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Diagnosis and treatment of exocrine pancreatic insufficiency in chronic pancreatitis: An international expert survey and case vignette study

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ABSTRACT

Introduction: Despite evidence-based guidelines, exocrine pancreatic insufficiency is frequently underdiagnosed and undertreated in patients with chronic pancreatitis. Therefore, the aim of this study is to provide insight into the current opinion and clinical decision-making of international pancreatologists regarding the management of exocrine pancreatic insufficiency.
Methods: An online survey and case vignette study was sent to experts in chronic pancreatitis and members of various pancreatic associations: EPC, E-AHPBA and DPSG. Experts were selected based on publication record from the past 5 years.
Results: Overall, 252 pancreatologists participated of whom 44% had $\geq$ 15 years of experience and 35% treated $\geq$ 50 patients with chronic pancreatitis per year. Screening for exocrine pancreatic insufficiency as part of the diagnostic work-up for chronic pancreatitis is performed by 69% and repeated annually by 21%. About 74% considers nutritional assessment to be part of the standard work-up. Patients are most frequently screened for deficiencies of calcium (47%), iron (42%), vitamin D (61%) and albumin (59%). In case of clinically steatorrhea, 71% prescribes enzyme supplementation. Of all pancreatologists, 40% refers more than half of their patients to a dietician. Despite existing guidelines, 97% supports the need for more specific and tailored instructions regarding the management of exocrine pancreatic insufficiency.
Conclusion: This survey identified a lack of consensus and substantial practice variation among international pancreatologists regarding guidelines pertaining the management of exocrine pancreatic insufficiency. These results highlight the need for further adaptation of these guidelines according to current expert opinion and the level of available scientific evidence.

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1. Introduction

Chronic pancreatitis (CP) is characterized by long-standing inflammation of pancreatic tissue with a considerable negative impact on quality of life (QoL) [1,2]. Estimating true prevalence rates of CP is difficult since not all patients receive specialized hospital care [3]. CP is often complicated by exocrine pancreatic insufficiency (EPI), which, when not treated properly, can lead to maldigestion and malnutrition [4]. Prevalence estimates for EPI among patients with CP range from 35% to 50% within 10 and 15 years after diagnosis and increase substantially after 15 years [3]. The clinical presentation of EPI varies widely between patients. While symptoms of EPI can include overt steatorrhea or other less specific symptoms such as diarrhea, weight loss, abdominal pain and abdominal distension, some patients remain asymptomatic. However, even asymptomatic patients often develop deficiencies of fat-soluble vitamins and micronutrients due to an abnormal digestion of macronutrients, also called 'subclinical EPI' [4–7]. Nutritional deficiencies in patients with CP are associated with an increased risk of malnutrition-related complications, cardiovascular events and mortality [8]. Importantly, EPI negatively impacts a patients' QoL and adequate treatment with pancreatic enzyme replacement therapy (PERT) is associated with improvements in patients' well-being [9]. Therefore, regular screening for and adequate treatment of EPI in patients with CP is crucial to reduce the risk of complications and improve patients' outcomes. For this reason, current guidelines advise testing for EPI at the time of diagnosis and annually thereafter if not present [10]. However, despite these recommendations, EPI is often underdiagnosed and undertreated in daily practice [11–13]. The Dutch Pancreatitis Study Group (DPSG) recently evaluated the level of care for CP patients in the Netherlands by using the HaPanEU-guidelines as reference standard [14]. A similar study was recently performed at the Karolinska University Hospital in Stockholm [15]. Both studies showed there is suboptimal compliance with these guidelines, especially for the management of EPI. These findings highlight the need for a more optimal implementation in clinical practice of the recommended standardized work-up and treatment strategy of EPI in patients with CP. Possible explanations for suboptimal compliance with existing guidelines are unawareness of their existence and a lack of consensus amongst pancreatologists regarding the proposed diagnostic criteria and appropriate testing for EPI. It is unclear whether similar issues exist in other countries. Therefore, the aim of this survey is to gain more insight into the current opinion and clinical decision-making process of international pancreatologists regarding the diagnostic approach and treatment of EPI in patients with CP.

2. Methods

2.1. Study design

We performed an online international expert survey and case vignette study to explore current practice regarding diagnosis and management of EPI in patients with CP. In order to obtain a broad impression of the level of current practice, this survey was distributed among both CP experts and members of different major associations of pancreatology and hepato-pancreato-biliary surgery, including the European Pancreatic Club (EPC), the European-African Hepato-Pancreato-Biliary Association (E-AHPBA) and Dutch Pancreatitis Study Group (DPSG). The membership lists of these associations were confidential and therefore the exact number of recipients that received an invitation to participate was not available. Experts were selected based on ≥ 5 publications on CP during the last five years and invited by email in January 2021 followed by a reminder every two weeks. Non-responders received up to two reminders.

The survey consisted of five questions regarding the respondents' profile and experience in treating patients with CP and 15 general questions focusing on the diagnosis and treatment of EPI and proceeded with five case vignettes and three statements. These case vignettes addressed different clinical cases including patients with subclinical EPI (*patient A, B and C*) as well as patients with an unsatisfactory response after pancreatic enzyme replacement therapy (*patient D and E*). Consensus was defined as agreement by at least 80% of all respondents. This level was chosen because the same level of agreement has been used by the HaPanEU-guidelines to grade the strength of recommendations [10]. The survey was designed by a multidisciplinary writing committee (FR, CV, MBes, JH, HS, JD, PJ, MB and RV). All questions were tested for clarity and content by a native English speaker. An overview of the survey content is provided in the Supplementary Appendix. Survey responses were anonymously collected by using REDCap electronic data capture tools hosted at St. Antonius Hospital (REDCap, Vanderbilt University, projectredcap.org) [16,17]. Incomplete responses were excluded from further analysis.

2.2. Statistical analysis

Standard descriptive statistics were applied. Data were presented as frequencies with percentages for categorical data and as mean with standard deviation (SD) or median with interquartile range (IQR) for continuous data depending on normality of distribution. Subgroup analyses were performed by using the Chi-square exact test or Fisher's exact test to compare management strategies between different subgroups of pancreatologists based on specialty and experience in treating patients with CP. A two-sided alpha <0.05 was considered as statistically significant. Data were analyzed by using IBM SPSS Statistics version 26.

3. Results

3.1. Respondents profile

A total of 310 international experts were identified based on their publication record and invited to participate in the survey. In total, 107 (35%) responded of whom 47 (44%) reported to be not or no longer actively involved in the treatment of CP (i.e. basic scientists, radiologists or retirees etc.) and who were therefore excluded from further analysis. A detailed description of the identification and selection process of international (expert) pancreatologists is provided in Fig. 1. Through society invitation, another 269 respondents were included. The overall response rate after society invitation could not be calculated due to privacy restrictions. In total 329 international pancreatologists participated in this survey. The survey was completed by 252 pancreatologists (77%): 102 surgeons (41%), 142 gastroenterologists (56%) and 8 (3%) experts of other medical specialties or researchers with specific expertise in pancreatic diseases. The majority of the specialists (74%) worked at an academic center and 80% originated from Europe. About 44% ($n = 111$) had more than 15 years of experience in treating patients with CP and 88 specialists (35%) treated more than 50 CP patients per year. Demographic characteristics of the 252 international pancreatologists are provided in Table 1.

3.2. Diagnostic approach of EPI

Data regarding the diagnostic approach of EPI are presented in Table 2. Screening for EPI as part of the standard diagnostic work-up in patients newly diagnosed with CP is performed by 175

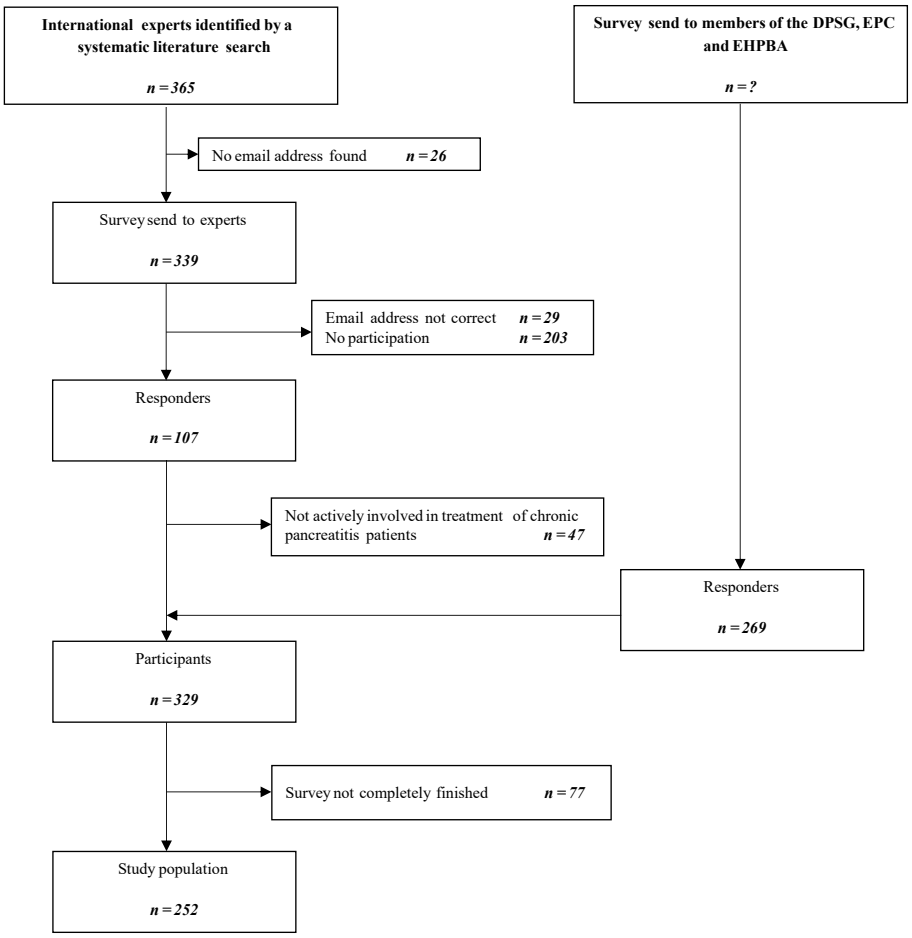

Fig. 1. Identification and selection of international expert pancreatologists.

Table 1
Demographic characteristics of the participating international pancreatologists (n = 252).

	N (%)	
Specialty		
Gastroenterologists	142	56.3%
Surgeons	102	40.5%
Other	8	3.2%
Radiologist	1	
Internist	1	
Researchers with specific expertise in pancreatic diseases	6	
Type of hospital		
Academic hospital	186	73.8%
Teaching hospital	59	23.4%
Non-teaching hospital	7	2.8%
Continent of origin		
Africa	7	2.8%
Asia	18	7.1%
Europe	202	80.2%
North-America	19	7.5%
Oceania	4	1.6%
South-America	2	0.8%
Years of experience in treating chronic pancreatitis patients		
<5 years	51	20.2%
5–15 years	90	35.7%
>15 years	111	44.0%
Number of chronic pancreatitis patients treated on an annual basis		
<10 patients	56	22.2%
10–50 patients	108	42.9%
>50 patients	88	34.9%

pancreatologists (69%). Only 54 pancreatologists (21%) agrees with annual screening for EPI and 65% (n = 163) indicates to perform a pancreatic function test (PFT) when clinical symptoms of EPI occur or deteriorate. About 87% of the pancreatologists indicates that in daily practice they consider faecal elastase-1 test (FE-1) as first-choice diagnostic modality to assess pancreatic function. No consensus is reached regarding the most appropriate cut-off value for this test. A FE-1 result of less than 200 μg/g is proposed as most optimal threshold by 59% of the pancreatologists. The vast majority (92%) agrees that the diagnostic work-up for EPI should at least include an evaluation of clinical symptoms, a PFT and measurement of nutritional laboratory markers and that when two out of these three are suspected for EPI, a diagnosis of EPI should be established (Table 5, consensus on statements). Interestingly enough, 79 pancreatologists (31%) point out that an abnormal PFT to establish EPI is required to diagnose EPI regardless of the presence of related symptoms or nutritional deficiencies. Furthermore, there is no consensus on screening for nutritional deficiencies as part of the standard work-up for EPI (74%). CP patients are most frequently screened for deficiencies of calcium (47%), iron (42%), vitamin D (61%) and albumin (59%). Data are stratified by specialty and experience with CP treatment (Supplementary Appendix, Table 2). Differences in agreement between subgroups were only significant regarding standard nutritional screening in favor of the gastroenterologists (84% vs. 59%, $p < 0.000$) and specialists treating more than 50 CP patients a year (83% vs. 69%, $p = 0.016$), both were associated with higher frequencies of screening for specific nutritional deficiencies (vitamin D, calcium and albumin).

Table 2
Survey results – diagnosis of EPI.

	Total population (n = 252)	
Indications for pancreatic function testing (multiple answers were possible)		
As part of the diagnostic work-up for CP	175	69.4%
Annually	54	21.4%
Every 1–2 years	31	12.3%
Every 2–5 years	15	6.0%
When clinical symptoms of EPI occur/deteriorate	163	64.7%
Type of diagnostic modality primarily performed in daily practice to screen for EPI		
Faecal elastase-1 test **(FE-1)**	218	86.5%
Other pancreatic function test	34	13.5%
Most appropriate cut-off value of FE-1 to discriminate between normal pancreatic function and EPI		
FE-1 < 500 μg/g	13	5.2%
FE-1 < 200 μg/g	148	58.7%
FE-1 < 100 μg/g	46	18.3%
FE-1 < 50 μg/g	9	3.6%
FE-1 < 15 μg/g	0	0.0%
No specific cut-off value	36	14.3%
An abnormal pancreatic function test is required to establish EPI		
Yes	79	31.3%
No	173	68.7%
Screening for nutritional deficiencies is part of the standard diagnostic work-up for EPI		
Yes	186	73.8%
No	66	26.2%
Nutritional blood markers (multiple answers were possible)		
Zinc	69	27.4%
Calcium	118	46.8%
Iron	105	41.7%
Magnesium	100	39.7%
Selenium	25	9.9%
Vitamin A	80	31.7%
Vitamin D	153	60.7%
Vitamin E	72	28.6%
Vitamin K	65	25.8%
Pre-albumin	78	31.0%
Albumin	149	59.1%
Retinol-binding protein	40	15.9%

3.3. Treatment of EPI

Data regarding the treatment of EPI are presented in Table 3. About 71% of respondents (n = 179) agrees that PERT is indicated when clinically evident steatorrhea occurs. Ninety-seven pancreatologists (39%) prescribe PERT in case of a positive PFT regardless of the presence of clinical signs of EPI. However, the majority of pancreatologists requires a positive PFT to be accompanied by either clinical symptoms of EPI (80%), weight loss (64%) or laboratory signs of malnutrition (60%) before starting PERT. For 23% of the pancreatologists, the initial starting dose of PERT depends on the patient's FE-1 level. About 79% agrees that nutritional assessment and support by a dietician have a prominent role in the treatment of CP irrespective of nutritional complications (Table 5, consensus on statements). However, less than half of the pancreatologists (40%) refers more than 50% of their CP patients to a dietician. Fifty-nine pancreatologists (23%) refer patients directly to a dietician without providing any dietary advice. A small majority (62%) provides nutritional counseling to every patient, while 25% (n = 62) only advises nutritional counseling to patients who they think would benefit from it and 14% (n = 35) does not address this topic because of time constraints. Dietary advice provided by at least more than half of the specialists regarding diet and PERT administration includes to consume small but frequent high-energy meals (53%), to swallow the capsules whole without chewing (71%) and to distribute the enzymes and spread out evenly over both meals and snacks (52%). A relief of maldigestion-related symptoms is pointed out by 92% of the pancreatologists as the most effective way to assess the efficacy of PERT, while 17% performs a PFT to check for efficacy (e.g. ^{13}C-MTG-BT, acid steatocrit and quantative faecal fat). In case of an unsatisfactory clinical response, 89% of pancreatologists increases the enzyme dose as a first step. About 150 pancreatologists (60%) prescribes a proton pump inhibitor as additional treatment for unresponsive patients, while 127 pancreatologists (50%) initiates a search for another cause of maldigestion. There is no agreement regarding the optimal timing of a follow-up visit to evaluate treatment effect. Almost everyone (97%) agrees that an international guideline to standardize the management of EPI is needed. (Table 5, consensus on statements). Data are stratified by specialty and experience with CP treatment (Supplementary Appendix, Table 3). Surgeons and specialists treating less than 50 CP patients annually tended to refer more patients to a dietician, while gastroenterologists and pancreatologists more experienced in treating CP patients do provide nutritional counseling and give instructions on the correct administration of PERT much more often.

3.4. Case vignettes

The results of the case vignettes are presented in Table 4. In none of the patients with subclinical EPI (patient A: positive FE-1 test and vitamin-D-deficiency in the absence of clinical symptoms, patient B: positive FE-1 test and clinical symptoms except steatorrhea, patient C: positive FE-1 test, multiple nutritional deficiencies and weight loss) consensus is reached regarding the diagnosis of EPI. The number of pancreatologists who agrees with the diagnosis are substantially higher for patient B (n = 183, 73%) and patient C (n = 149, 59%) compared with patient A (n = 112, 44%). In patient A,

Table 3
Survey results – treatment of EPI.

	Total population (n = 252)	
Indications for pancreatic enzyme replacement therapy (PERT) (multiple answers were possible)		
Clinically evident steatorrhea	179	71.0%
Positive pancreatic function test regardless of other symptoms of EPI	97	38.5%
Positive pancreatic function test and symptoms of EPI	202	80.2%
Positive pancreatic function test in combination with weight loss	160	63.5%
Positive pancreatic function test in combination with laboratory signs of malnutrition	150	59.5%
A patients' faecal elastase-1 influences the initial PERT starting dose		
Yes	59	23.4%
No	193	76.6%
Number of patients with EPI who are being referred to a dietician		
<50%	151	59.9%
≥50%	101	40.1%
Dietary advise provided to patients with EPI (multiple answers were possible)		
None, I always refer patients to a dietician	59	23.4%
To avoid high-fibre diet	28	11.1%
To avoid dietary fat-restriction	112	44.4%
To take small, frequent high-energy meals	133	52.8%
Instructions for the correct use of PERT (multiple answers were possible)		
To swallow the capsules whole and to not chew them	180	71.4%
To open the capsules and mix with an acidic substance, if a patient is unable to swallow the capsules	112	44.4%
To divide the enzymes over the meal	132	52.4%
To titrate the amount of enzymes according to the fat intake	110	43.7%
Strategies to evaluate the efficacy of PERT (multiple answers were possible)		
Relief of maldigestion-related symptoms	231	91.7%
Normalization of nutritional status	185	73.4%
The use of a pancreatic function test	42	16.7%
Next step in treatment in case of an unsatisfactory clinical response (multiple answers were possible)		
Increase the enzyme dose	223	88.5%
Add a proton pump inhibitor	150	59.5%
Refer to a dietician for adequate therapy instructions or for nutritional supplements	112	44.4%
Search for another cause of maldigestion	127	50.4%

50% (n = 127) starts with PERT as (temporary) treatment. For patient B and C this percentage is 77% and 75% respectively. In case of an unsatisfactory response after PERT treatment opinions are divided among pancreatologists with respect to the next therapeutic step. Patient D (current dose: 100.000 PhU for main meals and 50.000 PhU for snacks) reported weight loss and other EPI related symptoms despite PERT. The following therapeutic options are pointed out for patient D by more than half of the pancreatologists: addition of a proton pump inhibitor (69%), referral to a dietician (55%) and searching for another cause of maldigestion (53%). Patient E (current dose: 50.000 PhU for main meals and 25.000 PhU for snacks) reported a stable weight but still suffered from symptoms related to EPI. In patient E none of these therapeutic options listed above are preferred by a majority (>50%) of the respondents. In this case, most pancreatologists increase the enzyme dose (49%) or refer this patient to a dietician (41%). In both cases, most pancreatologists prefer to evaluate the nutritional status by calculating body mass index (BMI) and screening for deficiencies of nutritional laboratory markers.

4. Discussion

This international expert survey reveals a considerable lack of consensus and variation in current clinical practice patterns regarding the management of EPI in patients with CP despite various published clinical practice guidelines [7,14–16,18,20]. This is also reflected by the inconsistent diagnosis and proposed treatment strategies among international pancreatologists of the case vignettes. The fact that the clinical cases represent typical patients with characteristics of definite CP that are frequently encountered when treating CP makes our findings even more noteworthy.

The large percentage of respondents that did not routinely check for nutritional markers and PFT at time of diagnosis of CP (30%) and during follow-up (79%) suggests that many clinicians have a more reactive rather than proactive approach towards EPI. These clinicians do not consider routine screening to be clinically relevant as proposed in current guidelines despite the fact that most patients develop exocrine failure during follow-up because of an increasing loss of normal functioning pancreatic tissue due to disease progression [10,21–24]. Furthermore, even patients with no clinical symptoms of EPI often present with nutritional deficiencies [25]. Therefore guidelines recommend screening for EPI and nutritional status as part of the diagnostic work-up for CP and tests should be repeated at least annually [10]. The FE-1 test is preferred by most pancreatologists (87%) as first-choice diagnostic modality for EPI. Variation in clinical practice became also apparent when no optimal cut-off value of the FE-1 test could be established. A small majority of 59% uses <200 μg/g as cut-off for a positive test result, which corresponds to the intended use of this test (sensitivity: 63%–100% for mild-severe EPI, specificity: 93%) [26].

About 71% of pancreatologists prescribes PERT in case of clinically evident steatorrhea, which is surprisingly low since steatorrhea is considered to be a cardinal symptom of EPI and an indication for initiating PERT according to all international guidelines. However, the actual number of pancreatologists prescribing PERT in case of steatorrhea regardless of laboratory confirmation might be higher since misinterpretation of the question may have caused pancreatologists to select only one indication while multiple answers were allowed. Another interesting finding is that by 23% of the pancreatologists dose-adjustments of PERT are based on a patients' FE-1-level. There is no scientific foundation for this approach, since there is no direct relationship between FE-1-level and severity of EPI. Besides, the FE-1-test cannot be used to monitor PERT effectiveness since this test is specific to human elastase and not capable of measuring the porcine pancreatic elastase from which pancreatic enzyme preparations are composed

Table 4
Survey results – case vignettes.

Diagnostic approach				
Case Vignette	**Diagnosis of EPI** (n = 252)	**Additional testing required** (n = 252)	**PERT indicated** (n = 252)	
Patient A A positive FE-1-test and a vitamin-D-deficiency without other clinical symptoms related to EPI *Test results:* FE-1 level: 126 μg/g Vit-D-level: 23 (reference: 50–150 nmol/l)	112 (44.4%)	59 (23.4%)	**Yes** **Only as trial therapy** **No**	73 (29.0%) 54 (21.4%) 125 (49.6%)
Patient B A positive FE-1-test and symptoms of abdominal pain with dyspepsia and flatulence, but no presence of steatorrhea or nutritional deficiencies *Test results:* FE-1 level: 50 μg/g	183 (72.6%)	63 (25.0%)	**Yes** **Only as trial therapy** **No**	123 (48.8%) 72 (28.6%) 57 (22.6%)
Patient C A positive FE-1-test, weight loss, symptoms related to EPI and multiple nutritional deficiencies in the absence of clinically overt steatorrhea *Test results:* FE-1 level: 230 μg/g	149 (59.1%)	94 (37.3%)	**Yes** **Only as trial therapy** **No**	105 (41.7%) 84 (33.3%) 63 (25.0%)
Treatment of EPI				
Case Vignette	**Next therapeutic step** (multiple answers possible) (n = 252)		**Screening modality for nutritional status** (n = 252)	
Patient D Despite PERT symptoms related to EPI and weight loss *Current dose:* Meals: 100.000 PhU Snacks: 50.000 PhU	**Pancreatic function testing** **Increasing the enzyme dose** **Addition of a PPI** **Refer to a dietician** **Search for another cause**	56 (22.2%) 116 (46.0%) 174 (69.0%) 139 (55.2%) 134 (53.2%)	**BMI** **Anthropometric measurements** **MUST or NRS-2002** **Laboratory values** **Refer to a dietician**	133 (52.8%) 64 (25.4%) 66 (26.2%) 175 (69.4%) 93 (36.9%)
Patient E Despite PERT often abdominal pain, however no steatorrhea and stable weight *Current dose:* Meals: 50.000 PhU Snacks: 25.000 PhU	**Pancreatic function testing** **Increasing the enzyme dose** **Addition of a PPI** **Refer to a dietician** **Search for another cause**	42 (16.7%) 124 (49.2%) 62 (24.6%) 104 (41.3%) 83 (32.9%)	**BMI** **Anthropometric measurements** **MUST or NRS-2002** **Laboratory values** **Refer to a dietician**	70 (27.8%) 40 (15.9%) 44 (17.5%) 121 (48.0%) 51 (20.2%)

[10]. Instead adjustments in dosages of PERT should be based on the daily amount of fat intake and clinical symptoms [19].

With respect to the dietary management of EPI, dietary fat-restriction is no longer considered necessary according to international guidelines since it is associated with a reduced ability to absorb fat-soluble vitamins and malnutrition. Besides PERT proved to be more effective when administered with a high-fat diet [27]. Furthermore, high fiber diets should be avoided because high concentrations of dietary fiber interact with PERT by reducing its activity and are associated with an increase in fat excretion [28,29].

Table 5
Consensus on statements regarding the diagnosis and treatment of EPI.

	Total population n = 252	
The diagnostic work-up of EPI should include a clinical evaluation of symptoms, a pancreatic function test and measurement of nutritional markers. If at least two out of these three are suspected for EPI, it makes this diagnosis very likely and PERT is indicated.		
True	232	92.1%
False	20	7.9%
Dieticians must play a more prominent role in the treatment of patients with CP. All CP patients should be referred to a dietician irrespective of the presence of EPI to gain more insight into the (future) complications of their disease and how to maintain a healthy nutritional status		
True	199	79.0%
False	53	21%
A standard diagnostic work-up and treatment of EPI is needed. Development of an international guideline for the management of EPI would be very useful in clinical practice		
True	245	97.2%
False	7	2.8%

However, only 11% informs their patients about this matter. Despite the fact that several guidelines recommend to involve a dietician in the management of CP patients even when there are no signs of malabsorption or malnutrition, only 40% of pancreatologists refers more than 50% of their CP patients to a dietician [10,19,30]. This finding corresponds to the results of previously performed studies where less than half of the patients with EPI received individual dietary counseling by a dietician [11–13,31]. This is remarkably low since malnutrition is a common complication of EPI caused by an impaired digestion and absorption of primarily fat [32]. Besides, dieticians play a major role in providing dietary advice and instructions for the appropriate use of PERT.

As recommended in the guidelines, patients with EPI and suspected of malnutrition should be screened for deficiencies of fat-soluble vitamins, HbA1c and established blood markers of malnutrition, such as pre-albumin, retinol-binding protein and minerals including iron, zinc and magnesium (Statement 3–12 and 6-2.3) [9]. The vast majority of pancreatologists (92%) agrees that nutritional laboratory markers are part of the standard diagnostic work-up of EPI. However, this study showed that nutritional screening is not routinely performed (Supplementary Appendix, Table 2). There could be several explanations for this. First of all, the prevalence rates of nutritional deficiencies in CP vary among study populations which could possibly be due to differences in individual patients risks based on age, comorbidity and state of inflammation which negatively affects the serum level of albumin and trace elements [33]. Secondly, evidence regarding the relation between some nutrients deficits and EPI remains inconclusive. Deficiencies of fat-soluble vitamins A, D, E and K are frequently demonstrated in patients with EPI and should therefore be part of the standard diagnostic work-up for EPI [5,32,34]. In a meta-analysis of twelve studies including 548 patients with CP, the pooled prevalence rates for vitamin A, D and E deficiency were reported 16.8% (95% CI 6.9–35.7), 57.6% (95% CI 43.9–70.4) and 29.2% (95% CI 8.6–64.5) respectively [34]. Levels of magnesium, pre-albumin and retinol-binding protein below normal values and a HbA1c level above the upper limit are less frequent but are associated with EPI as well [7,33,35]. However, evidence regarding the potential benefits of measuring iron and zinc serum levels in EPI patients is scarce. Instead, previous studies have observed an increased absorption of iron in patients with EPI [36,37]. Furthermore, low serum levels of zinc have been detected in patients with CP, although these were not associated with EPI [38,39]. In conclusion, although various nutritional deficits have been observed in patients with CP, not all of them proved to be associated with EPI. Future studies should concentrate on evaluating the benefits of screening for micronutrients deficiencies in patients with CP suspected for EPI. Finally, since serum tests can be very expensive, screening may not be cost-effective since it does not always have clinical consequences as not all deficiencies can be treated easily by supplementation [10]. However, the goal of nutritional screening is not to evaluate the need of supplementation, but to identify those patients who would benefit from PERT as this can correct malnutrition without additional supplementation [40].

Our findings suggest that, despite several (inter)national guidelines, EPI is still underdiagnosed and undertreated, which is in line with studies performed previously [11–15,40]. There are several possible contributing factors associated with suboptimal adherence to these guidelines. First of all, the magnitude and complexity of these guidelines could prevent physicians from using them in clinical practice. Secondly, high quality evidence to support the optimal management strategy of EPI as recommended in these guidelines is lacking. For example, most recommendations of the HaPanEU-guidelines for the diagnosis and treatment of EPI are based on moderate level of evidence according to GRADE, reflecting the paucity of randomized controlled trials on this topic [10,41]. The lack of good quality evidence could perhaps render physicians to be reluctant to start with PERT in patients who present with micronutrient deficiencies but who lack any disabling symptoms. Physicians probably expect therapeutic compliance to be much lower in patients with subclinical EPI compared with symptomatic patients, since for these patients the advantages of PERT are less evident while PERT will significantly impact their daily-life since life-long treatment is indicated. Furthermore, PERT is expensive and these high costs may serve as a financial barrier for physicians to prescribe PERT especially in patients with no symptoms [42]. However, this does not explain why the percentage of pancreatologists who prescribes PERT in patients with overt clinical steatorrhea (71%) is low. PERT is one of the few non-invasive therapeutic options available for patients with CP and, when administered properly, is associated with improvement in QoL and a relief PEI-related symptoms of malabsorption [23]. Furthermore, some studies have also suggested that PERT improves patients' survival, however, these results are potentially biased since this has only been assessed for CP patients undergoing surgery and long-term data are lacking [9,43]. Current guidelines outline general principles regarding the management of EPI based on current available evidence and primarily focus on regular screening for EPI and optimization of PERT. In this survey, 97% of pancreatologists support the need for a new international guideline to standardize the management of EPI. Apparently, although society-endorsed guidelines do exist, doctors are either unaware of these publications or feel that they insufficiently address the issues faced when managing EPI in CP patients. However, most guideline recommendations are based on moderate to low-quality evidence and therefore some of them should be considered as optional until there is more scientific evidence for its clinical usefulness and cost-effectiveness.

This study has several limitations. First, most pancreatologists originated from Europe (80%) which may have caused selection bias and may limit the application of our results to the rest of the world. Secondly, given the fact that participants were selected based on their specific interest for CP one could suggest that our findings are even too optimistic and current adherence to guidelines with respect to general practice care is much lower. Thirdly, some questions may have been confusing or suggestive by its phrasing such as double negative (i.e. question 16) and the overlapping time-intervals and options given in multiple choice questions (i.e. question 6 and 13). This may have affected the responses to these questions, especially, since not all pancreatologists were native speakers and the survey was not validated in other languages. Finally, the number of pancreatologists who were personally invited and replied to our survey was limited to 107 (35%). Of this group, only 60 respondents (56%) were actively involved in the treatment of CP which could be explained by our selection method which was based on publication record. Thereby, we were inviting experts to participate to whom our survey was not applicable (i.e. basic scientists, radiologists, retirees etc.). As we aimed to reach as many international pancreatologists as possible, we have therefore requested various pancreatic associations to endorse and distribute our survey to their members. Although the exact response rate could not be calculated since the membership lists of the pancreatic associations were confidential, we believe the large number of respondents ensures an adequate reflection of international practice. Furthermore, our number of respondents is almost equal to a previously performed expert survey conducted by our study group regarding the diagnosis and treatment of CP [44]. Although adherence to existing guidelines has been explored by multiple studies in the past, we were specifically interested in current practice variation among international pancreatologists with respect to the management of EPI. Thereby, the present study aims

not so much at pointing out suboptimal care, however, is more focused on understanding it. As it seems, an important barrier towards implementing guidelines is lack of consensus on definitions and optimal treatment. The strength of this study is the highly experienced group of respondents. Although only 34% of respondents treats more than 50 patients with CP a year, we do not consider this as a limitation of our study. Instead, we believe our results are consistent with current practice since many patients with CP are treated in relatively low-volume centers, resulting in physicians to treat only a few patients with CP a year. Furthermore, the specialisms gastroenterology and surgery are both equally well represented in our study population. We therefore believe our results are a reliable representation of the current expert opinion regarding the management of EPI.

In conclusion, this international survey identified a lack of consensus and a substantial variety of practice among pancreatologists regarding the diagnostic and therapeutic approach of EPI in patients with CP. Furthermore, this study confirmed that EPI is currently underdiagnosed and undertreated. This is despite EPI being a hallmark feature of CP, one of the few complications of CP that can be adequately treated and has an impact on both somatic complications and quality of life. There is clearly need for more high-quality studies and further development and adaptation of current existing guidelines.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pan.2022.03.013.

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