Received: 23 May 2024 | Accepted: 12 August 2024

DOI: 10.1002/ueg2.12674

GUIDELINE

UNITED EUROPEAN GASTROENTEROLOGY ueg journal WILEY

European guidelines for the diagnosis and treatment of pancreatic exocrine insufficiency: UEG, EPC, EDS, ESPEN, ESPGHAN, ESDO, and ESPCG evidence-based recommendations

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Funding information
United European Gastroenterology, Grant/Award Number: Grant number unknown

Abstract

Pancreatic exocrine insufficiency (PEI) is defined as a reduction in pancreatic exocrine secretion below the level that allows the normal digestion of nutrients. Pancreatic disease and surgery are the main causes of PEI. However, other conditions and upper gastrointestinal surgery can also affect the digestive function of the pancreas. PEI can cause symptoms of nutritional malabsorption and deficiencies, which affect the quality of life and increase morbidity and mortality. These guidelines were developed following the United European Gastroenterology framework for the development of high-quality clinical guidelines. After a systematic literature review, the evidence was evaluated according to the Oxford Center for Evidence-Based Medicine and the Grading of Recommendations Assessment, Development, and Evaluation methodology, as appropriate. Statements and comments were developed by the working groups and voted on using the Delphi method. The diagnosis of PEI should be based on a global assessment of symptoms, nutritional status, and a pancreatic secretion test. Pancreatic enzyme replacement therapy (PERT), together with dietary advice and support, are the cornerstones of PEI therapy. PERT is indicated in patients with PEI that is secondary to pancreatic disease, pancreatic surgery, or other metabolic or gastroenterological conditions. Specific recommendations concerning the management of PEI under various clinical conditions are provided based on evidence and expert opinions. This evidence-based guideline summarizes the prevalence, clinical impact, and general diagnostic and therapeutic approaches for PEI, as well as the specifics of PEI in different clinical conditions. Finally, the unmet needs for future research are discussed.

KEYWORDS
cystic fibrosis, diabetes, diagnosis, fecal elastase, guidelines, malnutrition, pancreatectomy, pancreatic cancer, pancreatic enzyme replacement therapy, pancreatic exocrine insufficiency, pancreatitis, steatorrhea, treatment, weight loss

INTRODUCTION

Pancreatic exocrine insufficiency (PEI) has long been thought to be the result of a secretory deficiency of enzymes and/or bicarbonates from the pancreas.[1] As a result, PEI has been observed almost exclusively in the context of pancreatic diseases, primarily chronic pancreatitis (CP) and cystic fibrosis (CF) and later in pancreatic cancer (PC) or after resective pancreatic surgery. Accordingly, guidelines addressing PEI have focused almost exclusively on these four conditions. The first evidence-based guidelines using the Oxford or Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) systems to address PEI in the context of CP were published in 2012[2] (Figure 1). Following an award from the United European Gastroenterology (UEG),[28] the first European guidelines were developed and published in 2017.[24] It has recently been noted that there is a paucity of research on PEI in the general population and in patients with non-pancreatic diseases,[29] although the number of relevant publications is increasing.[30]

Two interrelated issues have emerged about PEI. Pancreatic exocrine insufficiency must be considered a maldigestion syndrome rather than an isolated organ defect. As a consequence, the diagnosis and treatment of PEI must go beyond the pancreas and require a more holistic view, which has led to a new definition of PEI (Chapter 1). In this guideline, we have reviewed many other conditions of PEI, some of which have anatomically intact pancreas but impaired intraluminal pancreatic enzyme activity. For "normal" digestion, food and pancreatic enzymes must meet at the right time, place, and environment.[31]

In addition to the need for a revised definition of PEI and increased awareness of this condition in some pancreatic and extrapancreatic diseases, the considerable variability in diagnostic and therapeutic approaches to PEI in different clinical scenarios and centers across

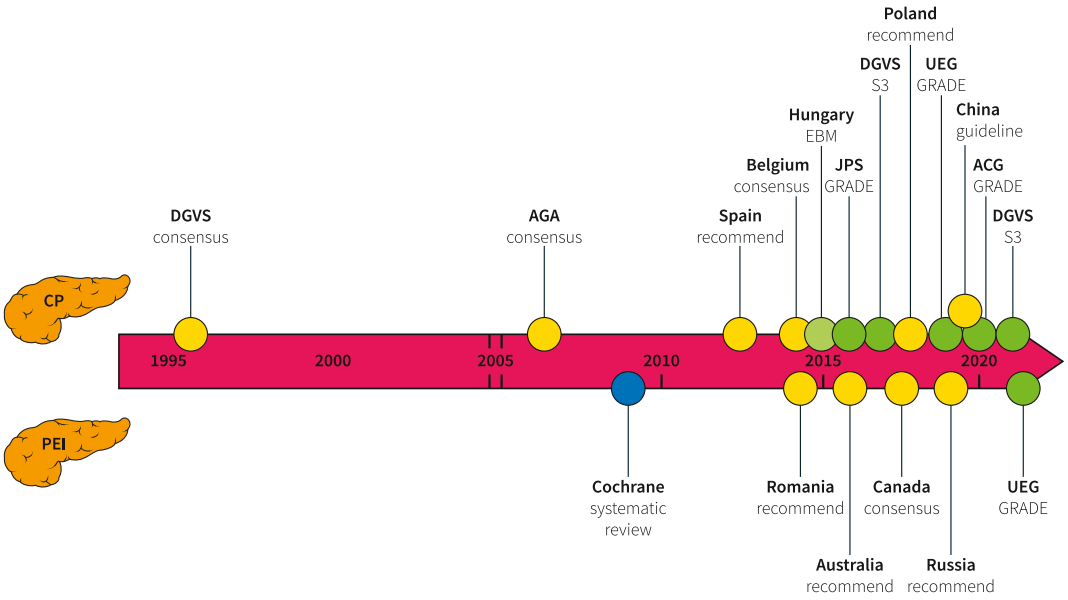

FIGURE 1 Overview of the various guidelines and consensus recommendations for CP (above) and PEI (below) referring to the following: American College of Gastroenterology (ACG)[3]; American Gastroenterological Association (AGA)[4]; American Pancreatic Association (APA)[5]; Australia[6–8]; Belgium[9]; Canada[10]; Cochrane[11]; German Society for Digestive and Metabolic Diseases (DGVS)[12]; Hungary[13]; Italy[14,15]; Japan Pancreas Society (JPS)[16]; Poland[17]; Russia[18,19]; Spain[20,21]; South Africa[22]; Turkey[23]; United European Gastroenterology (UEG)[24]; Romania[25]; Sweden [26]; United Kingdom.[27] CP, chronic pancreatitis; PEI, pancreatic exocrine insufficiency.

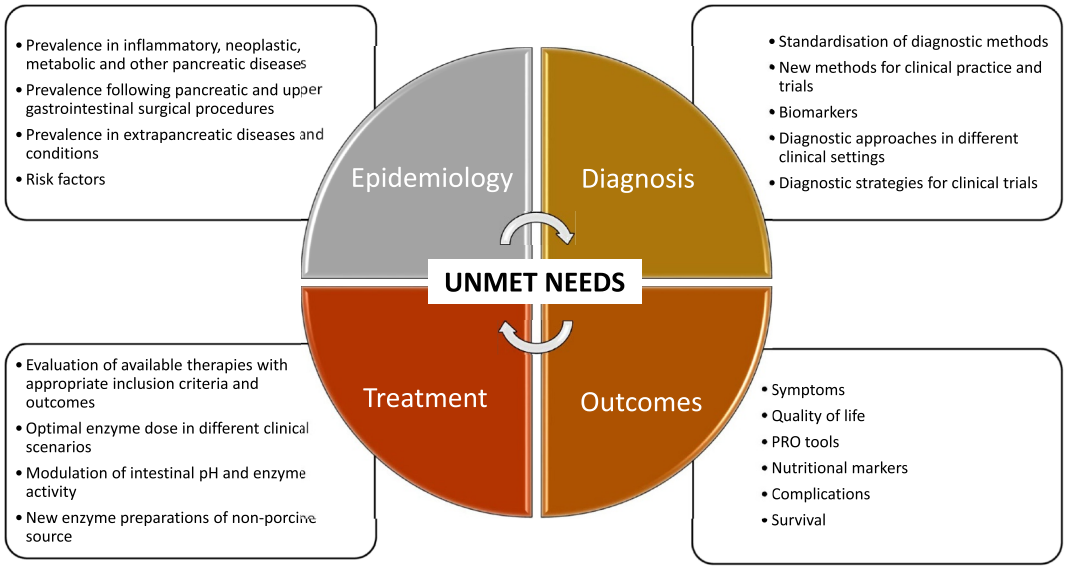

FIGURE 2 Unmet needs, lacking scientific evidence, and future directions.

Europe and non-European countries has been identified as an unmet need that justifies the development of this guideline.

We also found a lack of high-quality prospective clinical trials in many areas of PEI (Figure 2). These new UEG guidelines are therefore unique but can only be seen as the first attempt in this direction.

METHODS

The UEG framework for the development of high-quality clinical guidelines, as proposed by the UEG Quality of Care Taskforce, was adhered to throughout the guideline's development.[32]

Scope and purpose

In addition to defining the general concept, mechanisms, and consequences of PEI, this guideline aims to provide evidence-based recommendations for the general diagnosis and treatment of PEI in clinical practice. It also addresses the specificity of PEI under various pancreatic and extrapancreatic diseases and conditions. The primary health objectives of this guideline include accurate diagnosis, optimal treatment strategies, and prevention of complications. By following these guidelines, healthcare professionals will be able to better increase the quality of life (QoL), minimize symptoms, and improve overall outcomes in their patients.

Steering Committee and supporting societies

Members of the Steering Committee were selected based on their expertise in the field, ability to contribute to the work process, and personal experience as effective team members.[32] They were familiar with the methodology of several previous guidelines[12,24,33] and their evaluations.[34] On behalf of the European Pancreatic Club (EPC), four EPC members (lead, co-chair, and scientific secretaries) constitute the Steering Committee responsible for the design of the guideline protocol and the UEG application. The Steering Group consulted experts in methodology and research synthesis who were actively involved in all stages of the process.

The EPC invited other UEG Specialist Member Societies to join this project with the aim of developing transversal multidisciplinary guidelines to be adopted by all specialties in Europe. The following societies confirmed their participation: the European Digestive Surgery (EDS), European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), European Society for Clinical Nutrition and Metabolism (ESPEN), European Society of Digestive Oncology (ESDO), and European Society of Primary Care Gastroenterology (ESPCG). Several UEG National Member Societies and Patient Associations endorsed this proposal. The UEG provided both endorsement and financial support for the development of the guidelines.

Working groups

The Steering Committee, in collaboration with the other participating societies, designated Working Group (WG) representatives for the different topics within the guideline's scope and invited experts from a range of medical specialties to contribute to them. Conflict of interest (COI) forms were distributed to all participants, and signed scanned copies were sent to the UEG headquarters in Vienna in accordance with the UEG rules. A request was made to all of the participants for updated COIs to be provided at 6-month intervals over the duration of the working process.

TABLE 1 Overview of the working groups.

1. Concept, pathogenesis, and clinical relevance
2. A general diagnostic approach to PEI
3. A general therapeutic approach to PEI
4. PEI secondary to CP
5. PEI after acute pancreatitis (AP)
6. PEI associated with PC
7. PEI secondary to CF
8. PEI after pancreatic surgery
9. PEI after esophageal, gastric, and bariatric surgery
10. PEI in patients with type 1 and type 2 diabetes
11. PEI in other conditions

Abbreviations: CF, cystic fibrosis; CP, chronic pancreatitis; PC, pancreatic cancer; PEI, pancreatic exocrine insufficiency.

The first meeting of the group was held during the UEG Week in Vienna, Austria (October 2022). The WGs were finalized, and a leader responsible for each group was appointed (Table 1).

Definition of search questions (PICO)

Following the meeting in Vienna, the WGs commenced the formulation of the questions in accordance with the recommendations set forth by the Steering Committee (Appendix 1). These questions were subsequently endorsed by the entire group. In order to incorporate the patient perspective, questions were shared with patient associations. The PC Europe (PCE), the Swedish patient organization PALEMA, and the German "Arbeitskreis der Pankreatektomierten" (AdP) were engaged as organizations representing patients to provide their feedback on the drafted PICO questions (see acknowledgments section).

Search for scientific evidence

A comprehensive search for scientific evidence was performed across the MEDLINE, Embase, Scopus, and Cochrane Central Register of Controlled Trial databases. The search strategy used for each chapter is outlined in Appendix 1. A stepwise approach was used to include studies as follows: systematic reviews and meta-analyses, randomized controlled clinical trials, case-control studies, observational cross-sectional and longitudinal cohort studies, and other types of evidence. The following studies were considered eligible for inclusion: studies of PEI associated with any pancreatic or extrapancreatic disease or condition, including patients of any age, conducted in any country, and published in full text in English in peer-reviewed journals. The following studies were excluded: narrative reviews, editorials, abstracts or letters; those published in non-peer-reviewed journals; in

vitro and animal experimental studies; and studies published in languages other than English.

Grade quality of evidence, and definition of statements and comments

In light of the available evidence, statements were formulated in order to address these questions. The statement format included the question, statement and level of evidence. The statements were followed by qualifying comments written by each WG and reviewed by the Steering Committee. Relevant comments and suggestions from the global consensus group were also considered. Statements were formulated in the context of population/problem, intervention, comparison, and outcome (PICO) questions[35] where applicable (see Appendix 1). The quality of evidence was appraised according to the Oxford Center for Evidence-Based Medicine system[32,36] and the GRADE system.[37] The WGs were supported by two expert methodologists throughout the process of searching, selecting, and evaluating the scientific evidence as well as writing the statements. The methodologists also provided training in basic guideline methodology, advised during the development process, and reviewed the draft guideline manuscript.

Consensus process

All questions, statements, and related comments were uploaded to a designated platform and subjected to a repeated Delphi process for all of the participants in the Guideline Consortium. It was requested that members of the WGs provide updates on any potential conflicts of interest on a regular basis (see Appendix 2). In the event of a clear COI, members were obliged to abstain from voting on the specific topic in question. A secretary provided comprehensive assistance throughout the entirety of the working process.

A level of agreement of 80% or higher was deemed to be indicative of consensus. Statements with less than 80% agreement were returned to the WG for further consideration. Updated versions were discussed at the EPC meeting in Alpbach, Austria (June 2023), including a round of Test and Evaluation Directorate (TED) voting in accordance with the previously described methodology, until an agreement was reached.[24,33] The degree of consensus was indicated alongside the level of evidence for each of the statements included in the guideline.

In accordance with the consensus reached at EPC 2023, and following a final round of adjustments, the initial draft of the manuscript was prepared and distributed to the WG coordinators and methodologists for their comments. The resulting guidelines were then collated and sent to independent non-European expert pancreatologists representing the Japanese Pancreas Society, the Korean Biliopancreatic Association, and the Latin American Pancreatic Study Group for review and comments (see Acknowledgments). A final round of adjustments was then made. The key concepts and recommendations of the guidelines are highlighted in Figure 3.

CHAPTER 1: CONCEPT, PATHOGENESIS, AND CLINICAL RELEVANCE OF PEI

What is the definition of PEI?

Statement 1.1

PEI is defined as a reduction in the exocrine pancreatic secretion and/or intraluminal activity of pancreatic enzymes below the level that allows normal digestion of nutrients. PEI is associated with the malabsorption of nutrients and may result in intestinal symptoms and/or nutritional deficiencies.

Consensus; *Percentage of agreement*: *97.4%*

Comment: Failure of the exocrine pancreas to deliver the required levels of enzymes to the intestinal lumen for normal nutrient digestion is the main factor defining PEI.[24,27,38] However, the clinical manifestation of PEI is variably influenced by other relevant factors; therefore, the threshold for the clinical manifestation of PEI varies among patients. The concept of PEI implies that pancreatic enzyme replacement therapy (PERT) can restore the digestion and absorption of nutrients.

What are the mechanisms leading to PEI?

Statement 1.2

The mechanisms leading to PEI primarily include the reduced secretion of pancreatic enzymes and bicarbonates due to pancreatic disease or insufficient postprandial stimulation of the exocrine pancreas.

Level of evidence: *1*; *Percentage of agreement*: *97.6%*

Comment: Decreased pancreatic enzyme secretion is the primary mechanism of PEI. Common causes of decreased secretion include loss of functional exocrine pancreatic tissue, such as in CP, CF, necrotizing pancreatitis, or pancreatic resection, and pancreatic ductal obstruction, such as in PC.[39–42] Reduced postprandial vagal (autonomic nerve division) and hormonal (low cholecystokinin [CCK] and secretin release) stimulation of pancreatic secretion is an additional factor that leads to PEI in patients after pancreaticoduodenectomy, gastrectomy, or gastric bypass.[43–46]

What is the impact of factors other than pancreatic secretion on PEI?

Statement 1.3

Factors other than pancreatic secretion, mainly gastrointestinal anatomy and intraluminal pH, also play important roles in the clinical manifestations of PEI.

Level of evidence: *3*; *Percentage of agreement*: *97.6%*

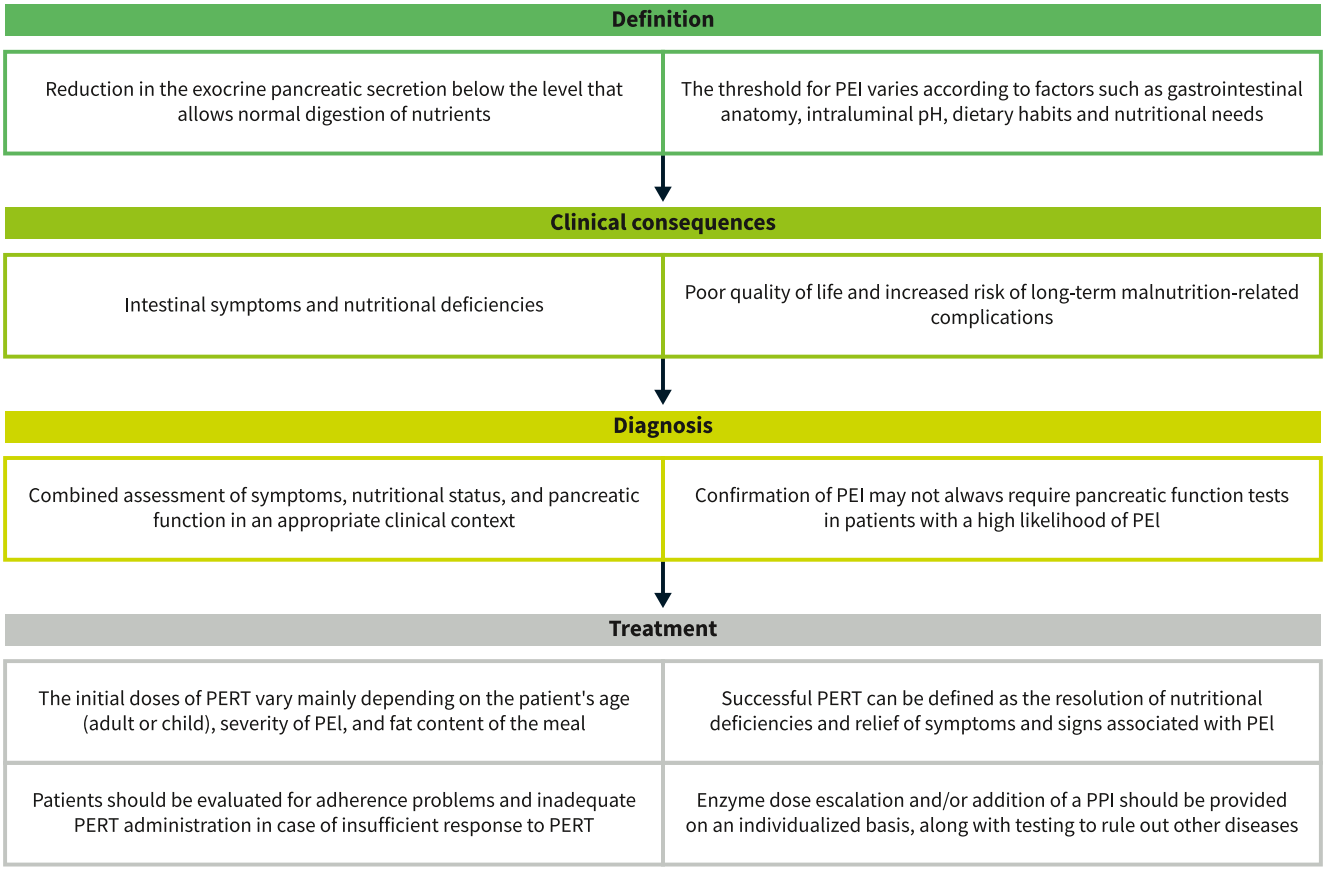

FIGURE 3 Key general concepts and recommendations. PEI, pancreatic exocrine insufficiency; PERT, pancreatic enzyme replacement therapy. PRO, Patient reported outcome.

Comment: The clinical manifestation of PEI is influenced by several factors, including gastrointestinal anatomy, intraluminal pH, compensatory activity of non-pancreatic digestive enzymes, bowel function, dietary habits, and nutritional requirements.[38,43,44] In addition to the altered vagal and hormonal postprandial stimulation of pancreatic secretion, changes in the upper gastrointestinal tract due to surgery may affect intraluminal protease activation (low intestinal endopeptidase secretion) and the mixing of pancreatic enzymes with chyme. The digestive activity of secreted pancreatic enzymes depends on the intraluminal pH, and pancreatic enzymes are inactivated at pH values below 4. Salivary amylase, gastric pepsin and lipase, and intestinal disaccharidases and peptidases partially compensate for pancreatic maldigestion. Bowel function, dietary habits, and nutritional requirements may influence the development of symptoms and nutritional deficiencies.

What are the consequences and clinical relevance of PEI?

Statement 1.4

Regardless of the cause of PEI, intestinal symptoms and nutritional deficiencies are the main clinical manifestations and consequences of PEI, which can affect the QoL and increase the risk of long-term malnutrition-related complications.

Level of evidence: 1; *Percentage of agreement*: 97.6%

Comment: Intestinal symptoms associated with PEI include diarrhea, steatorrhea, bloating, abdominal cramps, and flatulence.[47] Nutritional deficiencies typically include protein, fat-soluble vitamins, and other micronutrient deficiencies associated with weight loss, osteoporosis, and sarcopenia.[47–49] Patients with PEI are also prone to small intestinal bacterial overgrowth and other significant dysbioses of the gut microbiome.[50–52] Due to various factors that may influence the threshold and type of clinical manifestations of PEI, there is high variability in the symptoms and nutritional consequences of PEI among patients.[47] Therefore, PEI has a variable impact on the QoL and long-term complications in different patients.

CHAPTER 2: A GENERAL DIAGNOSTIC APPROACH TO PEI

When is a diagnostic work-up for the detection of PEI indicated?

Statement 2.1

Diagnostic work-up for PEI is indicated in the presence of pre-existing high-risk conditions such as CF, CP, acute necrotizing pancreatitis, PC, or previous pancreatic surgery. PEI may also be considered in the

differential diagnosis of patients with symptoms suggestive of maldigestion and malabsorption, such as steatorrhea or chronic diarrhea.

Level of evidence: *3*; *Percentage of agreement*: *97.0%*

Comment: Several pancreatic conditions warrant a diagnostic work-up to identify PEI due to a high pre-test probability.[8,27,53–55] Additionally, the diagnosis of PEI should be considered in the differential diagnosis of steatorrhea or chronic diarrhea, suggesting maldigestion and malabsorption of nutrients.[56]

How can PEI be diagnosed?

Statement 2.2.1

In general, the diagnosis of PEI should be based on a combined assessment of symptoms, nutritional status, and pancreatic function in an appropriate clinical context.

Level of evidence: *3*; *Percentage of agreement*: *97.3%*

Statement 2.2.2

Confirmation of PEI may not always require pancreatic function tests in patients with a high likelihood of PEI, such as those with pancreatic head cancer or those who have undergone pancreaticoduodenectomy or total pancreatectomy.

Level of evidence: *2*; *Percentage of agreement*: *97.3%*

Comments: Due to their limited specificity, PEI cannot be diagnosed solely based on commonly available pancreatic function tests.[57,58] Symptoms and nutritional deficiencies are not specific to PEI.[47] Therefore, a combined assessment of the symptoms, nutritional status, and pancreatic function in each pertinent clinical context may be appropriate for diagnosing PEI in clinical practice. The likelihood of PEI in patients with pancreatic head cancer and in those who have undergone total pancreatectomy or pancreaticoduodenectomy is greater than 90%.[41,59,60] In such cases, PERT can be initiated after assessing symptoms and nutritional status, and pancreatic function evaluation (e.g., with fecal elastase [FE-1]) can be avoided.

What is the role of symptoms in the diagnosis of PEI?

Statement 2.3

In patients with pancreatic disease or a history of previous pancreatic surgery, the diagnosis of PEI is supported by the presence of symptoms of malabsorption. However, these symptoms are neither sensitive nor specific to PEI, and additional nutritional evaluation and pancreatic function testing may be required.

Level of evidence: *3*; *Percentage of agreement*: *94.7%*

Comments: The symptoms commonly associated with PEI include steatorrhea, voluminous and foul-smelling stools, diarrhea, flatulence, bloating, abdominal discomfort, and weight loss. In clinical studies on patients with confirmed PEI secondary to different pancreatic diseases, the frequency of clinically evident steatorrhea ranged 15%–70%, and the frequency of flatulence ranged 55%–100%.[47] PEI can be diagnosed if clinically evident steatorrhea is present in patients with known pancreatic disease or history of pancreatic surgery.[61] However, owing to the low specificity of the symptoms, nutritional evaluation and pancreatic function testing should be strongly considered to support the diagnosis of PEI. Diagnosis of PEI in patients with an undiagnosed pancreatic disease or history of pancreatic surgery can be challenging because of the nonspecific nature of PEI symptoms.

What is the role of nutritional assessment in the diagnosis of PEI, and what methods can be used to assess the nutritional status of these patients?

Statement 2.4.1

Patients with PEI often have nutritional deficiencies, and nutritional assessment can aid in the diagnosis of PEI in patients with pancreatic disease or a history of pancreatic surgery.

Level of evidence: *3*; *Percentage of agreement*: *97.0%*

Statement 2.4.2

The nutritional status of patients with PEI is evaluated primarily using anthropometric parameters. If malnutrition is suspected, blood parameters of malnutrition should be assessed.

Level of evidence: *3*; *Percentage of agreement*: *95.5%*

Comment: There is limited evidence to support the use of nutritional markers for diagnosing PEI due to the lack of an appropriate reference method. Single assessments of body weight, body mass index, weight loss, lean body mass, and muscle mass are not sensitive enough for diagnosing PEI. Serial readings are more useful in this context. Limited evidence suggests that serum levels of fat-soluble vitamins, trace elements such as magnesium, selenium and zinc, and plasma proteins, including retinol binding protein, albumin, and prealbumin, may have diagnostic utility in PEI.[62–73] However, strong recommendations cannot be made due to the limited evidence.

How can exocrine pancreatic function be evaluated?

Statement 2.5

The exocrine pancreatic function can be evaluated through direct invasive tests that measure the stimulated pancreatic secretion in

duodenal fluid or non-invasive tests that quantify fecal pancreatic enzymes. Indirect non-invasive tests can be used to evaluate the effect of pancreatic enzyme deficiency on digestion.

Level of evidence: *3*; *Percentage of agreement*: *98.5%*

Comment: Pancreatic secretion can be accurately evaluated by bicarbonate and enzyme quantification in the duodenal fluid after intravenous administration of secretin and CCK. Duodenal contents can be obtained using a nasoduodenal tube or endoscope.[74,75] However, this test is invasive and cumbersome and is rarely used in clinical practice. An alternative method for quantifying pancreatic secretion is to measure the FE-1 concentration. This test is frequently used in clinical practice. However, its accuracy for PEI is low mainly because of its low levels of specificity and positive predictive value.[58,76] Non-invasive digestion tests are available, including quantification of the coefficient of fat absorption (CFA) after a 72-h stool collection with the patient on a standardized 100 g fat diet and the 13C-mixed triglyceride (MTG) breath test. Both tests evaluate the digestive function of the pancreas; however, false-positive results may occur in patients with other causes of maldigestion and fat malabsorption.[77,78]

What is the role of direct invasive tests in the diagnosis of PEI?

Statement 2.6

Direct pancreatic function tests should not be used for the diagnosis of PEI in clinical practice.

Level of evidence: *3*; *Percentage of agreement*: *100%*

Comment: Direct invasive tests accurately evaluate stimulated pancreatic secretion but do not assess the ability of secreted enzymes to digest ingested food. Therefore, in accordance with the definition of PEI, direct invasive tests are not applicable.

What is the role of non-invasive tests for the diagnosis of PEI?

Statement 2.7

Non-invasive tests such as FE-1 and 13C-MTG breath tests are recommended for assessing pancreatic exocrine function in clinical practice.

Level of evidence: *2*; *Percentage of agreement*: *98.5%*

Comment: The FE-1 test is commonly used as a non-invasive pancreatic function test. This test is widely available and requires only a small amount of stool sample for analysis. It is generally accepted that the lower the FE-1 concentration, the higher the probability of PEI. However, a cut-off for PEI cannot be established, although a threshold of 200 μg/g is frequently used.[58] The test is at risk of producing false-positive results in individuals with a low pre-test probability and false-negative results in those with a high pre-test probability. Whenever possible, the FE-1 concentration should be measured in a formed stool sample to reduce the rate of false positive results. The diagnosis of steatorrhea traditionally involves the quantification of CFA. However, this test is cumbersome and unpleasant and cannot differentiate between steatorrhea caused by PEI and other causes of fat malabsorption. The 13C-MTG breath test is considered a suitable alternative to CFA for diagnosing PEI and evaluating the effectiveness of PERT in clinical practice.[78,79] However, this test is not widely available and may produce false-positive results in patients with non-pancreatic causes of fat malabsorption.

What is the role of radiological imaging in the diagnosis of PEI?

Statement 2.8

PEI cannot be diagnosed using radiological imaging.

Level of evidence: *4*; *Percentage of agreement*: *98.5%*

Comment: Imaging with computed tomography (CT), magnetic resonance imaging (MRI), or ultrasonography is not used to diagnose PEI but is often used in patients with confirmed or suspected PEI to determine the underlying causes. However, secretin-enhanced magnetic resonance cholangiopancreatography (s-MRCP) can qualitatively and quantitatively assess pancreatic exocrine fluid secretion.[80,81] The clinical use of s-MRCP is limited due to the lack of availability of secretin in many countries.

Can the clinical response to PERT be used to diagnose PEI?

Statement 2.9

If the diagnosis of PEI cannot be established based on the combined evaluation of symptoms, nutritional status, and pancreatic function, assessing the clinical response to empirical PERT may be useful in the appropriate clinical context.

Level of evidence: *5*; *Percentage of agreement*: *97.3%*

Comments: Diagnosing PEI can be challenging in some cases owing to the low specificity of symptoms and nutritional deficiencies as well as the limited accuracy of the FE-I test. Therefore, in patients with confirmed pancreatic disease, the evaluation of the clinical response to PERT in terms of symptom relief and nutritional improvement may support the diagnosis of PEI. However, evidence supporting this approach is lacking.

CHAPTER 3: A GENERAL THERAPEUTIC APPROACH TO PEI

What are the general indications for the treatment of patients with PEI?

Statement 3.1.1

PEI should always be treated.

Level of evidence: *1*; *Percentage of agreement*: *98.8%*

Statement 3.1.2

PERT is indicated in patients with PEI secondary to CP, AP, PC, CF, history of pancreatic surgery, and possibly other metabolic or gastroenterological conditions.

Level of evidence: *1*; *Percentage of agreement*: *90.3%*

Comment: PERT should be provided to all patients diagnosed with PEI in agreement with PEI definition and the guidelines for CP.[24,82] PEI results in symptoms and nutritional deficiencies owing to maldigestion, malabsorption, and impaired nutrient metabolism.[83–85] Fat and protein absorptions increase significantly with PERT compared with baseline or placebo.[86] Further studies are needed to evaluate the long-term effects of PERT on the morbidity and mortality in patients with PEI.

What are the general benefits of PERT in patients with PEI?

Statement 3.2.1

PERT enhances fat and protein absorption in patients with PEI.

Level of evidence: *1*; *Percentage of agreement*: *96.4%*

Statement 3.2.2

PERT positively affects body weight, nutritional status, symptoms, and the QoL in patients with PEI.

Level of evidence: *1*; *Percentage of agreement*: *98.8%*

Statement 3.2.3

PERT may reduce morbidity and mortality in patients with PEI.

Level of evidence: *3*; *Percentage of agreement*: *90.4%*

Comment: Two meta-analyses on PEI secondary to CP reported that PERT decreases fecal fat excretion and improves the CFA and nitrogen absorption compared with baseline and placebo.[39,86] PERT reduces weight loss after AP[87], improves body weight, nutritional status, and the QoL in patients with CP[88–90], and improves body weight and symptoms of maldigestion in patients with PC.[39,41]

No randomized clinical trials with sufficiently long durations have evaluated the effect of PERT on the morbidity and mortality of patients with PEI. However, because malnutrition is the primary clinical consequence of PEI and has been linked to poor outcomes in various PEI-related diseases, it is reasonable to consider PERT as a treatment for preventing PEI-related morbidity and mortality.[41,91–93]

What enzyme preparations can be used for the treatment of patients with PEI?

Statement 3.3.1

Pancreatic enzyme preparations, particularly pancreatin, are the recommended first-line treatment for PEI.

Level of evidence: *1*; *Percentage of agreement*: *98.8%*

Statement 3.3.2

Small-sized enteric-coated pellets are the preferred pancreatin preparations for PEI.

Level of evidence: *2*; *Percentage of agreement*: *98.8%*

Statement 3.3.3

The most commonly used PERT preparations are of porcine origin. Patients should be informed of the porcine origin of PERT before initiating therapy.

Level of evidence: *5*; *Percentage of agreement*: *95.2%*

Comment: PERT is available in different preparations that vary in their lipase, amylase, and protease content. These preparations are labeled according to their lipase activity.[94–96] PERT preparations should mix well with chyme, resist inactivation by gastric juices, empty from the stomach with nutrients, and release enzymes rapidly in the proximal small intestine.[95,97] The particle size and size distribution of pancreatic enzyme preparation pellets have implications for their clinical efficacy.[98–100] Particles smaller than 2 mm may facilitate better dispersal and simultaneous emptying with chyme from the stomach to the duodenum.[24,94,101–104] Importantly, pancreatic enzyme preparations are pH sensitive. The enzymes are protected from gastric acidity by enteric coating, which disintegrates rapidly at pH $\geq$ 5.5, in the duodenum to release them.[94,100,105] Pharmacological inhibition of gastric acid secretion is required to avoid acid-mediated enzyme inactivation when uncoated enzyme preparations are used. PERT preparations with evidence of efficacy are of porcine origin. A non-porcine PERT formulation was developed but failed to meet its primary endpoint in a phase III clinical trial.[106] Patients on special diets, such as vegans or vegetarians, and those with religious reasons

may require non-porcine preparations. Although plant-based or fungal preparations are under development or available in some countries, their efficacy has not yet been well established.

What are the initial PERT doses for the treatment of PEI?

Statement 3.4

The initial doses of PERT vary mainly depending on the patient's age (adult or child), severity of PEI, and fat content of the meal.

Level of evidence: *3*; *Percentage of agreement*: *94.0%*

Comment: The dosages for PERT are based on lipase activity. The initial dose of lipase into the duodenum should be approximately 10% of the physiologically secreted dose.[24] However, randomized trials comparing different enzyme doses are lacking. Administration of a minimum dose of 40,000–50,000 units of lipase with main meals and half of that dose (20,000–25,000 units) with snacks has been shown to be effective in adult patients.[21,82] Some guidelines suggest starting with a lower dose of 25,000–40,000 units of lipase per meal[25,107]; however, evidence for doses below 40,000 units is scarce. A higher starting dose of PERT has been reported to be effective in patients with severe PEI, such as those who have undergone pancreaticoduodenectomy.

The initial enzyme dose for children can be calculated based on either body weight (500-2500 lipase units/kg/meal) or meal fat content (500-4000 units of lipase/g of fat/day).[107–110] For infants, there is a lack of data; therefore, the initial dose of PERT is based on expert consensus. The administration of 5, 000 lipase units per breastfeed or 100–120 ml of infant formula is recommended.[107,109,110]

How should PERT be administered to patients with PEI?

Statement 3.5

PERT preparations should be taken with meals and snacks.

Level of evidence: *2*; *Percentage of agreement*: *95.1%*

Comment: To ensure the efficacy of pancreatic enzyme supplements, it is necessary to mix them with chyme to simulate the action of endogenous pancreatic enzymes.[31] Prandial enzyme administration has been proven as effective as hourly administration in decreasing steatorrhea.[1] A recent randomized three-way crossover study compared three regimes of pancreatic enzyme administration: schedule A (immediately before meals), schedule B (immediately after meals), and schedule C (distributed along with meals).[111] The percentages of patients who achieved normalized fat digestion under therapy with schedules A, B, and C were found to be 50%, 54%, and 63%, respectively. It is important to note that the assessment was conducted on a small meal consisting of two pieces of toast with butter and water and that a prokinetic was administered. No other study has specifically addressed this administration schedule.[39] Two recent guidelines recommend distributing pancreatic enzymes with meals and snacks containing fat, protein, and polysaccharides (excluding disaccharide-based foods such as sugar confectioneries and most fruits).[24,112]

What is the definition of successful PERT?

Statement 3.6.1

Successful PERT can be defined as the resolution of nutritional deficiencies and relief of symptoms and signs associated with PEI.

Level of evidence: *5*; *Percentage of agreement*: *97.6%*

Statement 3.6.2

Some patients with PEI may not achieve complete treatment success with PERT; however, even partial success may justify continued PERT. Partial success occurs when some of the symptoms/signs or nutritional deficiencies are resolved or improved in a clinically meaningful way.

Level of evidence: *5*; *Percentage of agreement*: *97.6%*

Comment: The above definition of treatment success has not been tested in trials but is based on expert opinion. This suggests that successful PERT eliminates the abdominal symptoms caused by PEI and that the patient achieves and maintains a normal nutritional status. The primary outcome parameter used in most randomized controlled trials on the efficacy of PERT is fat absorption, but CFA is not a suitable parameter to define treatment success in clinical practice.[39,41,86] PERT increases serum nutritional parameters and improves gastrointestinal symptoms and the QoL in affected patients.[41] In patients with CF, improvement in nutritional status has often been demonstrated to be a primary outcome parameter.[113]

Long-term studies on PERT demonstrated clinically relevant and statistically significant improvements in nutritional parameters, including body weight and PEI-related symptoms, after 6–12 months.[88,114–116] Some patients may experience symptoms of maldigestion with PERT, but there is a significant improvement in diarrhea, steatorrhea, weight loss, recurrent pain, and the overall QoL.[88,89] The proportion of patients with micronutrient deficiencies on PERT remains unknown.[88] In patients with CF, PERT is associated with an improvement in essential nutritional parameters. However, long-term studies on this topic are lacking. For patients with PC, there is an increasing evidence that PERT is associated with survival benefit and may improve the QoL.[41,117]

What is the approach to patients with insufficient response to PERT?

Statement 3.7

Patients who do not respond or partially respond to PERT should be evaluated for adherence problems and inadequate PERT administration. Enzyme dose escalation and/or additional treatment with a proton pump inhibitor (PPI) should be provided on an individualized basis along with testing to rule out other diseases.

Level of evidence: *4*; *Percentage of agreement*: *98.8%*

Comment: For patients who do not respond to PERT, treatment adherence and proper PERT administration should be confirmed. Implementation of the next steps should be personalized, including dose-escalation[89,118–120] and/or the addition of a PPI.[121–124] The PERT dose should be increased stepwise to double or triple the initial dose to achieve an appropriate therapeutic response. However, the maximum enzyme dose has not yet been determined. PPI can be added to optimize enzyme release and improve enzyme activity in patients with acidic intraluminal pH.[55] Comorbid diseases associated with gastrointestinal symptoms that can mimic PEI, such as intestinal bacterial overgrowth, celiac disease (CeD), food intolerances, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), giardiasis, drug-induced diarrhea, bile acid malabsorption, microscopic colitis, and colorectal cancer should be excluded in patients with insufficient response to PERT and PPI.[50,66,125]

What adverse events may be associated with PERT?

Statement 3.8.1

PERT is not associated with major adverse effects, and most reported symptoms are consistent with the underlying disease.

Level of evidence: *1*; *Percentage of agreement*: *100%*

Statement 3.8.2

Close monitoring is necessary for patients with CF and PEI on high-dose PERT or those with comorbidities because of potential adverse effects.

Level of evidence: *4*; *Percentage of agreement*: *96.8%*

Comment: Few studies have reported that high doses of pancreatic extracts may induce symptoms such as nausea, constipation, and diarrhea, which are linked to transient intestinal upset.[126] Other symptoms, such as pruritus, urticaria, rash, blurred vision, myalgia, muscle spasm, and asymptomatic elevation of liver enzymes, have rarely been reported. These symptoms may be related to the hypersensitivity to these products.[127] There is also a theoretical concern regarding the potential viral transmission with preparations using porcine formulations; however, this has not been confirmed.[86] More recently, porcine-derived PERT was linked to chronic hepatitis E virus infection in lung transplant recipients with CF.[128] However, most studies involving PERT have found that treatment-emergency adverse events are similar to those of placebo and are generally consistent with the underlying disease.[39,129,130] Additionally, no drug interactions have been identified to date.[131]

The use of high doses of pancreatic enzymes in older patients with CF may increase the risk of fibrotic colonopathy.[131,132] This has been related to enzyme coatings containing methacrylic acid copolymers but has also been described in patients who are not on PERT.[126,130,133] In children with CF, hyperuricosuria has been described as dose-dependent because of the high purine content of the drug. Therefore, PERT should be used with caution in patients with gout, hyperuricemia, or renal impairment.[126]

How should PERT be applied to particular situations?

Statement 3.9.1

There is no evidence indicating any harmful effects of PERT during pregnancy or lactation.

Level of evidence: *4*; *Percentage of agreement*: *97.6%*

Statement 3.9.2

If required, PERT can be added to enteral nutrition; however, its efficacy has not yet been proven.

Level of evidence: *4*; *Percentage of agreement*: *94.0%*

Statement 3.9.3

Currently, there is no viable alternative to PERT for patients who avoid porcine derivatives.

Level of evidence: *3*; *Percentage of agreement*: *92.8%*

Statement 3.9.4

For patients with dysphagia, PERT products should be suspended in acidic and puree-consistent food.

Level of evidence: *5*; *Percentage of agreement*: *95.2%*

Comment: Clinical trials of PERT for PEI do not include pregnant or lactating women. Case reports of CF and other diseases do not suggest any adverse events associated with PERT during pregnancy.[134–136] By contrast, essential fatty acids and other nutrients are necessary for development during early gestation; therefore, discontinuing PERT may be counterproductive.[137]

PERT efficacy studies are typically conducted in patients receiving oral nutrition. However, in patients with PEI who require enteral nutrition, PERT must be administered through feeding tubes. In such cases, the delivery method should be modified to allow gastric

or jejunal administration and continuous or bolus feeding.[138] Enzymes can be combined with food and administered immediately after mixing.[139,140] Using liquid pancreatic enzymes, 125,000–250,000 units of lipase are required to achieve complete lipolysis in 1000 ml of polymeric feed compared with 37,500 units in 1000 ml of a peptide/semi-elemental product.[141] Cartridges containing lipase and designed to connect to enteral nutrition systems have been developed, but comparative studies on the addition of PERT to food are lacking.

Some individuals who follow vegan or vegetarian diets or who are of Jewish or Muslim faith may request a non-porcine alternative to PERT. Liprotamase is available in some countries as a non-animal-derived alternative.[142]

The intake of PERT capsules may be challenging in patients with dysphagia. Although evidence is lacking, there is a consensus that PERT can be suspended in acidic puree-consistent foods when capsules cannot be taken.[27]

What dietary interventions are recommended for patients with PEI?

Statement 3.10.1

PERT should be optimized to allow as normal a diet as possible.

Level of evidence: *5*; *Percentage of agreement*: *98.8%*

Statement 3.10.2

If PEI symptoms persist despite apparently adequate PERT, it may be necessary to restrict dietary fiber intake, especially in patients on a high-fiber diet.

Level of evidence: *4*; *Percentage of agreement*: *86.8%*

Statement 3.10.3

Patients diagnosed with PEI should access experienced dietitians for nutritional care.

Level of evidence: *4*; *Percentage of agreement*: *94.0%*

Statement 3.10.4

For patients with PEI receiving enteral nutrition, peptide- and medium-chain triglyceride (MCT)-based formulas may be worth considering if they are intolerant to standard polymeric feeds.

Level of evidence: *5*; *Percentage of agreement*: *91.6%*

Comment: Patients with PEI receiving adequate PERT usually do not require dietary fat restriction. No studies have evaluated the effect of dietary fat restriction on the nutritional or clinical outcomes of patients with PEI. In malnutrition cases, an excessively restricted diet may be counterproductive. Patients with PEI should be advised to consume a varied healthy diet and take an adequate dose of PERT. As PEI progresses and clinical symptoms become more challenging to manage, limiting fat intake may be beneficial if other causes of fat intolerance, such as bile acid malabsorption, are ruled out.[24] Consuming smaller portions and eating more frequently throughout the day can enhance the efficacy of PERT; however, the evidence is lacking. Restricting dietary fiber intake may alleviate malabsorptive symptoms in patients with PEI because fiber can bind to lipase, thereby reducing its availability.[105]

Patients with PEI should have access to a specialist dietitian specifically educated on pancreatic disorders.[24,27,107,143,144] Dietary counseling by a specialist dietitian results in improved anthropometric measurements, less pain, and improved fat absorption in patients with PEI. In addition, patients receive PERT more frequently and do not require artificial supplementation if guided by specialist dietitians.[145,146] Patients with PC and PEI who were able to improve their nutritional status showed significant improvements in their QoL and survival.[129] Despite this, management by nonspecialist dietitians who provide inadequate advice is common.[115,116,147]

Data on enteral interventions for PEI are lacking. Evidence suggests that enteral feeds that are peptide- or MCT-based may provide benefits in terms of weight maintenance and shorter hospital stays than standard polymeric feeds in patients with severe AP.[148]

CHAPTER 4: PEI SECONDARY TO CP

Question: 4.1. what is the prevalence of PEI in patients with CP?

Statement 4.1.1

The prevalence of PEI in CP is 20%–90%, depending on the duration, severity, and etiology of the disease.

Level of evidence 4; *Percentage of agreement*: *98.5%*

Statement 4.1.2

Based on clinical criteria and/or non-invasive tests, the reported pooled prevalence of PEI in patients with autoimmune pancreatitis (AIP) is approximately 45%.

Level of evidence: *3*; *Percentage of agreement*: *90.5%*

Comment: Depending on the severity and etiology of CP, PEI has been reported in 30%–85% of patients with CP within the first 10–15 years after diagnosis, with a marked increase later.[149] Large studies show a prevalence of PEI ranging 50%–75%, particularly in patients with alcohol-induced CP and prolonged disease.[150] Data from the Scandinavian Baltic Pancreatic Club study reflect a 68% prevalence of PEI in patients with CP,[151] with clinically significant PEI developing in

60%–90% of patients within a decade of diagnosis, with alcoholic CP, hereditary factors, and smoking increasing the risk of PEI.[152] In addition, a recent study showed that PEI was more common in patients with longer duration of CP, with the prevalence of PEI increasing from 20% after 5 years to 70% after 20 years of disease.[153]

No studies have evaluated the prevalence of PEI in patients with AIP using digestive tests, such as the CFA. A meta-analysis by Lanzillota et al. reported a 45% prevalence of PEI at the time of AIP diagnosis, based on clinical criteria and/or non-invasive tests.[154] The prevalence decreased to 36% during follow-up. A retrospective cohort study from Sweden reported low fecal elastase concentrations in 72.7% of patients at diagnosis of AIP and 63.5% during follow-up, with no significant effect of pharmacological treatment.[155]

What is the specific pathogenesis of PEI in patients with CP?

Statement 4.2

PEI in patients with CP results from loss of function of the pancreatic parenchyma and/or obstruction of the pancreatic duct.

Level of evidence: *1*; *Percentage of agreement*: *98.5%*

Comment: CP is a progressive IBD that causes the loss and fibrosis of functional pancreatic tissues, resulting in a decrease in the synthesis and secretion of pancreatic enzymes. Based on classic studies by Di Magno et al., the amount of enzyme-rich fluid secreted by the pancreas is approximately 10 times higher than that required for normal digestion. Therefore, although subtle changes in exocrine function can be detected in patients with early pancreatic disease, overt steatorrhea as a manifestation of PEI only occurs when enzyme secretion is reduced by more than 90%.[1] In addition to the loss of pancreatic parenchyma, PEI can be caused by main pancreatic duct obstruction owing to stenosis or calcification.[14,15]

How should PEI be diagnosed in patients with CP?

Statement 4.3

The diagnosis of PEI in patients with CP follows general recommendations (see Chapter 2).

Level of evidence: *1*; *Percentage of agreement*: *100%*

What are the clinical consequences of PEI in patients with CP?

Statement 4.4

The clinical consequences of PEI in CP are similar to those of other causes of PEI (see Chapter 1).

Level of evidence: *1*; *Percentage of agreement*: *98.6%*

What is the treatment of PEI in patients with CP?

Statement 4.5

PEI treatment in patients with CP follows general recommendations (see Chapter 3).

Level of evidence: *1*; *Percentage of agreement*: *100%*

What are the benefits of PERT in patients with PEI secondary to CP?

Statement 4.6.1

PERT improves digestion and nutrient absorption in patients with PEI secondary to CP.

Quality of evidence: moderate; Recommendation: strong (Grade 1B); Percentage of agreement: 100%

Statement 4.6.2

PERT improves the QoL of patients with PEI secondary to CP.

Level of evidence: *4*; *Percentage of agreement*: *98.5%*

Statement 4.6.3

The extent to which PERT can reduce mortality is unclear; however, it is likely to reduce long-term morbidity in patients with PEI secondary to CP.

Level of evidence: *3*; *Percentage of agreement*: *93.9%*

Statement 4.6.4

Similar to other causes of PEI, PERT is associated with few adverse events and is well-tolerated in patients with PEI secondary to CP (see chapter 3).

Quality of evidence: *high*; *Recommendation*: *strong* (*Grade* 1A); *Percentage of agreement*: *100%*

Comment: Meta-analyses by Gan et al.[86] and de la Iglesia et al.[39] showed that PERT significantly improves fat absorption and reduces fecal fat excretion in patients with CP. However, in some patients with CP and PEI, fat absorption is not fully normalized on the standard dose of PERT, with fecal fat excretion ranging 13–25 g/day (normal <7.5 g/day). PERT reduces fecal nitrogen excretion, a sign of protein malabsorption.[39] A significant reduction in fecal weight is also observed.

PEI-related malnutrition and abdominal symptoms, such as excessive bloating and steatorrhea, affect the QoL of patients with CP. Although most studies on PERT have been short-term, there is evidence of a positive impact on QoL. A large, 1-year, multicenter study showed that PERT significantly reduces recurrent abdominal

pain and gastrointestinal symptoms and improves the gastrointestinal QoL (GIQL) index, with improvements across several domains.[89] This positive effect of PERT on the QoL of patients with CP and PEI has been confirmed in other studies.[90] Specific tools for measuring PEI-related QoL are scarce, but a recent study introduced a new patient-reported outcome measure, the PEI-Q, which correlates well with GIQL scores.[156]

A consensus in national and international guidelines recognizes PEI-related maldigestion as a risk factor for increased morbidity and mortality in patients with CP.[8,27] This consensus is based on a fundamental understanding of digestive and nutritional deficiencies associated with PEI as evidenced in several studies.[31] Osteoporosis, often associated with CP, is a potential long-term morbidity outcome in which PERT plays a critical role by improving the absorption of fat-soluble vitamins including vitamin D.[157]

Observational research has also suggested an association between PEI and mortality in patients with CP.[91] Indirect evidence that PERT may improve long-term outcomes, including mortality, comes from an observational study in which the absence of PERT prescription at hospital discharge after surgery for CP was associated with an increased risk of mortality over a follow-up period of 5.3 years.[158]

The safety profiles of PERT in four placebo-controlled trials have shown controversial results.[129,159–161] Adverse events, mainly mild gastrointestinal symptoms such as abnormal stools, bloating, abdominal pain, and vomiting, were commonly reported in all studies.[129,159,160] A 2001 randomized controlled trial highlighted significant glycemic control problems associated with starting or stopping PERT in patients with diabetes.[162] Recent studies suggest that such serum glucose disturbances are rare and not higher in patients undergoing PERT than in controls.[159]

Long-term studies have reported mild adverse events, with gastrointestinal symptoms being the most common.[88,90] Serious events are rare and unrelated to the treatment. Fibrosing colonopathy, a serious complication of PERT, has been reported in children with CF but not in those with CP.[163]

How should patients with PEI secondary to CP be monitored?

Statement 4.7

In patients with PEI secondary to CP, a structured assessment including clinical symptoms, nutritional status, and biochemical parameters is suggested (Table 2). The frequency of assessment varies depending on the clinical situation of the patient and the disease severity.

Level of evidence: *4*; *Percentage of agreement*: *91.1%*

Comment: Patients with PEI secondary to CP are at risk of gastrointestinal symptoms and nutritional deficiencies.[164] There is a significant unmet need for standardized guidance on the management of gastrointestinal symptoms, diet, and digestion in these patients and their caregivers.[165] Although long-term data on structured follow-up are lacking, expert guidelines advocate regular nutritional, clinical, and biochemical monitoring.[24,27,112,166] Monitoring should include nutritional screening using tools such as the Nutritional Risk Index or Malnutrition Universal Screening Tool,[167,168] body weight, maldigestion-related symptoms, and key biochemical markers such as complete blood count, glucose status, plasma proteins, and fat-soluble vitamins. Therefore, other assessments should be tailored to individual needs. To prevent significant clinical and nutritional decline, a suggested frequency of 6-month assessment is suggested, with particular attention paid to pain management and PERT adherence.

CHAPTER 5: PEI AFTER AP

What is the prevalence of PEI in patients after AP?

Statement 5.1

The pooled reported prevalence of PEI after AP is 27%–35%. PEI is more common in patients with severe forms of AP, in those with extensive pancreatic necrosis, and after AP in those with alcohol abuse.

Level of evidence: *4*; *Percentage of agreement*: *98.4%*

Comment: Pooled data showed a prevalence of PEI of up to 62% at admission for AP, with a significant decrease to 27%–35% at follow-up.[40,169] A higher prevalence of PEI has been observed in patients with alcoholic AP, possibly due to preexisting pancreatic damage caused by alcohol.[170] Patients with necrotizing AP have a higher prevalence of PEI than those with interstitial AP (18.9%–24% vs. 24.8%–47.0%), but the extent of necrosis (more or less than 50% of the gland) was not significantly associated with the prevalence of PEI.[40] The prevalence of PEI is lower in patients with mild AP (19.4%–22.7%) than in those with severe CP (30.0%–33.4%).[169] Patients who undergo necrosectomy tend to have a higher prevalence of PEI after AP (relative risk 1.62; 95% confidence interval [CI] 0.77–3.44). The prevalence of PEI depends on the diagnostic method, with direct functional tests indicating PEI in 41.7% of patients after AP, compared with 24.4% when indirect tests are used. Given the limited sensitivity of the FE-1 test for mild-to-moderate reductions in pancreatic secretions, the true rate of PEI after AP may be underreported.[57]

What is the specific pathogenesis of PEI in patients with AP?

Statement 5.2

The pathogenesis of PEI in patients with AP is not completely understood; however, the loss of pancreatic acinar tissue due to necrosis, ductal stenosis, or leakage may be associated with this complication.

Level of evidence: *5*; *Percentage of agreement*: *96.9%*

Comment: The development of PEI after AP correlates with disease severity,[40,169,171,172] presence and extent of necrosis,[40,171,173]

TABLE 2 Suggested parameters for long-term follow-up of patients with pancreatic exocrine insufficiency and CP (according to British-, ESPEN-, DGVS-, and UEG guidelines).

Nutritional/Functional	Biochemical	Clinical	Dietary
Body weight BMI Weight loss	Full blood count and iron reserves	Compliance with treatment	Food avoidance owing to abdominal symptoms
Anthropometric - Mid-arm muscle circumference - Muscle mass quantification (bio-impedance and CT scan) every 2 years - DXA scan for bone and body composition every 2 years - Grip strength	Plasma proteins - Albumin - Prealbumin - Retinol-binding protein - Transferrin Micronutrient status - Magnesium - Fat-soluble vitamins - Zinc, selenium - Vitamin B12 and folate	Assessment of bowel symptoms: stool frequency and color - Presence of abdominal bloating/wind - Postprandial abdominal pain	24-h dietary recall with relevant PERT dose to assess adherence and ratio of PERT with nutrition
6-min walking test	CRP	Factors impacting QoL	Avoidance of fat-containing products
	Glucose and HbA1c	Change in medication (especially opioids and anti-emetic/anti-diarrheal medications)	Nutritional adequacy of diet
	Parathyroid hormone	Implementation of lifestyle advice (smoking and alcohol cessation, weight-bearing exercise, and sunlight exposure)	

Abbreviations: CP, chronic pancreatitis; CRP, C-reactive protein; CT, computed tomography; DGVS, German Society for Digestive and Metabolic Diseases; DXA, dual-energy X-ray absorptiometry; ESPEN, European Society for Clinical Nutrition and Metabolism; HbA1c, hemoglobin A1c; PERT, pancreatic enzyme replacement therapy; QoL, quality of life; UEG, United European Gastroenterology.

alcoholic etiology,[40,169,174,175] and invasive treatments such as necrosectomy.[169,176,177] PEI often results from the loss of exocrine pancreatic tissue owing to inflammation, necrosis, surgery, or long-term alcohol consumption. In addition, PEI is more common in cases where the main pancreatic duct is not visible or is only partially visible on imaging,[176,178] suggesting that ductal complications, such as strictures or leaks that impede the flow of pancreatic juice, contribute to PEI.

How should PEI be diagnosed specifically in patients with AP?

Statement 5.3

The diagnosis of PEI in patients with AP follows general recommendations (see Chapter 2).

Level of evidence: *3*; *Percentage of agreement*: *100%*

Which patients with/after AP should be tested for PEI?

Statement 5.4

All patients should be screened for PEI after an episode of AP, particularly those with severe disease, pancreatic necrosis, or alcoholic etiology. Although previously normal, screening for PEI should be repeated if symptoms attributable to PEI are present.

Level of evidence: *5*; *Percentage of agreement*: *87.5%*

Comment: As mentioned above, approximately 62% of patients develop PEI upon admission with AP, and about one third of patients have persistent PEI during follow-up. These figures support screening for PEI in patients after AP, especially in those with severe necrotizing disease or alcoholic etiology.[40,169]

Is a delay after AP recovery recommended to confirm the diagnosis of PEI?

Statement 5.5.1

No delay is recommended in confirming the diagnosis of PEI after recovery from AP.

Level of evidence: *5*; *Percentage of agreement*: *90.3%*

Statement 5.5.2

In patients with PEI after AP, rescreening for PEI during follow-up is recommended to re-evaluate the need to maintain PERT.

Level of evidence: *5*; *Percentage of agreement*: *90.3%*

Comment: There is a debate about whether pancreatic injury causing PEI in AP is temporary or permanent.[179,180] A study of 370 patients at admission and 1795 at follow-up reported a decrease in the prevalence of PEI from 62% at admission to 35% at 5 years, with the most significant decrease occurring in the first year.[40] This indicates that if PEI occurs, it may take several months or even years to resolve. To re-evaluate the presence of PEI and potentially discontinue PERT, re-testing for PEI at 3-month intervals after discharge is recommended. To rule out PEI resolution, it is recommended that those who remain on PERT be retested (e.g., at 6 and 12 months).[40]

Is there any scenario in which empirical treatment for PEI can be started without diagnostic tests?

Statement 5.6

Empirical treatment may be considered in the presence of symptoms of maldigestion or nutritional deficiencies, particularly after severe necrotizing pancreatitis. A clear response can be both diagnostic and therapeutic in PEI.

Level of evidence: *5*; *Percentage of agreement*: *95.3%*

Comment: Since the main goals of PEI therapy are to relieve gastrointestinal symptoms and improve the nutritional status of patients, empirical PERT may be considered in some patients after AP.[181] In cases with a high probability of PEI, such as patients with severe necrotizing pancreatitis, the negative predictive value of FE-1 as a pancreatic function test for the diagnosis of PEI is not strong enough to avoid starting empirical PERT.

What are the clinical consequences of PEI in patients with AP?

Statement 5.7

The clinical consequences of PEI in patients with AP are comparable with those with other PEI etiologies (see Chapter 1).

Level of evidence: *1*; *Percentage of agreement*: *96.9%*

Is PEI associated with delayed recovery after AP?

Statement 5.8

PEI may affect functional recovery, length of hospital stay, and the QoL during the early post-AP period.

Quality of evidence: *moderate*; *Recommendation*: *weak* (*Grade* 2B); *Percentage of agreement*: *92.3%*

Comment: In a double-blind randomized controlled trial of patients with abnormally low FE-1 test results in the early phase of AP, those who received PERT tended to recover faster, with fewer days in the hospital, less weight loss, and an increase in the QoL compared with those who received placebo.[87] This study suggests the impact of PEI and its treatment during AP; however, stronger evidence is lacking.

What is the treatment of PEI in patients after AP?

Statement 5.9

PEI treatment after AP follows general recommendations (see Chapter 3).

Level of evidence: *1*; *Percentage of agreement*: *98.5%*

Should PERT be added to enteral nutrition in patients with AP?

Statement 5.10

PERT can be added to enteral nutrition in patients with severely necrotizing AP; however, data on its efficacy and feasibility are scarce.

Level of evidence: *4*; *Percentage of agreement*: *93.5%*

Comment: For patients with PEI receiving enteral nutrition, PERT can be administered via a feeding tube that requires adjustments for gastric or jejunal delivery and is suitable for both continuous and bolus feeding methods.[27] Clinical improvements were observed when PERT was combined with enteral nutrition and used immediately.[112] Enzymes can be introduced into the feeding tube every 2 h or added directly to the formula.[27]

What are the specific benefits of PERT in patients with AP?

Statement 5.11

PERT is likely to relieve the symptoms of maldigestion and prevent nutritional deficiencies in patients with PEI after AP. However, specific data are lacking. There is insufficient evidence to support the use of PERT for PEI during admission for AP.

Level of evidence: *5*; *Percentage of agreement*: *93.8%*

Comment: In a study by Kahl et al., patients who underwent PERT tended to have better outcomes, but these improvements were not statistically significant. There was a positive trend in all QoL subscores associated with enzyme supplementation.[87] It should be noted that the sample size of this study was small, which limited the significance of the results. Similarly, Patankar et al. found no significant differences in laboratory or clinical outcomes, including total pain scores and analgesic requirements, between the groups.[182] The length of hospital stay was comparable between the placebo and PERT groups.

How should patients with PEI secondary to AP be monitored?

Statement 5.12

In patients with PEI secondary to AP, and as a general recommendation, clinical symptoms, nutritional status, a non-invasive test for PEI (e.g., FE-1), and adherence to PERT can be monitored at 3, 6, and 12 months after hospital discharge, and then every 6–12 months in the case of persistent PEI.

Level of evidence: *5*; *Percentage of agreement*: *92.1%*

Comment: No prospective randomized trial has reported the benefit of individualized monitoring in patients with PEI after an episode of AP. As pancreatic function may recover in the first few months after AP, this assessment can be performed at the end of the acute episode and then at 3, 6, and 12 months. If the assessment shows that exocrine pancreatic function has returned, further assessment can be stopped; however, if there is continuing evidence of PEI, monitoring should be continued at 6–12 months intervals. Monitoring includes clinical symptoms, FE-1 concentrations, compliance with PERT, and nutritional status. Further detailed recommendations for nutritional assessment in PEI can be found in the recent ESPEN guidelines.[112]

CHAPTER 6: PEI ASSOCIATED WITH PC

What is the prevalence of PEI in patients with PC?

Statement 6.1.1

PEI occurs in approximately 70% of patients with PC. It is more common in patients with tumors located in the pancreatic head and in those with advanced-stage disease.

Level of evidence: *1*; *Percentage of agreement*: *100%*

Statement 6.1.2

The prevalence of PEI in patients with advanced PC increases with disease progression.

Level of evidence: *4*; *Percentage of agreement*: *98.4%*

Comment: According to a meta-analysis, the pooled prevalence of PEI in advanced PC is 72% (95% CI: 55%–86%),[41] with significantly higher prevalence in tumors located in the pancreatic head (RR: 3.36, 95% CI: 1.07–10.54).[41] In a study using the 13C-MTG breath test, the prevalence of PEI in patients with unresectable PC was 80%.[183] Finally, in a systematic review, the median preoperative prevalence of PEI was 44% before pancreatoduodenectomy, 20% before distal pancreatectomy, 63% before total pancreatectomy, and 25%–50% in patients with locally advanced PC.[59]

A study of patients with a pancreatic head tumor showed that the prevalence of PEI at diagnosis was 66%, rising to 92% after a median follow-up of 2 months.[184]

What is the pathogenesis of PEI in patients with PC?

Statement 6.2

PEI in PC is primarily caused by tumor obstruction of the main pancreatic duct. Atrophy, replacement of the pancreatic parenchyma, and loss of pancreatic exocrine tissue may also play roles.

Level of evidence: *1*; *Percentage of agreement*: *93.6%*

Comment: The main causes of PEI in patients with PC are obstruction of the main pancreatic duct with subsequent parenchymal atrophy proximal to the obstruction and loss of exocrine pancreatic tissue or its replacement by tumors and fibrotic tissue.[41,183,185–187] This obstruction impedes the flow of pancreatic enzymes and bicarbonates necessary for neutralizing gastric acid.[186] A double-blind, prospective, randomized, single-center interventional study concluded that pancreatic endoscopic drainage was associated with a significant improvement in exocrine pancreatic function in patients with unresectable PC, supporting the major role of ductal obstruction in the pathogenesis of PEI in patients with PC.[183]

How can PEI be diagnosed in patients with PC?

Statement 6.3

Diagnosis of PEI in patients with PC follows general recommendations (Chapter 2).

Level of evidence: *3*; *Percentage of agreement*: *96.9%*

What are the clinical consequences of PEI in patients with PC?

Statement 6.4.1

PEI contributes to malnutrition and weight loss in patients with PC.

Level of evidence: *3*; *Percentage of agreement*: *100%*

Statement 6.4.2

PEI increases the risk of sarcopenia in patients with PC, which is associated with a poor prognosis.

Level of evidence: *3*; *Percentage of agreement*: *96.7%*

Statement 6.4.3

The severity of PEI based on the FE-1 test is correlated with survival in patients with advanced PC.

Level of evidence: *3*; *Percentage of agreement*: *89.7%*

Statement 6.4.4

Untreated PEI affects the QoL in patients with PC.

Level of evidence: *4*; *Percentage of agreement*: *93.6%*

Comment: Weight loss in patients with PC is often caused by multiple factors, including PEI, which leads to potential nutritional deficiencies. The patients with PEI tend to have lower albumin levels.[188] A higher, although not statistically significant, prevalence of PEI has been reported in malnourished or at-risk patients (42.7%) compared to their well-nourished counterparts (26.7%) prior to pancreaticoduodenectomy.[189] In addition, a mouse model showed that the reduced exocrine pancreatic function associated with PC contributes to adipose tissue loss.[190]

PEI is associated with sarcopenia in patients with pancreatic diseases, including cancer.[68] Sarcopenia, particularly during chemotherapy, is a predictor of poor survival in patients with PC.[191] Sarcopenia in patients undergoing surgery for PC is associated with a higher incidence of postoperative complications, higher 30-day mortality rates, and reduced overall survival.[192]

In the study by Partelli et al., FE-1 ≤20 μg/g was an independent predictor of survival in patients with advanced PC. Median overall survival was significantly longer in patients with FE-1 >20 μg/g (11 months) than in those with FE-1 <20 μg/g (7 months).[188]

The negative effect of PEI on QoL has been demonstrated using a structured questionnaire for patients with PC or their caregivers.[115] In this study, digestive symptoms and difficulties in managing diet were identified as significant problems. These factors negatively affect the QoL, increase feelings of social isolation, and contribute to caregiver distress.

What is the treatment of PEI in patients with PC?

Statement 6.5

Treatment of PEI in PC follows general recommendations (Chapter 3).

Level of evidence: *3*; *Percentage of agreement*: *93.8%*

What are the benefits of PERT in patients with PC?

Statement 6.6.1

PERT improves PEI-related symptoms in patients with PC.

Level of evidence: *3*; *Percentage of agreement*: *100%*

Statement 6.6.2

PERT can improve the nutritional status of patients with PC.

Level of evidence: *1*; *Percentage of agreement*: *98.4%*

Statement 6.6.3

PERT may positively affect overall survival in patients with PEI secondary to PC.

Level of evidence: *2*; *Percentage of agreement*: *91.8%*

Comment: In a pilot study, PERT significantly improved symptoms as measured by standardized QoL questionnaires. After 1 week of PERT, the calculated diarrhea scores, pancreatic pain, and liver pain improved significantly. After 3 weeks, there were significant improvements in pancreatic pain and bloating/gas symptoms.[193] In a retrospective analysis of patients with advanced PC receiving first-line gemcitabine/nab-paclitaxel, PERT significantly reduced floating or greasy/fatty stools at 3 months compared with controls. In addition, PERT doubled the number of patients who gained weight during the treatment.[194]

In a randomized controlled trial of patients with inoperable pancreatic head cancer, PERT significantly helped maintain body weight, which was associated with a significantly higher total daily energy intake, whereas the placebo resulted in weight loss over 8 weeks. The CFA increased by 12% in the PERT group and decreased by 8% in the placebo group (50). However, two randomized controlled trials involving patients with unresectable PC found no benefit of PERT for >8 weeks on body weight, nutritional markers, subjective global assessment, or survival.[195] A meta-analysis of three available randomized controlled trials showed only a trend toward a benefit for weight change with PERT.[196]

Retrospective data support the survival benefits of PERT in patients with PC.[92,185] A meta-analysis of prospective and retrospective observational studies showed a survival benefit of 3.8 months in patients treated with PERT as well as improvements in body weight and a trend toward better QoL.[41]

How should patients with PEI secondary to PC be monitored?

Statement 6.7

Patients with PC and PEI should be monitored regularly to ensure that they receive adequate management advice and that their symptoms are controlled. These patients should be reassessed regularly to ensure that they do not require enzyme dose escalation or nutritional support for anemia or other micronutrient deficiencies.

Level of evidence: *4*; *Percentage of agreement*: *95.1%*

Comment: After the initiation of PERT, patients with PEI should be reassessed to ensure an adequate response to therapy, as some patients may require enzyme dose escalation. Although scientific evidence is limited, many clinicians support individualized assessment.[27] A small qualitative study of patients who started PERT after pancreaticoduodenectomy reported persistent diarrhea and poor adherence to the PERT prescription information.[197] Further qualitative work with patients and their caregivers found that a lack of

information and advice on managing PEI was the most important unmet need and had a significant impact on the QoL.[115]

CHAPTER 7: PEI IN CF AND CFTR-RELATED DISORDERS (CFTR-RD)

What is the prevalence of PEI in CF and CFTR-RD?

Statement 7.1.1

PEI occurs in 75%–90% of patients with CF.

Level of evidence: *1*; *Percentage of agreement*: *96.49%*

Statement 7.1.2

The type of *CFTR* mutation determines the risk of PEI in patients with CF. Patients with severe biallelic (classes I, II, III, and VI) *CFTR* mutations develop PEI early in life.

Level of evidence: *1*; *Percentage of agreement*: *96.5%*

Statement 7.1.3

Patients with pancreatic sufficient (PS)-CF who develop pancreatitis have an increased risk of developing PEI over time.

Level of evidence: *3*; *Percentage of agreement*: *96.5%*

Statement 7.1.4

PEI has a wide prevalence in patients with CFTR-RD, with CP being the most common cause.

Level of evidence: *3*; *Percentage of agreement*: *96.5%*

Comment: Clinical studies have established an 80%–90% prevalence of PEI in patients with CF,[108,198,199] and only a small number maintain pancreatic function. In general, patients with CF develop PEI early in life, with the majority occurring before 1 year of age.[200] PEI is correlated with the genotype in patients with CF.[201,202] Individuals with two severe *CFTR* mutations (classes I, II, III, and VI) tend to develop PEI early, whereas those with two mild *CFTR* mutations (classes IV and V) or one severe and one mild mutation tend to develop PS at birth.[108,199,200,203,204] Alleles belonging to classes IV-V are supposed to have some residual chloride channel activity at the epithelial apical membranes; thus, these patients maintain residual pancreatic function to be PS. However, cohort studies have shown that patients with PS-CF with recurrent episodes of pancreatitis are at an increased risk (odds ratio[OR] 5.5) of developing PEI over time.[205] Patients with CFTR-RD exhibit minimal pancreatic function, which leads to PS. Some patients develop pancreatitis, which evolves into PEI over time.[198,206,207] The prevalence of PEI in CP increases with disease duration, ranging 30%–90% of all etiologies confounded,[149,198,208] and 17–39%[209] in inherited forms of CP. Specific data for patients with CFTR-RD are missing.

What is the specific pathogenesis of PEI in patients with CF and CFTR-RD?

Statement 7.2.1

Exocrine pancreatic function in patients with CF is affected by duct obstruction and progressive damage, with consequent loss of functional pancreatic parenchyma.

Level of evidence: *2*; *Percentage of agreement*: *96.6%*

Statement 7.2.2

CFTR mutations are a significant contributor to PEI in patients with or without CF.

Level of evidence: *Level 1 (CF)—Level 4 (CFTR-RD)*; *Percentage of agreement*: *96.6%*

Comment: Reduced or nonexistent CFTR channel function results in reduced volume of pancreatic juice and hyperconcentration of macromolecules. This can lead to protein precipitation in the duct lumen causing obstruction, progressive pancreatic damage, and pancreatic atrophy.[204,210] Pancreatic diseases in patients with CF begin in utero and continue after birth. In CFTR-RD, specific clinical features linked to CFTR dysfunction in which CF has been ruled out and carrying evidence of partially functioning CFTR protein,[211] PEI can appear due to reduced CFTR function or acute recurrent or CP.[212]

How can PEI be diagnosed in patients with CF and those with CFTR-RD?

Statement 7.3

The diagnosis of PEI in patients with CF follows general recommendations (Chapter 2).

Level of evidence: *1*; *Percentage of agreement*: *98.3%*

As from when and how frequent should PEI be screened in patients with CF and CFTR-RD?

Statement 7.4.1

In patients with CF:

The confirmation of PEI is required as soon as CF is diagnosed. A positive test result should be confirmed by a second test within 3 months. Patients with clearly established PEI do not need to undergo further PEI testing. Patients undergoing equivocal exocrine function tests should be monitored for PS.

Level of evidence: 4; *Percentage of agreement*: 92.5%

Children with pancreatic sufficiency should be monitored by annual FE-1 or additionally in cases of failure to thrive, weight loss, abdominal pain, or diarrhea.

Level of evidence: 4; *Percentage of agreement*: 92.5%

In PS adults (≥16 years age), surveillance for development of PEI can be individualized according to genotype.

- PS patients with a combination of two classes I-III known to be associated with intermediate to high prevalence of PEI could be evaluated with the FE-1 test annually and additionally if the development of PEI is suspected.
- Patients with one or more class IV-VI mutations, known to be associated with a low prevalence of PEI, could be evaluated upon suspected PEI development.

Level of evidence: 4; *Percentage of agreement*: 92.5%

Statement 7.4.2

In patients with CFTR-RD:

Evaluation of PEI is required as part of the workup for CFTR-RD at any age. A positive test result should be confirmed by a second test within 3 months.

Level of evidence: 5; *Percentage of agreement*: 92.5%

PS patients with CFTR-RD should be monitored by annual FE-1 during infancy and childhood or additionally in cases of failure to thrive, weight loss, deficiencies in fat-soluble vitamins, and episodes of AP or diarrhea.

Level of evidence: 4; *Percentage of agreement*: 92.5%

In PS adults (≥16 years age), surveillance for development of PEI can be individualized.

- Clinical subtypes with evident recurrent episodes of AP or signs of CP development should be monitored annually using FE-1.
- Clinical subtypes with other clinical manifestations (congenital bilateral absence of the vas deferens or disseminated bronchiectasis) can be evaluated based on the suspected development of PEI.

Level of evidence: 5; *Percentage of agreement*: 92.5%

Comment: PEI is observed in the majority of patients with CF and develops with increasing prevalence during the first year of life.[213–217] Patients initially diagnosed with PS early in life have a high risk of declining exocrine function.[217–220] The loss of exocrine function has implications for the nutritional state and life expectancy of patients with CF.[47,213,214,221] The goal of nutritional treatment for patients with CF during early life is normal growth and prevention of nutritional deficiencies. The detection and treatment of exocrine failure in early life is important for achieving these goals.[215,222] For PS patients with CF and those with CFTR-RD, the risk of developing PEI is more difficult to predict. Patients with signs of non-CF-specific pancreatic diseases such as recurrent AP or CP should be given extra attention during PEI surveillance testing.[199,223] Finally, monitoring for signs of exocrine failure (steatorrhea, weight loss, deficiencies in fat-soluble vitamins, or distal intestinal obstruction syndrome) is recommended in the follow-up of all PS patients with CF or CFTR-RD.[215,222]

What are the clinical consequences of PEI in CF and CF-related disorders?

Statement 7.5

The clinical consequences of PEI in CF and CF-related disorders are comparable to those of other etiologies (Chapter 1). Additionally, PEI and malnutrition in patients with CF negatively influence growth, pulmonary function, and survival.

Level of evidence: 1; *Percentage of agreement*: 96.6%

Comment: Historical studies convincingly highlight that a high-fat, high-calorie diet and PERT promote the growth and survival of patients with CF (55). Further studies have confirmed the negative effects of poor nutritional status on pulmonary function and survival.[224,225]

How should PERT be performed in patients with CF?

Statement 7.6.1

PEI treatment in CF follows general recommendations (Chapter 3), with the particularity that the enzyme dose must be calculated according to age and body weight.

Level of evidence: 1; *Percentage of agreement*: 96.2%

Statement 7.6.2

Patients treated with PERT should be monitored for growth, nutritional status, and abdominal symptoms at regular intervals to determine the adequacy of treatment at every clinic visit for infants and every 3 months for older children, adolescents, and adults.

Level of evidence: 4; *Percentage of agreement*: 96.2%

Comment: In clinical practice, administration of enzyme pellets to infants can be difficult. If the infant refuses to take the enzyme pellets from a spoon with a little expressed breast milk or formula, the administration of an acidic puree, such as applesauce, may be successful. If the infant still refuses pellets, the use of unprotected powdered enzymes may need to be considered temporarily. Pancreatic enzymes should not be added to infant feed. For patients of all ages, powdered enzymes can be used to help digest enteral tube feedings, for example, when oral administration of enzymes is not possible or when jejunostomy feeds are required.

Enzymes administered in this situation should not mix with the feed; they should be administered as bolus doses through enteral feeding tubes. When unprotected powdered enzymes are used, the addition of a PPI may help prevent the inactivation of lipase by gastric acid. For small children, enteric coated pancrelipase enzyme preparations have been shown to be safe, effective, and preferred by parents.

Monitoring of growth and nutritional status at regular intervals to determine the adequacy of treatment is recommended at each monthly clinic visit for infants, every 3 months for children and adolescents, and every 6 months for adults.

How should PERT be performed in patients with CFTR-RD?

Statement 7.7

PERT in patients with CFTR-RD follows general recommendations (Chapter 3).

Level of evidence: *2*; *Percentage of agreement*: *98.2%*

How does potentiator/modulator therapy affect PEI in patients with CF and those with CFTR-RD?

Statement 7.8.1

Potentiators and modulators may improve exocrine pancreatic function when started early in patients with CFTR-RD with eligible mutations.

Level of evidence: *3*; *Percentage of agreement*: *98.0%*

Statement 7.8.2

The current data are insufficient to amend the recommendations for PERT, nutritional requirements, and liposoluble vitamins in patients receiving potentiator/modulator therapy.

Level of evidence: *4*; *Percentage of agreement*: *98.0%*

Comment: Until the advent of modulation therapy, approximately 85% of patients with CF were reported to develop PEI by the age of 1 year. Recent clinical studies using the CFTR-potentiator Ivacaftor (ARRIVAL,[226] KIWI,[227] and KLIMB[228]) in children aged 1–5 years support the improvement or recovery of exocrine pancreatic function. The ARRIVAL study, studying Ivacaftor in children aged 4 to <12 months[229] and 12 to <24 months[226] with ≥1 CFTR gating mutation, evidenced that levels of FE-1 and immunoreactive trypsin (IRT) improved significantly between baseline and after 24 weeks of treatment. The KIWI[227] and follow-up KLIMB[228] studies performed in children aged 2–5 years with a *CFTR* gating mutation showed similar significant improvements in exocrine pancreatic function. In children aged 2–5 years with homozygous F580del-*CFTR* mutations treated with lumacaftor-ivacaftor, significant improvements in exocrine pancreatic function (FE-1 levels and IRT) were noted between baseline and 24 weeks of treatment.[230] Despite these encouraging results, the impact of modulators on PEI in older children is less clear, raising the question of a "window of opportunity" for reversing exocrine dysfunction.

Thus, these data support the beneficial effects of modulators on exocrine pancreatic function, especially in young children with CF and those with milder mutations. Nevertheless, further studies are required to validate the data in larger patient cohorts. In addition, the impact of modulators/potentiators on the PERT dose has not yet been studied.

In patients with PS-CF and CFTR-RD, a decline in exocrine function occurs later in life and may be accelerated by bouts of pancreatitis. Although data are limited, Ramsey et al. showed that the increased use of modulators (iva, iva + luma, or teza + iva) in patients with PS-CF was correlated with a 65% relative reduction in hospitalizations for pancreatitis.[231] These data are further supported by case reports showing that modulators can prevent pancreatitis episodes in patients with PS-CF and CFTR-RD.[232–234] Although very promising, longer follow-up is necessary to determine whether the use of modulators in patients with severe mutations (Class II) promotes the emergence of pancreatitis and secondary PEI development.

In conclusion, our data suggest that modulators may restore exocrine function in (young) patients with PEI-CF, preventing a further decline in pancreatic exocrine function in PS-CF and pancreatitis episodes in patients with CFTR-RD and PS-CF. The impact of modulators on nutritional support, liposoluble vitamin supplementation, and PERT recommendations requires further investigation.

CHAPTER 8: PEI AFTER PANCREATIC SURGERY

What is the prevalence of PEI in patients after pancreatic surgery?

Statement 8.1

The prevalence of PEI after pancreatic surgery is highly variable, ranging from 100% after total pancreatectomy to 10% in some reports after distal or central pancreatectomies.

Level of evidence: *1*; *Percentage of agreement*: *98.3%*

Comments: The prevalence of PEI after pancreatic surgery varies according to the surgical procedure, condition of the pancreas before surgery, tools used to diagnose PEI, and timing of pancreatic function assessment after surgery. The prevalence of PEI is 100% after total pancreatectomy, although more than half of patients do not develop PEI-related symptoms.[42,235–237] According to a systematic review, the prevalence of PEI after pancreaticoduodenectomy is 92%.[59,236,238,239] After distal and central pancreatectomies, the prevalence of PEI is 10%–80%.[59,236,238,239]

What is the pathogenesis of PEI after pancreatic surgery?

Statement 8.2

The pathogenesis of PEI after pancreatic surgery is multifactorial. The main contributing factors were the state of the pancreas before surgery, removal of the pancreatic parenchyma, disruption of the physiological postprandial stimulation of pancreatic secretion during duodenal resection, and inadequate mixing of pancreatic enzymes with nutrients after gastrointestinal reconstruction.

Level of evidence: *1*; *Percentage of agreement*: *98.4%*

Comments: The two main factors contributing to the development of PEI after pancreaticoduodenectomy are duodenal removal and loss of pancreatic parenchyma. The former leads to the disruption of autonomic control and inadequate activation of pancreatic digestive enzymes. The latter leads to an overall reduction in pancreatic exocrine secretion.[240–242] PEI after distal pancreatectomy and central pancreatectomy depends on the volume of the remnant pancreas,[243–247] with a remnant pancreatic volume <39.5% predictive of PEI.[247] In addition, direct inactivation of pancreatic enzymes by gastric acid may be a contributing factor when pancreatogastrostomy is performed after pancreaticoduodenectomy or central pancreatectomy.[248,249]

How should PEI be diagnosed in patients after pancreatic surgery?

Statement 8.3

The diagnosis of PEI in patients after pancreatic surgery mainly follows the general rules described in Chapter 2 with two exceptions. First, no diagnostic confirmation is required after total pancreatectomy, and second, the FE-1 test is not suitable for the diagnosis of PEI after pancreaticoduodenectomy.

Level of evidence: *1*; *Percentage of agreement*: *84.2%*

Comment: The anatomical and functional consequences of pancreaticoduodenectomy render the FE-1 test and the proposed cut-off values inadequate for the diagnosis of PEI. Therefore, a universally accepted approach for diagnosing PEI after pancreatic surgery is lacking. The most appropriate diagnostic test seems to be the calculation of CFA.[250,251] Another available but not fully validated diagnostic test is the 13C-MTG breath test.[24]

What are the clinical consequences of PEI after pancreatic surgery?

Statement 8.4

The clinical consequences of PEI after pancreatic surgery are similar to those of other clinical conditions (see Chapter 1).

Level of evidence: *2*; *Percentage of agreement*: *98.4%*

What is specific for the treatment of PEI in patients after pancreatic surgery?

Statement 8.5

PEI treatment after pancreatic surgery follows the general rules described in Chapter 3. However, the initial oral dose of pancreatic enzymes required in patients after total pancreatectomy and pancreaticoduodenectomy may be higher than that generally recommended for patients with PEI secondary to other conditions.

Level of evidence: *4*; *Percentage of agreement*: *91.7%*

What are the benefits of PERT after pancreatic surgery?

Statement 8.6

The benefits of PERT in patients with PEI after pancreatic surgery are similar to those in patients with other clinical conditions (see Chapter 3).

Level of evidence: *2*; *Percentage of agreement*: *98.4%*

How should patients with PEI after pancreatic surgery be monitored?

Statement 8.7

Recommendations for the monitoring and follow-up of patients with PEI after pancreatic surgery follow the general rules described in Chapter 3.

Level of evidence: *5*; *Percentage of agreement*: *98.3%*

Comment: Particularly, after pancreatic surgery, other causes of abdominal symptoms should be investigated if the clinical response to PERT is inadequate. The differential diagnoses of PEI after surgery include superior mesenteric artery revascularization, dissection-associated diarrhea syndrome, small intestinal bacterial overgrowth, and dumping syndrome. Similar to other causes of PEI, oncological metabolic factors leading to malnutrition, bile acid malabsorption, infectious diarrhea (e.g., Clostridium difficile), lactase deficiency, food intolerance, CeD, IBD, IBS, and diabetic diarrhea should be considered in patients with an inadequate clinical response to PERT.

CHAPTER 9: PEI AFTER UPPER GASTROINTESTINAL (ESOPHAGEAL, GASTRIC, AND BARIATRIC) SURGERIES

What is the prevalence of PEI in patients who have undergone upper GI surgery?

Statement 9.1

The prevalence of PEI after upper gastrointestinal surgery is 9%–67%, depending on the type of surgery and the test used to diagnose PEI.

Level of evidence: *3*; *Percentage of agreement*: *96.9%*

Comment: Three prospective cohort studies measured exocrine pancreatic function after esophagectomy and found PEI in 16%–57% of patients.[252–255] Clinical data on the prevalence of PEI after gastric surgery are limited to small studies.[256–258] A study using pancreatic stimulation with intravenous secretin and cerulein showed that patients after gastric surgery had lower bicarbonate and lipase secretions and 67% had steatorrhea.[258] After total gastrectomy for gastric cancer, all patients develop severe PEI, as measured by the secretin-cerulein test, within 3 months of surgery.[256] Subtotal gastrectomy leads to altered fat digestion and absorption in about two-thirds of patients, particularly after Roux-en-Y reconstruction compared with Billroth I reconstruction.[257] Based on a small number of studies, the prevalence of PEI after bariatric surgery is 9%–48%.[259–261] In a study using FE-1, 48% of the patients after distal Roux-en-Y gastric bypass (RYGB) and 19% after proximal RYGB showed reduced pancreatic secretion.[259] In another study, low pancreatic secretions were found in 10.3% and 4.2% of the patients after RYGB and gastric sleeve, respectively.[260] Using the 13C-MTG breath test, the prevalence of PEI in patients after bariatric surgery ranges from 4.3% after general surgery and 8.3% after RYGB to 75% after biliopancreatic diversion with duodenal switch (22).

What is the specific pathogenesis of PEI in patients who undergo upper gastrointestinal surgery?

Statement 9.2

PEI after upper gastrointestinal surgery may be the result of impaired stimulation of digestive enzyme secretion (humoral and neural) and postprandial gastrointestinal asynchrony.

Level of evidence: *5*; *Percentage of agreement*: *98.4%*

Comment: Upper gastrointestinal surgery results in physiological changes that contribute to the development of PEI due to impaired postprandial stimulation of pancreatic secretion and asynchrony between the gastric emptying of nutrients and biliopancreatic secretion.[43] Therefore, the accuracy of quantifying pancreatic secretion using FE-1 testing for the diagnosis of PEI in these conditions was lower than that in patients with normal gastrointestinal anatomy.

How can PEI be diagnosed in patients who underwent upper gastrointestinal surgery?

Statement 9.3.1

FE-1 is not a reliable test for PEI after upper gastrointestinal surgery.

Level of evidence: *5*; *Percentage of agreement*: *83.6%*

Statement 9.3.2

Although not specific to PEI, symptoms of maldigestion and nutritional deficiencies can be used to suspect PEI in patients who have undergone upper gastrointestinal surgery.

Level of evidence: *5*; *Percentage of agreement*: *84.6%*

Statement 9.3.3

The 13C-MTG breath test and quantification of the CFA could be used to diagnose PEI after upper gastrointestinal surgery.

Level of evidence: *5*; *Percentage of agreement*: *91.8%*

Comment: PEI after upper gastrointestinal surgery cannot be diagnosed using the same methodology as that in patients with normal gastrointestinal anatomy (see Chapter 2). FE-1 allows the assessment of pancreatic secretion but does not measure the effect of postprandial asynchrony between gastric emptying of chyme and pancreatic secretion during food digestion. In contrast to FE-1, the 13C-MTG breath test and fecal fat quantification assess the digestion and absorption of fat, and can therefore be used to diagnose PEI after upper GI surgery.[43]

What are the clinical consequences of PEI in patients who undergo upper gastrointestinal surgery?

Statement 9.4

The clinical consequences of PEI in patients after upper gastrointestinal surgery may be similar to those of other causes PEI (see Chapter 1).

Level of evidence: *3*; *Percentage of agreement*: *93.9%*

What is the treatment of PEI in patients who undergo upper gastrointestinal surgery?

Statement 9.5

PEI treatment after upper gastrointestinal surgery follows general recommendations (see Chapter 3).

Level of evidence: *5*; *Percentage of agreement*: *96.9%*

Comment: There is little evidence on whether PERT capsules should be opened and the pellets swallowed with acidic liquid or semi-solid food (pH < 5.5) after gastrectomy to allow their better mixing with food.[262] PERT has been suggested to prevent postoperative maldigestion and weight loss.[256] After bariatric surgery, appropriate PERT should be considered part of the management algorithm for patients with confirmed PEI and symptoms or nutritional deficiencies suggestive of this complication.[263] However, the role of PERT in these patients is unclear because there is insufficient

evidence to determine whether or to what extent, this therapy interferes with the goals of bariatric surgery.[259]

CHAPTER 10: PEI AND DIABETES MELLITUS (DM)

What is the prevalence of PEI in patients with DM?

Statement 10.1

Reduced pancreatic secretion, as assessed by FE-1 levels, is common in patients with type 1 and type 2 DM. The prevalence of PEI, according to the agreed-upon definition (Chapter 1) is unknown.

Level of evidence: *3*; *Percentage of agreement*: *94.2%*

Comment: Reduced pancreatic secretion, defined by low FE-1, is consistently more common in people with DM than in controls, with a prevalence of 10%–50%.[264,265] A meta-analysis reported a pooled prevalence of 22% (95% CI: 15%–31%) in type 2 DM.[266] These figures may be overestimated because studies that strictly excluded pancreatogenic diabetes reported a prevalence of 5.4%.[267] Reduced pancreatic secretion, as defined by low FE-1, appears more common in type 1 DM than in type 2 DM and may correlate with DM duration,[268–270] but this is still debated.

What is the pathogenesis of PEI in patients with DM?

Statement 10.2

The pathogenesis of PEI in patients with DM is multifactorial, complex, and incompletely understood.

Level of evidence: *4*; *Percentage of agreement*: *97.1%*

Comment: The proposed mechanisms of PEI in patients with DM include the loss of the trophic and stimulatory effects of insulin on the exocrine pancreas,[271] pancreatic atrophy, autonomic dysfunction,[271,272] fibrosis, pancreatic steatosis, and dysregulation of other islet hormones such as glucagon and somatostatin.[271]

How can PEI be diagnosed in patients with DM?

Statement 10.3

The diagnosis of PEI in patients with DM follows general recommendations (Chapter 2).

Level of evidence: *1*; *Percentage of agreement*: *100%*

Comment: PEI symptoms are usually mild in patients with DM. Typical abdominal discomfort, diarrhea, and flatulence may be misinterpreted as drug-related (metformin and glucagon-like peptide-1 agonists) or secondary to diabetic neuropathy. Studies showing weak correlations between fecal fat excretion, pancreatic function tests, and FE-1 levels in individuals with DM emphasize the need to consider alternative causes of steatorrhea such as CeD and bacterial overgrowth in the small intestine.[268]

Should patients with DM be screened for PEI?

Statement 10.4

Patients with types 1 and 2 DM should only be screened for symptoms or nutritional deficiencies consistent with PEI.

Level of evidence: *3*; *Percentage of agreement*: *94.2%*

Comment: Although reduced pancreatic secretions may be common in patients with DM, general screening is not recommended. However, symptoms consistent with PEI should be carefully assessed. If type 3c (pancreatogenic) DM is suspected, exocrine pancreatic function should be assessed.

What are the specific clinical consequences of PEI in patients with DM?

Statement 10.5

The clinical consequences of PEI in patients with DM are similar to those in other clinical conditions (Chapter 1). The development of PEI in patients with DM should raise awareness of possible underlying pancreatic diseases to ensure early diagnosis and treatment.

Level of evidence: *5*; *Percentage of agreement*: *98.6%*

Comment: Both pancreatitis and pancreatic malignancies are associated with PEI. As patients with DM are at an increased risk of both conditions, the development of PEI may require further investigation in suspected cases.

What is the specific treatment of PEI in patients with DM?

Statement 10.6

PEI treatment in patients with DM patients follows general recommendations (Chapter 3).

Level of evidence: *5*; *Percentage of agreement*: *97.2%*

What are the specific benefits of PERT in patients with DM?

Statement 10.7

In addition to the general benefits of PERT mentioned in Chapter 3, glucose homeostasis may also be positively influenced by PERT;

however, the evidence is conflicting. Treatment with PEI may improve cardiovascular risk in patients with DM.

Level of evidence: *5*; *Percentage of agreement*: *86.2%*

Comment: PEI is associated with an increased cardiovascular risk.[273] Therefore, its treatment may be particularly beneficial for patients with DM who are at a high risk of cardiovascular disease.

How should patients with DM and PEI be monitored?

Statement 10.8

Monitoring of patients with DM and PEI follows general recommendations (Chapter 3).

Level of evidence: *3*; *Percentage of agreement*: *98.6%*

Comment: Special attention should be paid to the diagnosis and treatment of osteoporosis as it is a common complication of both conditions.[72,274]

What is the relation between PEI and type 3c (pancreatogenic) DM?

Statement 10.9

Both PEI and type 3c DM result from the same pancreatic injury, most commonly CP, PC, or previous pancreatic surgery, and less commonly from AP, CF, or hemochromatosis.

Level of evidence: *5*; *Percentage of agreement*: *97.0%*

Comment: Surgical resection of the pancreas is perhaps the most obvious cause of type 3c DM, but it accounts for only 2% of cases.[275]

CHAPTER 11: PEI IN OTHER CONDITIONS

What is the prevalence and clinical relevance of PEI in aging?

Statement 11.1

Exocrine pancreatic function may be impaired with aging. Low FE-1 levels have been reported in 21.7% of patients aged >60 years and 11.5% of people aged 50–75 years.

Level of evidence: *4*; *Percentage of agreement*: *93.9%*

Comment: Aging is associated with changes in the pancreatic volume, structure, and perfusion.[276] Although studies on exocrine pancreatic function in older patients do not unanimously favor old age as a risk factor for PEI,[277–279] other reports support this claim.[280–288] In the old age, significantly lower enzyme and/or bicarbonate output following the secretin test has been reported[281–285] and confirmed using FE-1 as an indicator of exocrine secretion.[287,288] The largest study conducted so far in a population-based cohort of 914 participants aged 50–75 years showed low FE-1 levels (<200 μg/g) in 11.5% of the study participants.[287] In another study of 159 patients, low FE-1 levels were reported in 21.7% of participants aged >60 years.[288] Although the clinical relevance of PEI in aging is unknown, older individuals with proven PEI should not be treated differently from other patients with this condition.

What is the prevalence and clinical relevance of PEI in non-alcoholic fatty pancreas disease?

Statement 11.2

The clinical relevance of fatty pancreas and whether it can cause PEI remain unclear.

Level of evidence: *4*; *Percentage of agreement*: *95.3%*

Comment: A systematic review of five studies on fatty pancreas showed PEI in 9%–56% of patients.[289] Among 31 patients with MRI signs of pancreatic steatosis and 25 controls, FE-1 levels were lower in the fatty pancreas group.[290] Another study that used the N-benzoyl-L-tyrosyl-p-amino benzoic acid (BT-PABA) pancreatic function test did not find any association between the amount of pancreatic fat on CT and PEI.[291] In contrast, an inverse relationship between the amount of pancreatic fatty accumulation on MRI and FE-1 levels was reported in a large population-based study.[292] Fatty pancreas is particularly common in patients with non-alcoholic fatty liver disease; one out of each of the four patients has a low FE-1, but the 13C-MTG-breath test is normal, and symptoms of PEI and nutritional deficiencies are lacking.[289]

What is the prevalence and clinical relevance of PEI in hemochromatosis?

Statement 11.3

The prevalence and clinical relevance of PEI in hemochromatosis is not known.

Level of evidence: *5*; *Percentage of agreement*: *98.4%*

Comment: Data on the association between hemochromatosis and PEI are lacking. Two small studies were published decades ago[293,294] and a few case reports were published thereafter.[295,296] All other available data came from studies performed on patients with other iron overload disorders such as beta-thalassemia major.[297–299] The studies were heterogeneous and used different methods to diagnose PEI, making the results difficult to interpret.

What is the prevalence and clinical relevance of PEI in celiac disease?

Statement 11.4

Low FE-1 levels and pathological BT-PABA test have been reported in 10.5%–46.5% of new patients with CeD (pooled prevalence 26.2%). PEI testing should be considered if significant malnutrition is

present at the diagnosis of CeD or if there are persisting symptoms that do not respond to a gluten-free diet (GFD).

Level of evidence: *4*; *Percentage of agreement*: *97.1%*

Comment: The mechanism of PEI in newly diagnosed CeD is likely reduced CCK and secretin release, with intrinsically normal pancreatic morphology and function.[300–302] A systematic review and meta-analysis reported a pooled prevalence of PEI (based on FE-1 or BT-PABA test) of 26.2% (range, 10.5%–46.5%) in patients with newly diagnosed CeD versus 8% in those on a GFD.[303] In a Swedish nationwide study, patients with CeD had a 5.34-fold increased risk of receiving pancreatic enzyme product supplementation after CeD diagnosis.[304] A double-blind prospective study including 40 children (mean age: 14.3 months) showed a limited benefit of PERT at diagnosis (an increased weight gain for patients taking PERT was detected in the first 30 days but not thereafter).[305] Although pancreatic function tests are not routinely recommended for patients with newly diagnosed CeD, testing with FE-1 and PERT may be considered for patients with significant malnutrition. Reassessment should be recommended after 30 days according to Italian guidelines.[14] Other international guidelines recommend testing FE-1 in patients with CeD with a partial response to a GFD.[306,307]

What is the prevalence and clinical relevance of PEI in IBD?

Statement 11.5

Low FE-1 values have been reported in 0%–41% of patients with IBD and in 19%–31% of patients with AIP and IBD.

Level of evidence: *4*; *Percentage of agreement*: *93.9%*

Comment: A Reduced pancreatic secretion based on the secretin-cerulein test was reported in 41% of patients with IBD.[308] Low FE-1 levels have been reported in 18% of patients with IBD, which was associated with more than three bowel movements per day, loose stools, and previous gastrointestinal surgery,[309] and in 10% of patients according to a systematic review.[310] In contrast, FE-1 was normal in 20 patients with Crohn's disease, most of them with FE-1 values > 500 µg/g, which strongly indicated the absence of PEI.[311] In patients with IBD and AIP, low FE-1 values were reported in 19%[312] and 31% of patients,[313] respectively. However, the clinical relevance of PEI in patients with IBD remains unclear.

What is the prevalence and clinical relevance of PEI in patients fulfilling the criteria of IBS?

Statement 11.6

There is symptomatic crossover between diarrhea-predominant irritable bowel syndrome (IBS-D) and PEI. Low FE-1 values have been reported in 4%–13% of patients with D-IBS. Whether PEI coexists with IBS or causes symptoms suggestive of IBS remains unclear.

Level of evidence: *4*; *Percentage of agreement*: *88.1%*

Comment: FE-1 <200 µg/g and <100 µg/g have been reported in 7.1%–13.3% and 4.4%–6% of patients with D-IBS, respectively.[314–317] A recent systematic review and meta-analysis evaluated the prevalence of somatic conditions in patients with IBS[318] and reported a crude pooled prevalence of PEI of 4.6%. Investigations of the pancreas using imaging have not been uniform or systematic in most studies. Underlying pancreatic abnormalities, including pancreatic atrophy, fatty pancreas, and CP, have been found in patients with IBS.[314,317,319] In the absence of any underlying pancreatic disease, false-positive FE-1 results cannot be excluded in patients with D-IBS, and comparisons with other exocrine pancreatic function tests have not been reported. Treatment with PERT is not well-documented in this setting, and no randomized or blinded studies have been conducted. Symptomatic improvement in patients with IBS on PERT has been described in small open studies.[314] A double-blind randomized controlled trial found no benefit from PERT in D-IBS; however, pancreatic function was not evaluated.[320] Other studies have described some patients reporting benefits from PERT; however, these studies were of low quality with a high placebo effect.[321,322]

What is the prevalence and clinical relevance of drug-related PEI?

Statement 11.7

Low FE-1 values have been reported in 1%–10% of patients treated with immune-checkpoint inhibitors and tyrosine kinase inhibitors.

Level of evidence: *4*; *Percentage of agreement*: *95.2%*

Comment: Pancreatic atrophy has been reported in 7.7% of patients with cancer treated with immune-checkpoint inhibitors, and 1.1% developed PEI that resolved with PERT.[323] A low FE-1 level was reported in 10% of patients with hepatocellular carcinoma (HCC) treated with sorafenib, and malabsorption symptoms in these patients resolved with PERT.[324] Similarly, steatorrhea that resolved with PERT has been described in 35% of patients with HCC or renal cell carcinoma treated with sorafenib in a study that also reported vitamin D deficiency, hypophosphatemia, and secondary hyperparathyroidism in these patients.[325] Significant pancreatic atrophy, but not PEI, has been described in patients with gastrointestinal stromal tumor treated with sunitinib compared with controls,[326] and pancreatic volume was found to be significantly reduced in patients with colorectal cancer after bevacizumab therapy, but none developed PEI.[327]

What is the prevalence of PEI in rare/inherited disease?

Statement 11.8

PEI can occur in patients with Shwachman-Bodian-Diamond syndrome (SBDS), Johanson-Blizzard syndrome (JBS), Pearson syndrome,

Shteyer syndrome, or other rare inherited diseases. The prevalence of PEI in these inherited diseases is unknown because of their rarity.

Level of evidence: 4; *Percentage of agreement*: 98.4%

Comment: After CF (see Chapter 7), SBDS is the second most common inherited cause of PEI, with an estimated incidence of 1:50,000.[328] PEI improves with age in these patients. While 90% of infants and young children experience steatorrhea, approximately half of patients in their second decade of life have a sufficient pancreas and no longer require PERT.[329]

JBS is a peculiar nasal malformation with hypo- or aplasia of the nasal wings and oligodontia of the permanent teeth and presents as congenital PEI.[330] The onset of PEI in patients with JBS may be delayed until adolescence.[331]

PEI has been reported in patients with Pearson syndrome,[332] Shteyer syndrome,[333] complete or incomplete pancreatic agenesis,[334,335] heterozygous *HNF1B* mutations,[336,337] isolated inherited deficiencies of pancreatic digestive enzymes or duodenal enteropeptidase (enterokinase),[338] and mutations in chymotrypsin-like elastase (*CELA*) gene. Additionally, mutations in the carboxyl ester lipase (*CEL*) gene have been reported to cause diabetes and pancreatic exocrine dysfunction.[339]

What is the prevalence of PEI in infectious diseases?

Statement 11.9

Low FE-1 levels have been reported in 20%–50% of patients with HIV. PEI is possible in other infectious diseases, but its prevalence remains unknown.

Level of evidence: 4; *Percentage of agreement*: 93.8%

Comment: Symptomatic PEI has been documented in 20%–50% of patients with chronic HIV infection.[340–343] There are many studies in the literature indicating an association between bacterial pathogens and AP.[344] However, the existing literature is usually of low quality and ancient. Tuberculosis has been described in the first patient ever treated with pancreatic extracts for PEI; however, the rate of PEI is unknown.[345] Parasites with reported AP associations include Ascaris lumbricoides, Fasciola hepatica, and Echinococcus granulosus.[344] One of the largest studies in an Indian endemic area found ascariasis in 23% of patients with AP; however, no data on PEI are available.[346]

What is the prevalence of PEI in chronic liver/biliary diseases?

Statement 11.10

There is no strong evidence for PEI in patients with chronic hepatobiliary diseases other than excessive alcohol consumption (see statement 11.2 for PEI in non-alcoholic fatty liver disease and non-alcoholic fatty pancreas disease).

Level of evidence: 4; *Percentage of agreement*: 98.5%

Comment: Reduced exocrine pancreatic function is rarely observed in patients with biliary or hepatic disease.[347] A retrospective analysis of 37 patients (10 children and 27 adults) who underwent endoscopic retrograde cholangiopancreatography for choledochal cysts revealed no evidence of PEI.[348] In a study of 40 children with extrahepatic and intrahepatic cholestasis, FE-1 levels were within the normal range.[349] Normal exocrine pancreatic function was demonstrated by the secretin-pancreozymin test in five patients with Wilson's disease, either without or with cirrhosis, but without portal hypertension.[350]

What is the prevalence of PEI in chronic renal failure/chronic uremia?

Statement 11.11

The prevalence of PEI in chronic kidney disease (CKD) has been reported in up to 72% of patients. However, these studies are of low quality.

Level of evidence: 4; *Percentage of agreement*: 92.3%

Comment: Pancreatic secretion, as assessed using the secretin-pancreozymin test, was found to be abnormal in 72% of patients with CKD.[351] Another study using the same test showed significantly reduced amylase secretion, total secretory volume, and bicarbonate secretion in patients with CKD.[352] There are no specific data on the PEI and PERT in these patients.

What is the prevalence of PEI in patients under somatostatin treatment?

Statement 11.12

The prevalence of PEI varies from 8% to 24% in patients treated with somatostatin analogs (SSAs).

Level of evidence: 4; Percentage of agreement: 98.5%

Comment: SSAs significantly inhibit pancreatic enzyme secretion and suppress the release of hormones, including secretin, CCK, and motilin.[353–356] In a study of patients treated with lanreotide alone or in combination with interferon alpha, steatorrhea was present in 8% of patients treated with lanreotide alone but in none of those treated with combined therapy.[357] Pancreatic secretion, as assessed by the FE-1 test, was slightly reduced in 20% of patients with non-pancreatic neuroendocrine tumors (NETs) treated with SSAs for at least 1 year, with no patients having an FE-1 <100 μg/g.[358] In another study involving 50 patients with well-differentiated NET, PEI was reported in 12 (24%) patients at a median of 2.9 months after initiation of SSAs.[359] The quantitative fecal fat test was abnormal in 17% of patients with NET on SSA therapy, with a median time to PEI of 12 months.[360]

What is the prevalence of PEI in patients with pancreatic tumors other than PC?

Statement 11.13

The prevalence of PEI in patients with pancreatic neoplasms other than ductal adenocarcinoma remains unknown. Most studies on these patients reported postoperative PEI. Patients with pancreatic NETs may develop PEI, which may be due to long-term treatment with SSAs.

Level of evidence: 4; Percentage of agreement: 92.5%

Comment: Most available studies on PEI in patients with PNETs present data on pancreatic function and nutritional status in patients treated with SSAs (see Statement 11.12) or after tumor resection (see Chapter 8). In a retrospective study of 82 patients (von Hippel-Lindau, $n = 25$; multiple endocrine neoplasia type I, $n = 20$; sporadic, $n = 37$) who underwent resection of PNETs, none had a recorded preoperative PEI.[361] In a prospective study using the FE-1 test, pancreatic secretion was reduced in 24% of patients with well-differentiated NET.[359] However, in another study, FE-1 levels in patients with gastroenteropancreatic NET tended to be lower but were not significantly different in patients with or without SSA therapy.[362]

What is the prevalence of PEI in patients with chronic heart failure (CHF)?

Statement 11.14

Low levels of FE-1 have been reported in 6.9%–56.7% of patients with CHF.

Level of evidence: 4; Percentage of agreement: 88.9%

Comment: Reduced splanchnic blood flow may affect pancreatic function in patients with CHF. Pancreatic secretion, as assessed using the FE-1 test, was abnormally low in 6.9% of patients with CHF.[363] In addition, FE-1 levels were significantly lower in patients with CHF than in controls.[364] In another study, PEI was reported in 56.7% of patients with CHF and in none of the patients with normal heart function.[365] In this study, patients with PEI were randomized to receive PERT or a placebo, and PERT was associated with a significant improvement in appetite loss.[365]

What is the prevalence of PEI in patients with Sjögren's syndrome?

Statement 11.15

The prevalence of PEI in patients with Sjögren's syndrome (SS) varies widely, ranging 0%–63%, depending on the method used for PEI diagnosis. However, the quality of the evidence is low.

Level of evidence: 4; Percentage of agreement: 92.1%

Comment: Pancreatic function based on the BT-PABA test was found to be abnormal in 37.5% of patients with SS compared with none of the controls.[366] In a similar study, 63% of the patients were reported to have abnormal pancreatic function.[367] Pancreatic dysfunction has been found in 25%–33% of patients with SS using sMRCP and the Lundh test.[368] Finally, pancreatic function, as evaluated by FE-1 and 13C-MTG breath tests, was reported as normal in 57 patients with primary SS.[369]

DISCUSSION

The first relevant consensus reached in this document is the definition of PEI as a reduction in exocrine pancreatic secretion to the level that prevents normal digestion of nutrients. This has important clinical implications as the threshold for PEI can be influenced by several factors; therefore, reduced pancreatic secretion should not be considered synonymous with PEI. It is generally accepted that a reduction in pancreatic secretion of more than 90% of normal is required for maldigestion to develop.[1] The common clinical scenario of pancreatic secretion that is reduced but sufficient for normal nutrient digestion cannot be defined as PEI but as exocrine pancreatic dysfunction. This concept should be considered in the diagnosis of PEI in clinical practice and future clinical trials.

The second important consequence of this definition is that it challenges existing scientific evidence on PEI. Many clinical studies on PEI have used abnormal results in pancreatic secretion tests such as FE-1 as criteria for defining PEI. Consequently, patients with pancreatic dysfunction are often mistakenly diagnosed as having PEI, leading to biased results.

Because tests to assess nutrient digestion are either cumbersome (e.g., CFA) or of limited availability (e.g., 13C-MTG breath test), this guideline proposes, as a general rule, the global assessment of PEI-related symptoms, nutritional status, and pancreatic secretion to diagnose PEI in an appropriate clinical scenario until simple and accurate digestion tests are widely available. Different likelihoods of PEI in different clinical conditions significantly influence the diagnostic approach for PEI in clinical practice. The specificities of PEI-based diagnosis for different diseases are presented in this document.

Due to the malabsorption of nutrients, abdominal and bowel symptoms and nutritional deficiencies are among the consequences of PEI that affect patients' QoL and are associated with long-term malnutrition-related complications.[27,45–47,62,66,86–89,156,190,270] Therefore, PEI always requires treatment, and relief of symptoms and normalization of nutritional status are the therapeutic goals. Other clinical consequences of PEI are disease-specific and are described in this document.

Generally, the PEI treatment is based on nutritional advice and support and PERT. The PERT dose should be individualized and is likely to be influenced by the severity of PEI and dietary habits (amount, calories, and fat content of food). Although a starting dose of 40,000–50,000 units with main meals and half of this dose with snacks is generally recommended for adult patients,[24] this dose may be insufficient in patients with severe PEI, such as those with PC and those who have undergone pancreatoduodenectomy or total

pancreatectomy.[182,248] Acidic intraluminal gut pH is a known factor that influences the efficacy of PERT, and the addition of PPI to PERT may be required.[121,122] The specificities of the PEI therapy for different diseases are outlined in this document.

Unmet needs and future directions (Figure 2)

The unmet needs identified in each chapter were derived from a review of relevant scientific evidence, and were proposed by each WG. They were then endorsed by consensus.

Despite the large number of published studies, the scientific evidence on PEI is rather weak. The change in the concept of PEI, as a reduction in pancreatic secretion severe enough to affect the digestion of nutrients, means that a relevant proportion of previously published studies no longer fit the new concept.

Considering the concept of PEI reported in these guidelines, the actual prevalence of PEI in various pancreatic diseases, pancreatic and gastrointestinal surgeries, and other clinical conditions remains largely unknown. Most studies rely on the results of the FE-1 test, which reflects the secretion but not the digestive capacity of the pancreas. Although the FE-1 test is sensitive for diagnosing PEI, its specificity is not higher than expected. The prevalence of PEI may have been overestimated in different clinical scenarios. Therefore, there is a need for new epidemiological studies that include patients diagnosed with PEI based on the current recommendations.

Therefore, the development of a test or biomarker for diagnosing PEI is urgently required. The CFA remains the reference method for PEI diagnosis. However, this test is cumbersome, unpleasant, and difficult to comply with. The 13C-MTG breath test is a promising alternative to CFA, but is currently only available in a limited number of countries, and standardization is still required.[76] Therefore, research on new biomarkers for the diagnosis of PEI should be encouraged.

The treatment of PEI is another area where there are still many unmet needs. Except for the clinical trials that included patients based on CFA, most other therapeutic trials on PERT are biased by the inappropriate inclusion of patients. In contrast, the requirement of using CFA as the main outcome to evaluate the efficacy of PERT in patients with PEI significantly limits the inclusion of patients in clinical trials. In this context, the 13C-MTG breath test is much simpler and probably as effective as CFA[76,77]; however, it has not yet been approved by drug authorities. Other outcomes such as symptom relief, QoL using patient-reported outcome instruments, and nutritional improvement are clinically relevant.

Most of the available evidence on PERT is based on enzyme preparations containing small enteric-coated pellets of porcine origin.[27,39,84,193] Other preparations, including those commercially available in certain countries, have been evaluated to a lesser extent. Furthermore, owing to the limited production capacity of porcine enzymes, new enzyme preparations from other sources are urgently needed.

The optimal and most effective enzyme dose for different diseases and clinical conditions, the relationship between the enzyme dose and clinical effect, and the importance of modifying the intraluminal pH on the efficacy of PERT are areas where more robust evidence is needed.

CONCLUSION

The definition, pathogenesis, clinical consequences, diagnosis, treatment, and monitoring of PEI in different clinical conditions have been systematically reviewed, and a consensus has been reached regarding these multidisciplinary, evidence-based European clinical guidelines. It also highlights the unmet needs and areas where scientific evidence is weak or lacking to guide future research. PEI is associated with maldigestion and malabsorption of nutrients, resulting in intestinal malabsorption and nutritional deficiencies that negatively affect the patients' QoL and are associated with long-term malnutrition-related complications and mortality. Along with appropriate management of the underlying conditions causing PEI, knowledge of when and how to diagnose PEI, optimal therapy and therapeutic goals, and appropriate monitoring of patients are essential to reduce the risk of complications and improve the QoL and survival of patients with PEI.

ACKNOWLEDGMENTS

The authors thank the following member societies of the United European Gastroenterology (UEG) for participating in and endorsing these guidelines: European Digestive Surgery (EDS), European Society for Primary Care Gastroenterology (ESCPG), European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), European Society for Clinical Nutrition and Metabolism (ESPEN), European Society of Digestive Oncology (ESDO), and European Society of Primary Care Gastroenterology (ESPCG). We thank the UEG for the unrestricted educational grant, which enabled the independent conduct of these guidelines. The authors are indebted to Dawn Swibold, general manager at the EPC, for assisting in the development of these guidelines. The authors would like to express their gratitude to Jin Lee (President of the Korean Pancreatobiliary Association, Hallym University Dongtan Sacred Heart Hospital, South Korea), Kyoichi Takaori (Kyoto University, Dept. of Surgery, Division of Hepatobiliary-Pancreatic Surgery and Transplantation, Japan), and Oscar Mazza (Department of Surgery, Hospital Italiano, Buenos Aires, Argentina) for their invaluable contributions as an independent group of experts. The authors would like to thank the patient organizations PC Europe (PCE), PALEMA (Sweden), and the German "Arbeitskreis der Pankreatektomierten" (AdP) for their invaluable contributions to the development of these guidelines. The following colleagues contributed as WG members and as members of the European PEI Multidisciplinary Group are co-authors of these guidelines: Hana Algül: Comprehensive Cancer Center Munich TUM, Institute for Tumor Metabolism, Technical University of Munich, Munich, Germany. Livia Archibugi: Pancreatobiliary Endoscopy and Endosonography Division, Pancreas Translational & Clinical Research Center, IRCCS San Raffaele Scientific Institute, Milan, Italy; Vita-Salute San Raffaele University, Milan, Italy. Marianna Arvanitakis: Service de Gastroenterologie, d'Hepato-Pancreatologie et d'Oncologie digestive, Hopital Erasme, HUB, Bruxelles, Belgium. Sorin Barbu, Ovidiu Fabian: 4th Surgery Department, University of Medicine and Pharmacy "Iuliu Hatieganu" Cluj-Napoca, Romania. Georg Beyer, Julia Mayerle: Department of

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CONFLICT OF INTEREST STATEMENT

The authors' conflicts of interest are listed in Appendix 2.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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How to cite this article: Dominguez-Muñoz JE, Vujasinovic M, de la Iglesia D, Cahen D, Capurso G, Gubergrits N, et al. European guidelines for the diagnosis and treatment of pancreatic exocrine insufficiency: UEG, EPC, EDS, ESPEN, ESPGHAN, ESDO, and ESPCG evidence-based recommendations. United European Gastroenterol J. 2024;1–48. https://doi.org/10.1002/ueg2.12674

APPENDIX 1

Basis for the design of PICO questions

The following constituted the basis for the design of PICO questions:

Observational studies: patients, adults or children with PEI; intervention/exposure, underlying disease, risk factor or mechanism; comparator, control population if available; outcome, prevalence, clinical consequences.

Studies on diagnostic tests and diagnostic approaches: patients, adults or children with PEI; intervention, diagnostic test or procedure; comparator, reference method; outcome, diagnostic accuracy.

Studies on treatment and therapeutic approaches: patients: adults or children with PEI; intervention: active treatment or therapeutic approach; comparator: either placebo or the standard of care; outcome: efficacy, which is measured in terms of digestion, symptom relief, quality of life, or nutritional improvement, and safety.

Search strategy

Search of scientific evidence was performed until July 2022 in Medline, Embase, Scopus and Cochrane Central Register of Controlled Trial. The search strategy in each individual group was as follows.

Chapter 1

(((((((("exocrine pancreatic insufficiency"[MeSH Terms] OR ("exocrine pancreatic insufficiency"[MeSH Terms] OR ("exocrine"[All Fields] AND "pancreatic"[All Fields] AND "insufficiency"[All Fields]) OR "exocrine pancreatic insufficiency"[All Fields])) AND "pancreatic juice"[MeSH Terms]) OR ("pancreatic juice"[MeSH Terms] OR ("pancreatic"[All Fields] AND "juice"[All Fields]) OR "pancreatic juice"[All Fields] OR ("pancreatic"[All Fields] AND "secretion"[All Fields]) OR "pancreatic secretion"[All Fields])) AND "malnutrition"[MeSH Terms]) OR ("malnutrition"[MeSH Terms] OR "malnutrition"[All Fields] OR ("nutritional"[All Fields] AND "deficiencies"[All Fields]) OR "nutritional deficiencies"[All Fields])) AND "morbidity"[MeSH Terms]) OR ("epidemiology"[MeSH Subheading] OR "epidemiology"[All Fields] OR "morbidity"[All Fields] OR "morbidity"[MeSH Terms] OR "morbid"[All Fields] OR "morbidities"[All Fields] OR "morbids"[All Fields])) AND "mortality"[MeSH Terms]) OR ("mortality"[MeSH Terms] OR "mortality"[All Fields] OR "mortalities"[All Fields] OR "mortality"[MeSH Subheading])

Chapter 2

(("exocrine pancreatic insufficiency"[MeSH Terms] OR ("exocrine"[All Fields] AND "pancreatic"[All Fields] AND "insufficiency"[All Fields]) OR "exocrine pancreatic insufficiency"[All Fields]) AND ("diagnosable"[All Fields] OR "diagnosis"[All Fields] OR "diagnosis"[MeSH Terms] OR "diagnosis"[All Fields] OR "diagnose"[All Fields] OR "diagnosed"[All Fields] OR "diagnoses"[All Fields] OR "diagnosing"[All Fields] OR "diagnosis"[MeSH Subheading])) OR ("pancreatic function tests"[MeSH Terms] OR ("pancreatic"[All Fields] AND "function"[All Fields] AND "tests"[All Fields]) OR "pancreatic function tests"[All Fields] OR ("pancreatic"[All Fields] AND "function"[All Fields] AND "test"[All Fields]) OR "pancreatic function test"[All Fields]) OR (("faecally"[All Fields] OR "fecally"[All Fields] OR "fecals"[All Fields] OR "feces"[MeSH Terms] OR "feces"[All Fields] OR "faecal"[All Fields] OR "fecal"[All Fields]) AND ("elastases"[All Fields] OR "pancreatic elastase"[MeSH Terms] OR ("pancreatic"[All Fields] AND "elastase"[All Fields]) OR "pancreatic elastase"[All Fields] OR "elastase"[All Fields])) OR ("secretin"[MeSH Terms] OR "secretin"[All Fields] OR "secretins"[All Fields]) OR (("faecally"[All Fields] OR "fecally"[All Fields] OR "fecals"[All Fields] OR "feces"[MeSH Terms] OR "feces"[All Fields] OR "faecal"[All Fields] OR "fecal"[All Fields]) AND "fat"[All Fields]) OR (("coefficiencies"[All Fields] OR "coefficiency"[All Fields] OR "coefficient"[All Fields] OR "coefficient s"[All Fields] OR "coefficients"[All Fields]) AND "fat"[All Fields] AND ("absorptance"[All Fields] OR "absorptances"[All Fields] OR "absorption"[MeSH Terms] OR "absorption"[All Fields] OR "absorptions"[All Fields] OR "absorptive"[All Fields] OR "absorptivities"[All Fields] OR "absorptivity"[All Fields])) OR (("nutrition s"[All Fields] OR "nutritional status"[MeSH Terms] OR ("nutritional"[All Fields] AND "status"[All Fields]) OR "nutritional status"[All Fields] OR "nutrition"[All Fields] OR "nutritional sciences"[MeSH Terms] OR ("nutritional"[All Fields] AND "sciences"[All Fields]) OR "nutritional sciences"[All Fields] OR "nutritional"[All Fields] OR "nutritionals"[All Fields] OR "nutritions"[All Fields] OR "nutritive"[All Fields]) AND ("marker"[All Fields] OR "markers"[All Fields])) OR ("diagnosis"[MeSH Subheading] OR "diagnosis"[All Fields] OR "symptoms"[All Fields] OR "diagnosis"[MeSH Terms] OR "symptom"[All Fields] OR "symptom s"[All Fields] OR "symptomes"[All Fields]) OR ("steatorrhoea"[All Fields] OR "steatorrhea"[MeSH Terms] OR "steatorrhea"[All Fields]) OR ("diarrhea"[MeSH Terms] OR "diarrhea"[All Fields] OR "diarrheas"[All Fields] OR "diarrhoea"[All Fields] OR "diarrhoeas"[All Fields]) OR ("breath tests"[MeSH Terms] OR ("breath"[All Fields] AND "tests"[All Fields]) OR "breath tests"[All Fields] OR ("breath"[All Fields] AND "test"[All Fields]) OR "breath test"[All Fields]) OR (("nutrition s"[All Fields] OR "nutritional status"[MeSH Terms] OR ("nutritional"[All Fields] AND "status"[All Fields]) OR "nutritional status"[All Fields] OR "nutrition"[All Fields] OR "nutritional sciences"[MeSH Terms] OR ("nutritional"[All Fields] AND "sciences"[All Fields]) OR "nutritional sciences"[All Fields] OR "nutritional"[All Fields] OR "nutritionals"[All Fields] OR "nutritions"[All Fields] OR "nutritive"[All Fields]) AND ("assesed"[All Fields] OR "assesment"[All Fields] OR "assesments"[All Fields])) OR ("weight loss"[MeSH Terms] OR ("weight"[All Fields] AND "loss"[All Fields]) OR "weight loss"[All Fields]) OR ("body mass index"[MeSH Terms] OR ("body"[All Fields] AND "mass"[All Fields] AND "index"[All Fields]) OR "body mass index"[All Fields]) OR ("anthropometries"[All Fields] OR "anthropometry"[MeSH Terms] OR "anthropometry"[All Fields]) OR ("tomography, x ray computed"[MeSH Terms] OR ("tomography"[All Fields] AND "x ray"[All Fields] AND "computed"[All Fields]) OR "x-ray computed tomography"[All Fields] OR ("computed"[All Fields] AND "tomography"[All Fields]) OR "computed tomography"[All Fields]) OR ("magnetic resonance imaging"[MeSH Terms] OR ("magnetic"[All Fields] AND "resonance"[All Fields] AND "imaging"[All Fields]) OR "magnetic resonance imaging"[All Fields]) OR (("empiric"[All Fields] OR "empirical"[All Fields] OR "empirically"[All Fields] OR "empirics"[All Fields]) AND ("pancreas"[MeSH Terms] OR "pancreas"[All Fields] OR "pancreatic"[All Fields] OR "pancreatitides"[All Fields] OR "pancreatitis"[MeSH Terms] OR "pancreatitis"[All Fields]) AND ("enzyme replacement therapy"[MeSH Terms] OR ("enzyme"[All Fields] AND "replacement"[All Fields] AND "therapy"[All Fields]) OR "enzyme replacement therapy"[All Fields]))

Chapter 3

((((“exocrine pancreatic insufficiency”[MeSH Terms] OR (“exocrine pancreatic insufficiency”[MeSH Terms] OR (“exocrine”[All Fields] AND “pancreatic”[All Fields] AND “insufficiency”[All Fields]) OR “exocrine pancreatic insufficiency”[All Fields])) AND ((“pancreas”[MeSH Terms] OR “pancreas”[All Fields] OR “pancreatic”[All Fields] OR “pancreatitides”[All Fields] OR “pancreatitis”[MeSH Terms] OR “pancreatitis”[All Fields]) AND “enzyme replacement therapy”[MeSH Terms])) OR ((“pancreas”[MeSH Terms] OR “pancreas”[All Fields] OR “pancreatic”[All Fields] OR “pancreatitides”[All Fields] OR “pancreatitis”[MeSH Terms] OR “pancreatitis”[All Fields]) AND (“enzyme replacement therapy”[MeSH Terms] OR (“enzyme”[All Fields] AND “replacement”[All Fields] AND “therapy”[All Fields]) OR “enzyme replacement therapy”[All Fields])))) AND (“nutritional status”[MeSH Terms] OR “nutritional sciences”[MeSH Terms])) OR (“nutrition s”[All Fields] OR “nutritional status”[MeSH Terms] OR (“nutritional”[All Fields] AND “status”[All Fields]) OR “nutritional status”[All Fields] OR “nutrition”[All Fields] OR “nutritional sciences”[MeSH Terms] OR (“nutritional”[All Fields] AND “sciences”[All Fields]) OR “nutritional sciences”[All Fields] OR “nutritional”[All Fields] OR “nutritionals”[All Fields] OR “nutritions”[All Fields] OR “nutritive”[All Fields])

((((((((((((((((((((nutritional intervention[Title/Abstract]) OR (dietary intervention[Title/Abstract])) OR (dietary therapy[Title/Abstract])) OR (nutritional therapy[Title/Abstract])) OR (dietary advice [Title/Abstract])) OR (dietary counseling[Title/Abstract])) OR (dietary supplementation[Title/Abstract])) OR (dietary supplements[Title/Abstract])) OR (enteral feeding[Title/Abstract])) OR (tube feeding [Title/Abstract])) OR (parenteral feeding[Title/Abstract])) OR (intravenous feeding[Title/Abstract])) OR (vitamin deficiency[Title/Abstract])) OR (nutrient deficiency[Title/Abstract])) OR (vitamin supplement[Title/Abstract])) OR (nutrient supplement[Title/Abstract])) OR (meal plan[Title/Abstract])) OR (dietary plan[Title/Abstract])) OR (dietary pattern[Title/Abstract])) OR (nutritional status [Title/Abstract])) AND ((pancreatic exocrine insufficiency[Title/Abstract]) OR (exocrine pancreatic insufficiency[Title/Abstract]))

((chronic pancreatitis[Title/Abstract]) AND ((pancreatic exocrine insufficiency[Title/Abstract]) OR (exocrine pancreatic insufficiency [Title/Abstract]))) AND (((management[Title/Abstract]) OR (intervention[Title/Abstract])) OR (treatment[Title/Abstract]) AND (clinicaltrial[Filter] OR randomizedcontrolledtrial[Filter]))

Chapter 4

((((“exocrine pancreatic insufficiency”[MeSH Terms] OR (“exocrine pancreatic insufficiency”[MeSH Terms] OR (“exocrine”[All Fields] AND “pancreatic”[All Fields] AND “insufficiency”[All Fields]) OR “exocrine pancreatic insufficiency”[All Fields])) AND ((“chronic pancreatitis”[MeSH Terms]) OR (“chronic pancreatitis”[All Fields])) AND (“enzyme replacement therapy”[MeSH Terms] OR (“enzyme”[All Fields] AND “replacement”[All Fields] AND “therapy”[All Fields]) OR “enzyme replacement therapy”[All Fields])) AND (“malnutrition”[MeSH Terms]) OR (“malnutrition”[MeSH Terms] OR “malnutrition”[All Fields] OR (“nutritional”[All Fields] AND “deficiencies”[All Fields]) OR “nutritional deficiencies”[All Fields])) AND “morbidity”[MeSH Terms]) OR (“epidemiology”[MeSH Subheading] OR “epidemiology”[All Fields] OR “morbidity”[All Fields] OR “morbidity”[MeSH Terms] OR “morbid”[All Fields] OR “morbidities”[All Fields] OR “morbids”[All Fields])) AND “mortality”[MeSH Terms]) OR (“mortality”[MeSH Terms] OR “mortality”[All Fields] OR “mortalities”[All Fields] OR “mortality”[MeSH Subheading])

Chapter 5

(“exocrine pancreatic insufficiency”[MeSH Terms] OR (“exocrine”[All Fields] AND “pancreatic”[All Fields] AND “insufficiency”[All Fields]) OR “exocrine pancreatic insufficiency”[All Fields]) AND (“pancreatitis”[MeSH Terms] OR “pancreatitis”[All Fields] OR (“acute”[All Fields] AND “pancreatitis”[All Fields]) OR “acute pancreatitis”[All Fields])

Chapter 6

((“exocrine pancreatic insufficiency”[MeSH Terms] OR (“exocrine”[All Fields] AND “pancreatic”[All Fields] AND “insufficiency”[All Fields]) OR “exocrine pancreatic insufficiency”[All Fields]) AND (“pancreatic neoplasms”[MeSH Terms] OR (“pancreatic”[All Fields] AND “neoplasms”[All Fields]) OR “pancreatic neoplasms”[All Fields] OR (“pancreatic”[All Fields] AND “cancer”[All Fields]) OR “pancreatic cancer”[All Fields])) OR ((“pancreas”[MeSH Terms] OR “pancreas”[All Fields] OR “pancreatic”[All Fields] OR “pancreatitides”[All Fields] OR “pancreatitis”[MeSH Terms] OR “pancreatitis”[All Fields]) AND “ductal”[All Fields] AND (“adenocarcinoma”[MeSH Terms] OR “adenocarcinoma”[All Fields] OR “adenocarcinomas”[All Fields] OR “adenocarcinoma s”[All Fields])) OR ((“faecally”[All Fields] OR “fecally”[All Fields] OR “fecals”[All Fields] OR “feces”[MeSH Terms] OR “feces”[All Fields] OR “faecal”[All Fields] OR “fecal”[All Fields]) AND (“elastases”[All Fields] OR “pancreatic elastase”[MeSH Terms] OR (“pancreatic”[All Fields] AND “elastase”[All Fields]) OR “pancreatic elastase”[All Fields] OR “elastase”[All Fields])) OR ((“pancreas”[MeSH Terms] OR “pancreas”[All Fields] OR “pancreatic”[All Fields] OR “pancreatitides”[All Fields] OR “pancreatitis”[MeSH Terms] OR “pancreatitis”[All Fields]) AND (“functional”[All Fields] OR “functional s”[All Fields] OR “functionalities”[All Fields] OR “functionality”[All Fields] OR “functionalization”[All Fields] OR “functionalizations”[All Fields] OR “functionalize”[All Fields] OR “functionalized”[All Fields] OR “functionalizes”[All Fields] OR “functionalizing”[All Fields] OR “functionally”[All Fields] OR “functionals”[All Fields] OR “functioned”[All Fields] OR “functioning”[All Fields] OR “functionings”[All Fields] OR “functions”[All Fields] OR “physiology”[MeSH Subheading] OR “physiology”[All Fields] OR “function”[All Fields] OR “physiology”[MeSH

Terms])) OR ((“pancreas”[MeSH Terms] OR “pancreas”[All Fields] OR “pancreatic”[All Fields] OR “pancreatitides”[All Fields] OR “pancreatitis”[MeSH Terms] OR “pancreatitis”[All Fields]) AND (“enzyme replacement therapy”[MeSH Terms] OR (“enzyme”[All Fields] AND “replacement”[All Fields] AND “therapy”[All Fields]) OR “enzyme replacement therapy”[All Fields]))

Chapter 7

((“exocrine pancreatic insufficiency”[MeSH Terms] OR (“exocrine”[All Fields] AND “pancreatic”[All Fields] AND “insufficiency”[All Fields]) OR “exocrine pancreatic insufficiency”[All Fields]) AND (“cystic fibrosis”[MeSH Terms] OR (“cystic”[All Fields] AND “fibrosis”[All Fields]) OR “cystic fibrosis”[All Fields])) OR “CFTR”[All Fields] OR ((“faecally”[All Fields] OR “fecally”[All Fields] OR “fecals”[All Fields] OR “feces”[MeSH Terms] OR “feces”[All Fields] OR “faecal”[All Fields] OR “fecal”[All Fields]) AND (“elastases”[All Fields] OR “pancreatic elastase”[MeSH Terms] OR (“pancreatic”[All Fields] AND “elastase”[All Fields]) OR “pancreatic elastase”[All Fields] OR “elastase”[All Fields])) OR ((“faecally”[All Fields] OR “fecally”[All Fields] OR “fecals”[All Fields] OR “feces”[MeSH Terms] OR “feces”[All Fields] OR “faecal”[All Fields] OR “fecal”[All Fields]) AND “fat”[All Fields]) OR ((“pancreas”[MeSH Terms] OR “pancreas”[All Fields] OR “pancreatic”[All Fields] OR “pancreatitides”[All Fields] OR “pancreatitis”[MeSH Terms] OR “pancreatitis”[All Fields]) AND (“enzyme replacement therapy”[MeSH Terms] OR (“enzyme”[All Fields] AND “replacement”[All Fields] AND “therapy”[All Fields]) OR “enzyme replacement therapy”[All Fields]))

Chapter 8

((“exocrine pancreatic insufficiency”[MeSH Terms] OR (“exocrine”[All Fields] AND “pancreatic”[All Fields] AND “insufficiency”[All Fields]) OR “exocrine pancreatic insufficiency”[All Fields] OR ((“pancreas”[MeSH Terms] OR “pancreas”[All Fields] OR “pancreatic”[All Fields] OR “pancreatitides”[All Fields] OR “pancreatitis”[MeSH Terms] OR “pancreatitis”[All Fields]) AND (“dysfunctional”[All Fields] OR “dysfunctionals”[All Fields] OR “dysfunctioning”[All Fields] OR “dysfunctions”[All Fields] OR “physiopathology”[MeSH Subheading] OR “physiopathology”[All Fields] OR “dysfunction”[All Fields]))) AND ((“pancreas”[MeSH Terms] OR “pancreas”[All Fields] OR “pancreatic”[All Fields] OR “pancreatitides”[All Fields] OR “pancreatitis”[MeSH Terms] OR “pancreatitis”[All Fields]) AND (“surgery”[MeSH Subheading] OR “surgery”[All Fields] OR “surgical procedures, operative”[MeSH Terms] OR (“surgical”[All Fields] AND “procedures”[All Fields] AND “operative”[All Fields]) OR “operative surgical procedures”[All Fields] OR “general surgery”[MeSH Terms] OR (“general”[All Fields] AND “surgery”[All Fields]) OR “general surgery”[All Fields] OR “surgery s”[All Fields] OR “surgerys”[All Fields] OR “surgeries”[All Fields]))) OR ((“pancreas”[MeSH Terms] OR “pancreas”[All Fields] OR “pancreatic”[All Fields] OR “pancreatitides”[All Fields] OR “pancreatitis”[MeSH Terms] OR “pancreatitis”[All Fields]) AND (“resect”[All Fields] OR “resectability”[All Fields] OR “resectable”[All Fields] OR “resectates”[All Fields] OR “resected”[All Fields] OR “resecting”[All Fields] OR “resection”[All Fields] OR “resectional”[All Fields] OR “resectioned”[All Fields] OR “resectioning”[All Fields] OR “resections”[All Fields] OR “resective”[All Fields] OR “resects”[All Fields])) OR (“pancreatectomy”[MeSH Terms] OR “pancreatectomy”[All Fields] OR “pancreatectomies”[All Fields]) OR (“pancreaticoduodenectomy”[MeSH Terms] OR “pancreaticoduodenectomy”[All Fields] OR “pancreatoduodenectomies”[All Fields] OR “pancreatoduodenectomy”[All Fields])

Chapter 9

(((“Pancreatic exocrine insufficiency” OR “Exocrine Pancreatic Insufficiency” AND English[LA]) NOT (editorial[PT] OR historical article [PT] OR comment[PT] OR case reports[PT])) NOT („animals“[MeSH] NOT „humans“[MeSH]))) AND (1960 :2018/11/30[dp]) AND (upper gastrointestinal surgery OR bariatric surgery OR general surgery OR esophagectomy OR gastrectomy OR short bowel syndrome) AND (diagnosis OR treatment OR monitoring)

((“exocrine pancreatic insufficiency”[MeSH Terms] OR (“exocrine”[All Fields] AND “pancreatic”[All Fields] AND “insufficiency”[All Fields]) OR “exocrine pancreatic insufficiency”[All Fields]) AND (“esophagectomy”[MeSH Terms] OR “esophagectomy”[All Fields] OR “esophagectomies”[All Fields] OR “oesophagectomies”[All Fields] OR “oesophagectomy”[All Fields])) OR (“gastrectomy”[MeSH Terms] OR “gastrectomy”[All Fields] OR “gastrectomies”[All Fields]) OR (“bariatric surgery”[MeSH Terms] OR (“bariatric”[All Fields] AND “surgery”[All Fields]) OR “bariatric surgery”[All Fields]) OR (“gastric bypass”[MeSH Terms] OR (“gastric”[All Fields] AND “bypass”[All Fields]) OR “gastric bypass”[All Fields]) OR ((“gastrics”[All Fields] OR “stomach”[MeSH Terms] OR “stomach”[All Fields] OR “gastric”[All Fields]) AND (“sleeve”[All Fields] OR “sleeved”[All Fields] OR “sleeves”[All Fields] OR “sleeving”[All Fields])) OR ((“duodenitis”[MeSH Terms] OR “duodenitis”[All Fields] OR “duodenum”[MeSH Terms] OR “duodenum”[All Fields] OR “duodenal”[All Fields]) AND (“switch”[All Fields] OR “switched”[All Fields] OR “switches”[All Fields] OR “switching”[All Fields] OR “switchings”[All Fields]))

Chapter 10

((“exocrine pancreatic insufficiency”[MeSH Terms] OR (“exocrine”[All Fields] AND “pancreatic”[All Fields] AND “insufficiency”[All Fields]) OR “exocrine pancreatic insufficiency”[All Fields]) AND (“diabetes mellitus”[MeSH Terms] OR (“diabetes”[All Fields] AND “mellitus”[All Fields]) OR “diabetes mellitus”[All Fields])) OR ((“pancreas”[MeSH Terms] OR “pancreas”[All Fields] OR “pancreatic”[All Fields] OR “pancreatitides”[All Fields] OR “pancreatitis”[MeSH Terms] OR “pancreatitis”[All Fields]) AND (“functional”[All Fields] OR “functional s”[All Fields] OR “functionalities”[All Fields] OR “functionality”[All

Fields] OR "functionalization"[All Fields] OR "functionalizations"[All Fields] OR "functionalize"[All Fields] OR "functionalized"[All Fields] OR "functionalizes"[All Fields] OR "functionalizing"[All Fields] OR "functionally"[All Fields] OR "functionals"[All Fields] OR "functioned"[All Fields] OR "functioning"[All Fields] OR "functionings"[All Fields] OR "functions"[All Fields] OR "physiology"[MeSH Subheading] OR "physiology"[All Fields] OR "function"[All Fields] OR "physiology"[MeSH Terms])) OR (("faecally"[All Fields] OR "fecally"[All Fields] OR "fecals"[All Fields] OR "feces"[MeSH Terms] OR "feces"[All Fields] OR "faecal"[All Fields] OR "fecal"[All Fields]) AND ("elastases"[All Fields] OR "pancreatic elastase"[MeSH Terms] OR ("pancreatic"[All Fields] AND "elastase"[All Fields]) OR "pancreatic elastase"[All Fields] OR "elastase"[All Fields])) OR (("pancreas"[MeSH Terms] OR "pancreas"[All Fields] OR "pancreatic"[All Fields] OR "pancreatitides"[All Fields] OR "pancreatitis"[MeSH Terms] OR "pancreatitis"[All Fields]) AND ("enzyme replacement therapy"[MeSH Terms] OR ("enzyme"[All Fields] AND "replacement"[All Fields] AND "therapy"[All Fields]) OR "enzyme replacement therapy"[All Fields])) OR (("endocrinal"[All Fields] OR "endocrine system"[MeSH Terms] OR ("endocrine"[All Fields] AND "system"[All Fields]) OR "endocrine system"[All Fields] OR "endocrine"[All Fields] OR "endocrines"[All Fields] OR "endocrinic"[All Fields] OR "endocrinous"[All Fields]) AND ("exocrine pancreatic insufficiency"[MeSH Terms] OR ("exocrine"[All Fields] AND "pancreatic"[All Fields] AND "insufficiency"[All Fields]) OR "exocrine pancreatic insufficiency"[All Fields] OR ("pancreatic"[All Fields] AND "insufficiency"[All Fields]) OR "pancreatic insufficiency"[All Fields]))

Chapter 11

("Pancreatic Exocrine Insufficiency"[MeSH Terms] OR "pancreatic exocrine insufficiency"[All Fields] OR "exocrine insufficiency"[All Fields] OR "ageing"[MeSH Terms] OR "ageing"[All Fields] OR "fatty pancreas"[All Fields] OR "non alcoholic fatty pancreas disease"[All Fields] OR "hemochromatosis"[MeSH Terms] OR "hemochromatosis"[All Fields] OR "celiac"[MeSH Terms] OR "celiac"[All Fields] OR "celiac disease"[All Fields] OR "inflammatory bowel disease"[MeSH Terms] OR "inflammatory bowel disease"[All Fields] OR "irritable bowel syndrome"[MeSH Terms] OR "irritable bowel syndrome"[All Fields] OR "drug"[All Fields] OR "drug related"[All Fields] OR "rare disease"[MeSH Terms] OR "rare disease"[All Fields] OR "inherited disease"[All Fields] OR "infectious disease"[MeSH Terms] OR "infectious disease"[All Fields] OR "chronic hepatobiliary disease"[All Fields] OR "chronic renal disease"[All Fields] OR "chronic uremia"[All Fields] OR "chronic kidney disease"[All Fields] OR "somatostatin"[MeSH Terms] OR "somatostatin"[All Fields] OR "pancreatic tumors"[MeSH Terms] OR "pancreatic tumors"[All Fields] OR "chronic heart failure"[MeSH Terms] OR "chronic heart failure"[All Fields] OR "Sjogren's syndrome"[MeSH Terms] OR "Sjogren's syndrome"[All Fields]) AND ("pancreas"[MeSH Terms] OR "pancreas"[All Fields] OR "pancreatic diseases"[MeSH Terms] OR "pancreatic diseases"[All Fields])

APPENDIX 2

Conflicts of interest

The authors listed below report the following conflicts of interest:

Livia Archibugi—has received honoraria from Viatris

Georg Beyer—has received honoraria from the Falk Foundation

Stefanos Bonovas—spouse is an employee of Novartis

Dmitry Bordin—has received honoraria from Abbott Laboratories

Marco Bruno—has received research grants from Boston Scientific, Pentax Medical, Mylan, AMBU, ChiRoStim, and honoraria from Boston Scientific, Pentax Medical, AMBU, and Cook Medical

Gabriele Capurso—has received honoraria from Viatris, Amgen, Boston Scientific, Pangenix

Ferdinando D´Amico—has received research grants from Pfizer, AbbVie, Ferring, Galapagos, Janssen, and Nestlé, and honoraria from Sandoz, Janssen, Galapagos, Omega Pharma, Tillotts, and Takeda

Enrique de-Madaria—has received research grants from Abbott and Viatris

Daniel de la Iglesia Garcia—has received honoraria from Abbott and Viatris

Enrique Dominguez-Muñoz—has received honoraria from Abbott and Viatris, and research grants from Viatris.

Asbjørn Drewes—has received grants from Digestive Care Inc and Shionogi, and honoraria from Coloplast, Pangenics, and Shionogi

Sinead Duggan—has received research grants from the Meath Foundation, Department of Public Expenditure & Reform Innovation (Government of Ireland), and honoraria from Mylan

Nils Ewald—has received honoraria from Lilly, Novo Nordisk, and Novartis

Pierluigi Fracasso—has received honoraria from Schwabe and Reckitt

Luca Frulloni—has received honoraria from Viatris

Andrew Hopper—has received honoraria from Viatris

Pali Hungin—has received research grants from Ricketts and is a member of the ROME Foundation for Functional GI Disorders

Julio Iglesias-Garcia—has received research grants and honoraria from Viatris and Abbott

Jutta Keller—has received a research grant from Canon Medical, and honoraria from Enterra, Falk, GE Healthcare, Medtronic, Mylan, Repha GmbH, Standard Instruments, Takeda

Alexander Kleger—has received honoraria from Sanofi, Sobi, and Falk Foundation

Andrea Laghi—has received honoraria from Lument, Bracco, GE Healthcare, Geurbet Bayer

José Larino-Noia—has received honoraria from Viatris and Abbott

John Leeds—has received honoraria from Viatris

Björn Lindkvist—has received honoraria from Viatris, Takeda,

J. Matthias-Löhr—has received honoraria from Abbott, Viatris, and Nordmark

Emma Martinez-Moneo—has received honoraria from Viatris

Julia Mayerle—has received research grants from DFG, BMBF, DKH, and honoraria from the Falk Foundation

Johanna Ockenga—has received a research grant from the Innovationsfond, GBA (German government)

Alexey Okhlobystin—has received honoraria from Abbott Laboratories

Salvatore Paiella—has received honoraria from AlphaTau Medical

Lukas Perkhofer—has received research grants from Deutsche Forschungsgesellschaft, German Cancer Aid, and honoraria from AstraZeneca, Servier, and Roche

Mary Phillips—has recieved honoraria from Viatris and Nutricia Clinical Care

Goran Poropat—has received honoraria from Abbott Nutrition, Fresenius, Sandoz, and Krka Farma

Vinciane Rebours—has received research grants and honoraria from Mayoly Spindler and Viatris

Jonas Rosendahl—has received honoraria from the Falk Foundation, Nordmark, Viatris, Alexxion, MicroTech

Oleg Shvets—has received honoraria from Abbott, Takeda, Berlin-Chemie, Nutricia, B.Braun

Hester Timmerhuis—has received honoraria from Viatris and Tramedico

Miroslav Vujasinovic—has received honoraria from Viatris and Abbott

Michael Wilschanski—has received a research grant from Vertex Pharmaceuticals, and honoraria from Synspira