worker, etc.).

2.6 | Question 6. How do we address obesity in NEN?

Although the relationship between obesity, metabolic dysfunction, and various cancers is well established, the specific implications for NEN remain underexplored.[58] Whether NEN are included in the list of obesity-related cancers and the impact of obesity on NEN outcomes has yet to be established due to the scarce data on this subject.

The evidence of a link between obesity, insulin resistance, inflammation, and metabolic syndrome (MetS) with cancer is now established, and there is a growing list of cancer sites and types associated with obesity.[58] Initial observations of incidental NEN, particularly gastric NET, were reported in obese patients undergoing upper endoscopy prior to bariatric surgery, suggesting a possible link between obesity and subclinical NEN development.[59,60] A meta-analysis published by Leoncini et al. described two case–control studies linking BMI with pancreatic NEN, but there was no association with small intestine or rectal NEN.[61] A case–control study[62] found that well-differentiated GEP-NEN were associated with MetS and some of the MetS individual components, such as elevated waist circumference, fasting triglycerides, and fasting plasma glucose. Moreover, the association was significantly increased if four or five individual MetS components were present. An association between grade (G1) and stage (stage IV) and MetS in well-differentiated GEP-NEN was also described.[63] Two retrospective Korean cohort studies identified obesity, low HDL-C, and the metabolic syndrome as independent risk factors for rectal NEN, although these findings require validation in other ethnic populations.[64,65] Diabetes mellitus (DM) is also linked with GEP-NEN. The association of DM with panNEN was described in several studies.[66–69] Besides, DM may occur as a paraneoplastic manifestation in functioning tumors (e.g., glucagonoma), but is more frequently a consequence of treatment (e.g., SSA-induced exocrine insufficiency, or post-pancreatectomy state).[70]

The mechanisms underlying this association are beginning to be clarified. Obesity-induced hyperinsulinaemia stimulates tumorigenesis by enhancing cell proliferation and suppressing apoptosis in NEN.[71] It also promotes a pro-inflammatory state, marked by elevated cytokines like IL-6, TNF-α, and CRP, which contribute to cancer development, including NEN.[71,72] Dysregulated adipokines, such as pro-tumorigenic leptin and anti-tumorigenic adiponectin, influence NEN progression by modulating key tumour processes. Mechanisms involved in tumour initiation and progression include also DNA damage, cell signalling alterations, and modifications in the tumour microenvironment.[73,74] Additionally, ghrelin and leptin influence NEN biology by modulating BMI maintenance, tumour progression, and metabolic interactions.[75] Evidence on obesity and MetS on the prognosis of patients with NEN is still very scarce. Visceral obesity was found to be associated with reduced progression-free survival (PFS) in patients with well-differentiated GEP-NEN.[76] Worsening of the clinicopathological characteristics in GEP-NEN was associated with higher presence of MetS and metabolic dysfunction-associated steatotic liver disease (MASLD).[77] DM exacerbation was independently associated with an increased risk of recurrence in patients with panNEN post-operatively.[78] Although there are some experimental studies with aspirin, metformin, and statins in NEN,[79–81] their role on chemoprevention, as in other cancers, still needs to be clarified. Metformin offers potential synergistic activity with everolimus and SSAs in inhibiting the pro-carcinogenic PI3K/AKT/mTOR axis.[82,83] Dipeptidyl peptidase IV (DPP-IV) inhibitors and glucagon receptor type 1 receptor (GLP1-R) agonists could potentially stimulate NEN growth, as GLP1 receptors are frequently expressed in NEN.[84] This has led to controversy whether these drugs should be used in patients with NEN. Outcomes after bariatric surgery, described in other cancers, still need to be confirmed in NEN.[85]

In summary, the role of obesity,[86] MetS and chronic inflammation in NEN pathogenesis is a new field that needs to be explored through both basic research and multicentre prospective studies designed for this purpose.

Key points:

- There is clear evidence of the link between obesity, insulin resistance, inflammation, and metabolic syndrome with specific cancers. However, there are scarce data on whether NEN are included in the list of obesity-related cancers and on the impact of obesity on NEN outcomes, and vice versa.
- Obesity and diabetes mellitus have been suggested as negative prognostic factors in patients with NEN.
- The decision upon the use of DPP-IV inhibitors and GLP-1R agonists in patients with NEN with morbid obesity and/or uncontrolled diabetes mellitus should be individualised, as long-term data on the effect of these drugs on NEN progression is still to be defined. Specific advantages and drawbacks must be discussed in the MDT, and patients with NEN at high-risk of cardiovascular complications should be carefully followed up while on treatment.

2.7 | Question 7. How to promote research in nutrition in NEN?

2.7.1 | The role of specialised societies

Research on nutrition in NEN is crucial for improving patient outcomes. However, it remains an underexplored field. Tumour-related factors such as obesity, weight loss, malnutrition, vitamin deficiencies, and metabolic changes, together with the side effects of treatment, impact patients with NEN and their clinical trajectories. While these factors are often studied individually, there is a lack of systematic integration to fully understand their collective role in NEN nutrition. A multidisciplinary approach involving NEN specialists (oncologists, endocrinologists, gastroenterologists, surgeons), nutritionists, and clinical researchers is necessary to advance this field. But how can such an integrated approach be effectively implemented?

A key strategy is the involvement of dedicated societies that unite professionals across disciplines, enhance funding opportunities, establish evidence-based guidelines, and promote clinical and translational research. Organisations such as ESPEN, the *American Society for Parenteral and Enteral Nutrition* (ASPEN), and the *British Association for Parenteral and Enteral Nutrition* (BAPEN) play a vital role in shaping nutritional science for NENs. Likewise, endocrinology-focused societies, including the *Endocrine Society*, *European Society of Endocrinology* (*ESE*), *and American Association of Clinical Endocrinology* (AACE), should prioritise research on hormonal regulation, metabolic dysfunction, and dietary influences on tumour progression.

Surgical societies, such as the *American Association of Endocrine Surgeons* (AAES) and the *European Society of Endocrine Surgeons* (ESES), can contribute by investigating the postoperative nutritional challenges faced by patients with NEN. These organisations should foster interactions between researchers and clinicians through funding from governmental, non-governmental, and non-profit institutions. Collaboration with NEN-focused groups-such as ENETS, *North American Neuroendocrine Tumour Society* (NANETS), and *Asia-Pacific Neuroendocrine Tumour Society* (APNETS), is essential to incorporating nutrition research into clinical guidelines and promoting global research initiatives. Oncology societies such as ASCO and ESMO should advocate for the inclusion of nutritional studies in clinical trials.

By expanding funding, interdisciplinary research, and education, these societies can ensure that nutrition becomes a core component of NEN management. Additionally, developing standardised nutrition protocols will enhance clinical practice and trial design, ultimately improving patient outcomes.

2.7.2 | Clinical trials focused on nutrition

Clinical studies and trials assessing dietary patterns—such as Mediterranean, ketogenic, and intermittent fasting—are vital to increase our understanding of factors contributing to patient well-being and NEN progression, as discussed in previous questions.

Such research can evolve into evidence-based nutritional recommendations, emphasizing the necessity of routine nutritional assessments and interventions. Increased funding for nutrition research in NENs will facilitate large-scale studies and the development of

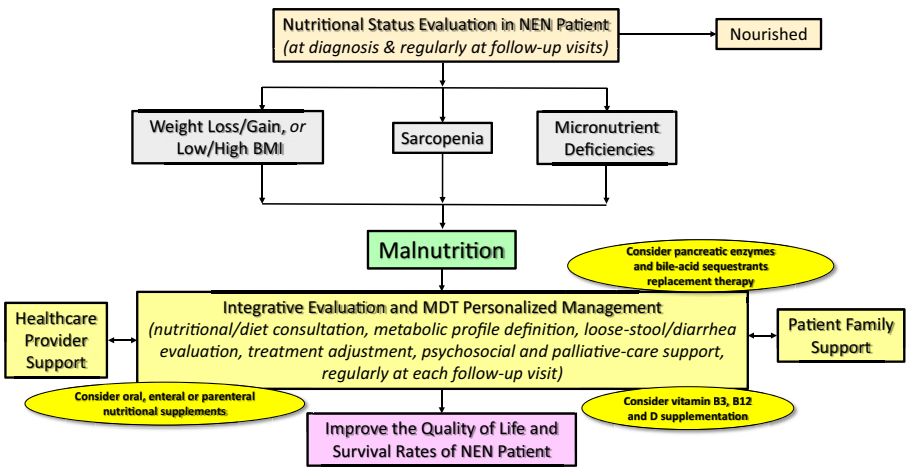

FIGURE 1 Flowchart of suggested stepwise and multidisciplinary strategies that incorporate nutritional support and interventions aimed at preventing or mitigating malnutrition in NEN patients. BMI, body mass index; MDT, multidisciplinary team; NEN, neuroendocrine neoplasms.

comprehensive dietary guidelines. By implementing these strategies and supporting ongoing research, the medical community can deepen its understanding of nutritional needs in patients with NEN, leading to improved clinical management and patient outcomes.

The clinical community can ensure that dietary strategies become a fundamental aspect of NEN management. The integration of nutrition into NEN research and clinical practice is long overdue. Addressing this critical gap will enhance patient well-being and improve clinical outcomes and quality of life for individuals living with NEN.

Key points:

- Engaging dedicated societies is a key strategy for advancing research into nutrition in patients with NEN, as it fosters collaboration among professionals across disciplines, promotes both clinical and translational research, expands funding opportunities, and establishes evidence-based guidelines.
- Standardizing nutrition protocols will enhance clinical practice and trial design, leading to better patient outcomes.

3 | SUMMARY AND FUTURE DIRECTIONS

The complex interplay between (mal-) nutrition, sarcopenia and NEN highlights the need for multidisciplinary management strategies that incorporate nutritional support and interventions aimed at preventing or mitigating malnutrition and sarcopenia. Further research is essential to unravel the detailed mechanisms underlying these relationships and to develop optimised therapeutic approaches that improve the quality of life and survival rates of NEN patients (Figure 1).

AUTHOR CONTRIBUTIONS

Simona Grozinsky-Glasberg: Conceptualization; methodology; software; data curation; investigation; validation; formal analysis; supervision; project administration; writing – original draft; writing – review and editing; resources. **Johannes Hofland:** Conceptualization; methodology; software; data curation; writing – original draft; writing – review and editing; resources. **Stephanie Alband:** Conceptualization; methodology; resources; writing – original draft; writing – review and editing. **Yasmin Chotai de Lima:** Conceptualization; methodology; resources; writing – original draft; writing – review and editing. **Adina Croitoru:** Conceptualization; methodology; resources; writing – original draft; writing – review and editing. **Wanda Geilvoet:** Conceptualization; methodology; resources; writing – review and editing; writing – original draft. **Peter Igaz:** Conceptualization; methodology; resources; writing – review and editing; writing – original draft. **Beata Kos-Kudła:** Conceptualization; methodology; writing – original draft; writing – review and editing; resources. **Guenter J. Krejs:** Conceptualization; methodology; writing – original draft; writing – review and editing; resources. **Alessandro Laviano:** Conceptualization; methodology; resources; writing – original draft; writing – review and editing. **Francesco Panzuto:** Conceptualization; methodology; writing – original draft; writing – review and editing; resources. **Anguraj Sadanandam:** Conceptualization; methodology; writing – original draft; writing – review and editing; resources. **Ana Paula Santos:** Conceptualization; methodology; writing – original draft; writing – review and editing; resources. **Staffan Welin:** Conceptualization; methodology; writing – original draft; writing – review and editing; resources. **Rajaventhan Srirajaskanthan:** Conceptualization; methodology; software; data curation; resources; supervision; writing – review and editing; writing – original draft.

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CONFLICT OF INTEREST STATEMENT

Simona Grozinsky-Glasberg reports consultation fees from ITM and Camurus. Johannes Hofland reports speaker or consultation fees from Ipsen, Novartis, and Serb. Adina Croitoru has received grants/research reports from BMS, MSD, Roche, Amgen, Astellas, ICON, and reports honoraria or consultation fees from BMS, AstraZeneca, Roche, Amgen, Merck, Genesis Biopharma, Ipsen, Lilly, Novartis, Genekor, and Bayer. Wanda Geilvoet reports honoraria or consultation fees from CORE2ED in 2022. Beata Kos-Kudla reports honoraria or consultation fees from Merck, Ipsen, Novartis, Pfizer, and has participated in a company-sponsored speaker's bureau atMerck, IBSA, Ipsen, Novartis, and Pfizer. Dr. Laviano reports honoraria from nutritional industries for independent lectures at scientific and educational events. Anguraj Sadanandam is the co-founder of Oncoassign company and advisor for Diagnostring Laboratories. Staffan Welin reports honoraria or consultation fees from MSD, Serb, Novartis, and Ipsen. Raj Srirajaskanthan has received grants/research supports from Novartis and Ipsen, and reports honoraria or consultation fees from Novartis, Ipsen, Terumo, ITM, and Advanz. The remaining authors declare no conflicts of interest.

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DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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