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Prescribing of pancreatic enzyme therapy for malabsorption in unresectable pancreatic cancer: Cross-sectional survey across New Zealand and Australia

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ABSTRACT

Objective: To investigate the practices of clinicians prescribing pancreatic enzyme replacement therapy (PERT) for unresectable pancreatic cancer in Aotearoa New Zealand and Australia.
Methods: A mixed media advertising campaign was used to recruit appropriate clinicians to complete a questionnaire that collected demographic data, information regarding prescribed medication, and awareness of PERT guidelines.
Results: The study recruited 161 clinicians, with 93 and 68 respondents from Aotearoa New Zealand and Australia respectively. Most respondents from both countries were experienced gastrointestinal surgeons and dietitians. Aotearoa New Zealand clinicians and dietitians used faecal elastase more frequently to diagnose PEI than other groups. Clinicians had a tendency to under-prescribe PERT, and to advise incorrectly on the timing of the medication. The majority of clinicians from Aotearoa New Zealand and Australia were not aware of any best practice clinical guidelines for PERT (70 % and 77 %, respectively).
Conclusion: This study suggests clinicians are over-reliant on faecal elastase to diagnose PEI and are uncertain about the correct dose and timing of PERT for optimal patient benefit in those with unresectable pancreatic cancer. Most clinicians were not aware of best practice guidelines.

1. Introduction

Pancreatic cancer has a poor prognosis globally, with overall 5-year survival rates of 10–12 % [1,2]. Surgical resection is the best treatment option, but only 8 % are eligible due to advanced disease at presentation. Pancreatic exocrine insufficiency (PEI) is highly prevalent in patients with pancreatic cancer due to both direct and indirect effects of the cancer and/or resection [3,4]. PEI, or 'pancreatic failure', is defined as the reduced production or asynchrony of pancreatic enzyme delivery, which impairs absorption. There is evidence that the prevalence of PEI in patients with inoperable pancreatic cancer, and after resection of pancreatic cancer, is between 50 and 100 %. Pancreatic cancer in the head of the gland is more likely to be associated with PEI [3,4]. The detection of PEI remains challenging with clinicians having a low index of suspicion, and the potential for under-diagnosis due to a lack of accurate, convenient and available diagnostic options [5].

PEI leads to malabsorption and a range of symptoms, including abdominal discomfort, bloating, flatus, nausea, diarrhoea and

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steatorrhea [6]. The longer term effects of malabsorption in pancreatic cancer include weight loss, sarcopenia and nutritional deficiencies [7] which are associated with increased risk of complications with treatment, especially surgery [8]. Pancreatic enzyme replacement treatment (PERT) is the current standard of treatment for PEI. PERT has been shown to be well tolerated and safe [9]. There is evidence that PERT reduces symptoms of PEI [10], improves quality of life [9] and possibly survival [11] in pancreatic cancer. The involvement of a dietitian with skills in enzyme replacement and nutrition in malignancy is advisable to ensure optimisation of nutrition and supportive cancer care.

There are best practice guidelines available that recommend how PERT should be prescribed in the management of pancreatic cancer, including correct dose and timing [12,13]. Despite these guidelines, there is a lack of definitive clinical trial evidence to guide health professionals with dose and timing, and sub-groups that may benefit most from PERT. This evidence and knowledge gap about the optimal use of PERT may lead to uncertainty for clinicians [14,15]. Health professional and patient education is important to improve prescribing and compliance with enzyme replacement [16,17]. The aim of this study was to identify decision-making and prescribing patterns of PERT by clinicians for patients with unresectable pancreatic cancer in Aotearoa New Zealand (AoNZ) and Australia (AUS), to inform future implementation interventions.

2. Methods

Statement of ethics

Ethics approval was obtained from the Auckland Health Research Ethics Committee (reference 24174). Participant clinicians were informed about the aim of the study, the anonymous data collection method, and the data storage arrangements and were required to consent to the study at the commencement of the survey.

2.1. Questionnaire development and recruitment

The questionnaire was developed through multi-disciplinary consultation with input from clinicians, dietitians and consumers. The draft questionnaire was uploaded online via Qualtrics (Qualtrics, Provo, UT) and was reviewed by the wider research team members not directly involved with the study. The feedback was used to modify the final questionnaire. The questions focused on collecting demographic data of the clinicians and clinical decision-making processes for prescribing PERT, including choice regarding dosing and timing. Recruitment for the study occurred using a multi-media campaign across AoNZ and Australia as previously described in the literature [18]. Dedicated social media pages on Facebook, Instagram, Twitter, LinkedIn and Google were created. The study was promoted on these pages using a link that directed individuals to a webpage providing more information and the option to consent and proceed to the questionnaire. The questionnaire was also disseminated through relevant partnership organisations such as Pancreatic Cancer Aotearoa New Zealand, Royal Australasian College of Physicians, the Australian New Zealand Hepatic Pancreatic and Biliary association, Palliative Care Nurses Australia and Palliative Care Australia. Dietitians New Zealand advertised the study through their newsletter.

2.2. Statistical analysis

For each questionnaire, participation and completion rates were documented. Survey results were analysed through descriptive statistical methods to obtain percentages, mean scores, standard deviations and ranges for each question. A p value < 0.05 was considered significant.

3. Results

3.1. Respondents

The survey was accessible from May 2022 to Sept 2022 and was targeted at clinicians across AoNZ and AUS involved in the treatment of pancreatic cancer. As the questionnaire was disseminated through social media and relevant organisational channels, it is difficult to state the number of potential participants (denominator) reached. The study recruited 93 participants from AoNZ (n = 77, 83 % completing diagnostic questions) and 68 respondents from AUS (n = 45, 66 % completion). Most AUS participants heard about the survey via a professional group (47 %), while the most common response for AoNZ participants was 'other' (32 %), which included via direct email from study researchers or through colleagues.

3.2. Demographics

Most participants from AoNZ worked in large urban areas such as Auckland (23 %), and Canterbury (22 %). The Australian respondents were mainly from the states of New South Wales (31 %) and South Australia (27 %). For both the AoNZ and AUS groups, respectively 65 % and 57 % of participants stated their clinical role was '*doctor*'(Table 1).

Among respondents identifying as '*doctor*', over 80 % from both countries were at the level of consultant. The most common medical specialty for both doctors and dietitians was surgery, at a rate of 57 % and 64 % respectively. The medical professionals were much more likely to be experienced with 50 % stating they had been in their roles for over 20 years.

Of all health professionals who participated in the survey, 89 % of the doctors and dietitians prescribed PERT. Only one of the two nurse practitioners and 2/11 of the unknown participants prescribed PERT. Overall, 83 % of the participants prescribed PERT in their clinical roles. Doctors tended to be more experienced than dietitians in using PERT for pancreatic cancer (Fig. 1).

When comparing the health professionals who most often prescribe PERT (namely doctors and dietitians), we found more doctors prescribe regularly; however, both doctors and dietitians were not prescribing PERT frequently in their practice overall. (Fig. 2).

3.3. PEI diagnosis

The most common diagnostic criteria AoNZ clinicians (n = 77) used for PEI were clinical signs of steatorrhea (90 %), weight loss (73 %) and faecal elastase (65 %). From the AUS clinicians who responded (n = 47), the three most common criteria used to diagnose PEI were clinical signs of steatorrhea (96 %), weight loss

Table 1
Participant characteristics.

	AoNZ (N = 93)	AUS (N = 68)	Overall (N = 161)
Job Title			
Dietitian	29 (31.2 %)	19 (27.9 %)	48 (29.8 %)
Doctor	60 (64.5 %)	39 (57.4 %)	99 (61.5 %)
Nurse Practitioner	2 (2.2 %)	0 (0 %)	2 (1.2 %)
Other: please specify	2 (2.2 %)	9 (13.2 %)	11 (6.8 %)
Missing	0 (0 %)	1 (1.5 %)	1 (0.6 %)

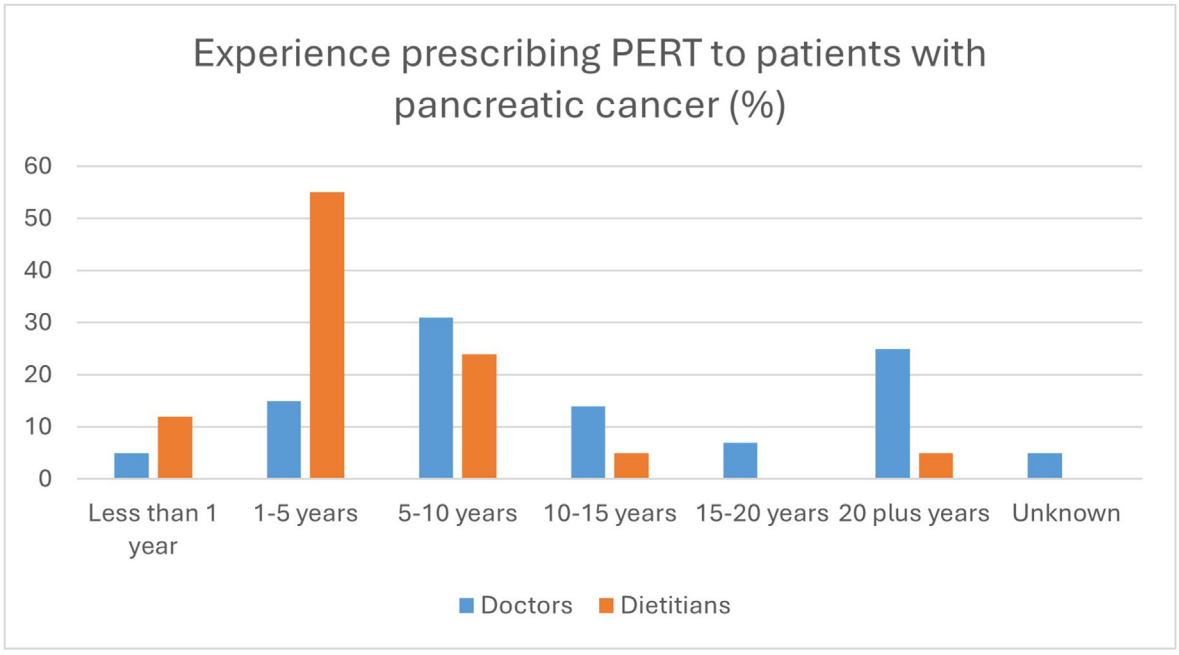

Fig. 1. Experience of doctors and dietitians in prescribing PERT to patients with unresectable pancreatic cancer.

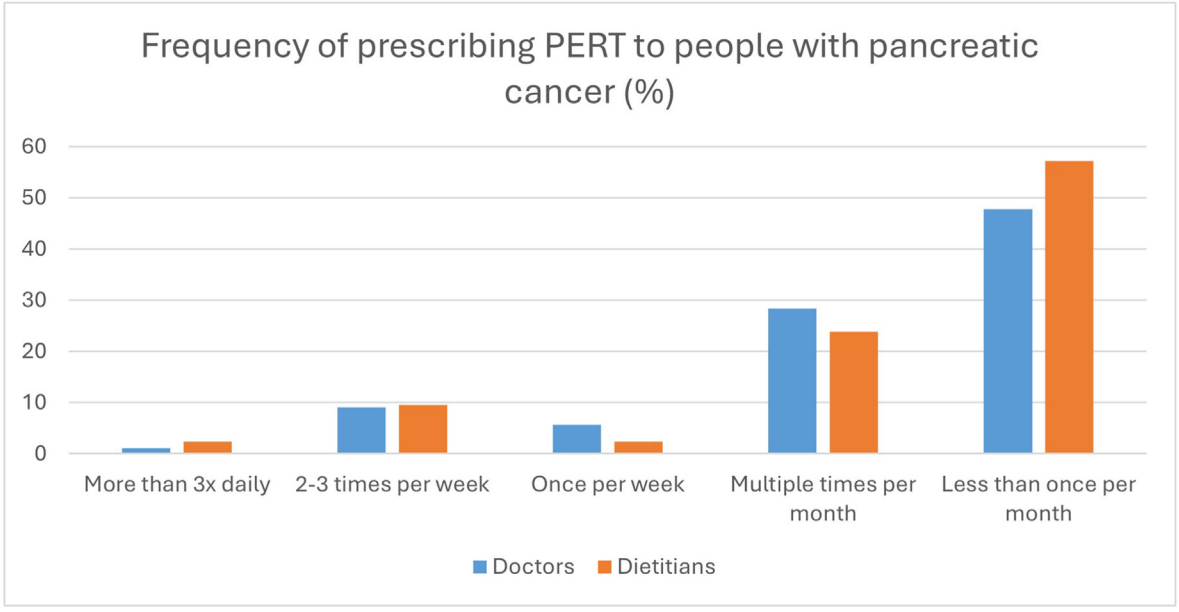

Fig. 2. Frequency of doctors and dietitians prescribing PERT to people with unresectable pancreatic cancer.

(84 %) and computerised tomography (CT) proven pancreatic duct dilation/atrophy (53 %) (Table 2). There were two significant differences between doctors and dietitians with diagnostic criteria, with dietitians more frequently using faecal elastase and micronutrient testing.

3.4. PERT dosing and timing

The most common starting PERT doses prescribed by clinicians for meals and snacks to patients with unresectable pancreatic cancer was 25,000IU. The next most common dose for meals was 50,000IU, favoured by more dietitians. For snacks, almost 40 % of doctors prescribed 10,000IU. Only the 10,000IU and 25,000IU options are available in AoNZ, while all dose options are available in AUS. For both population groups, all clinicians but one in the AoNZ group used Creon as their PERT therapy with a single clinician stating they would use Panzytrat if the patient had a sulphur allergy.

The top two recommended times were '*At first bite*' and '*30 min before meals*'. Over 30 % of doctors recommended to patients they take their PERT 30 min before a meal, as opposed to 11 % of dietitians. Almost 80 % of dietitians advised their patients to take the enzymes at the start of the meal. Prescribing doses and timing recommendations were compared to international guidelines

Table 2
Frequency of diagnostic criteria for pancreatic exocrine insufficiency as percentage of participants.

	AoNZ (N = 77)[a]	AUS (N = 45)[a]	P-value[b,c]	Dietitian (N = 41)[a]	Doctor (N = 78)[a]	P-value[b,c]
Clinical signs of steatorrhea						
No	8 (10.4 %)	2 (4.4 %)	0.321	3 (7.3 %)	6 (7.7 %)	1
Yes	69 (89.6 %)	43 (95.6 %)		38 (92.7 %)	72 (92.3 %)	
Weight loss						
No	21 (27.3 %)	7 (15.6 %)	0.207	9 (22.0 %)	17 (21.8 %)	1
Yes	56 (72.7 %)	38 (84.4 %)		32 (78.0 %)	61 (78.2 %)	
Pancreatic duct dilation/atrophy on CT scan						
No	42 (54.5 %)	21 (46.7 %)	0.514	23 (56.1 %)	37 (47.4 %)	0.481
Yes	35 (45.5 %)	24 (53.3 %)		18 (43.9 %)	41 (52.6 %)	
Faecal Elastase-1 <200ug/g						
No	27 (35.1 %)	28 (62.2 %)	**0.007**	11 (26.8 %)	42 (53.8 %)	**0.009**
Yes	50 (64.9 %)	17 (37.8 %)		30 (73.2 %)	36 (46.2 %)	
Micronutrient Deficiency						
No	54 (70.1 %)	22 (48.9 %)	**0.032**	19 (46.3 %)	55 (70.5 %)	**0.017**
Yes	23 (29.9 %)	23 (51.1 %)		22 (53.7 %)	23 (29.5 %)	
Co-efficient of fat absorption test						
No	75 (97.4 %)	45 (100 %)	0.531	40 (97.6 %)	77 (98.7 %)	1
Yes	2 (2.6 %)	0 (0 %)		1 (2.4 %)	1 (1.3 %)	
13C-mixed triglyceride breath test						
No	77 (100 %)	42 (93.3 %)	**0.048**	40 (97.6 %)	76 (97.4 %)	1
Yes	0 (0 %)	3 (6.7 %)		1 (2.4 %)	2 (2.6 %)	

[a] Participants who prescribe pancreatic enzyme replacement therapy (PERT) were included, additionally 6 out of 83 (7.2 %) Aotearoa New Zealand and 5 of 50 (10 %) of Australian PERT prescribers who were missing answers for diagnostic criteria were excluded.
[b] Pearson's χ^2 test.
[c] Fisher's exact test applied to variables where more than 20 % of cells have expected frequencies <5 (Clinical signs of steatorrhea, Co-efficient of fat absorption test, 13C-mixed triglyceride breath test).

(Table 3). Doctors were less aligned with these guidelines than their dietitian colleagues.

3.5. Education about PEI and PERT

PERT education was provided by 82.4 % of AoNZ clinicians and 73 % of AUS clinicians. According to the clinicians who provided education to those commencing PERT, their preferred method was the '*PERT patient pamphlet*'. The majority of AoNZ (70 %) and AUS (77 %) respondents were not aware of any standard clinical guidelines for the use of PERT. From the clinicians in AoNZ and AUS, 77 % and 67 % respectively stated their patients did not encounter barriers to PERT accessibility. Of those who responded affirmatively, the main barriers reported were financial and awareness by their GP.

4. Discussion

This study investigated the use of PERT by clinicians in those with unresectable pancreatic cancer across AoNZ and AUS. The majority of clinicians were senior surgical medical specialists, followed by dietitians working in a similar field. All health professionals prescribed infrequently, as pancreatic cancer is a relatively rare malignancy. Differences existed between countries and roles in the way diagnostic criteria were applied, suggesting a need for improved guidelines. A significant proportion of clinicians were potentially under-dosing PERT at both meal and snack times. Clinicians appeared to have little awareness of clinical guidelines, which was reflected in the wide range of dosing regimens and advice given around the timing of the medication.

4.1. Comparison to current literature

There is evidence to suggest that PERT utilisation by clinicians in pancreatic cancer is sub-optimal in health care systems internationally [19,20]. Evidence also suggests that the decision to prescribe PERT by surgeons is influenced by factors such as number of pancreatic cancer surgeries, tumour location and the confidence a surgeon has in the efficacy of PERT [21]. Few surgeons diagnose PEI, or 'pancreatic failure', before starting PERT, or follow up on therapy effectiveness after commencement [21]. Resectable pancreatic cancer patients are also more likely to receive PERT than unresectable patients, suggesting an inequality of healthcare in those with a palliative focus [22]. Overall, doctors appear to prescribe PERT on a case-by-case basis rather than following standardised guidelines, which may lead to inconsistent patient selection, duration of therapy and therapy monitoring [19]. In AoNZ, dietitians have been able to prescribe PERT since 2015; however, their counterparts in AUS currently do not have the same ability. Dietitian prescribers are therefore less experienced overall in initiating PERT.

The decision to prescribe PERT should be made primarily on the clinical likelihood of PEI alongside clinical signs and symptoms, with faecal elastase and micronutrient deficiency test (MDT) adding to the overall picture. Current literature suggests the faecal elastase test is the most reliable biochemical test in the diagnosis of PEI [23]. While it is not the gold-standard, it is non-invasive and less time consuming than alternatives such as the co-efficient of fat absorption [5]. Our study indicates that AoNZ clinicians and dietitians use faecal elastase most frequently to aid PEI diagnosis. However, it is important faecal elastase results are interpreted in conjunction with clinical symptoms and diagnosis. AUS clinicians and dietitians favoured MDT as their most frequently utilised test for diagnosis. Murphy et al. conducted a prospective study on the micronutrient status of patients with suspected pancreatico-biliary malignancies [24] and reported select micronutrients levels may be reduced in this group. It is especially important to diagnosis and treat these reductions to optimise outcomes for those undergoing surgery. MDT may, therefore, be used to help determine PEI likelihood if standard, more reliable tests of pancreatic function are restricted and if confounding causes of malnutrition are reduced [25].

Variation in the timing and dosage of PERT prescribing amongst clinicians was reported in our study. A recent study investigating PERT use in the US found that dosing of PERT in patients with

Table 3
Compliance by doctors and dietitians in prescribing PERT according to international guidelines.

PERT prescribing	Internationally recommended guideline	% of respondents following recommended guidelines	
		Doctors	Dietitians
Dose with snacks	25,000+	59	70
Dose with meals	40,000–50,000	37	44
Timing of PERT	At first bite	65	89

The international guidelines recommend doses per snacks and meals. The guidelines also recommend PERT be taken at the start and during the length of the meal [13].

pancreatic cancer is often inappropriate, inconsistent and infrequent [19]. Our results demonstrated doctors are frequently instructing patients to take the medication at incorrect times, which may lead to sub-optimal efficacy of the enzymes on digestion. This timing issue may be clinician extrapolation from antiemetic regimes where patients are educated to take medication 30 min before meals.

There is debate in the literature regarding the doses required in patients with pancreatic cancer at both meals and snack times. The most common recommendation in multiple international guidelines is 40,000–50,000IU with each meal and 25,000IU with snacks [26]. However, other experts recommend higher initial doses such as 75,000IU per meal in patients with unresectable pancreatic cancer [27]. Our study revealed all groups tended towards under-dosing, with dietitians prescribing higher doses on average than doctors.

Our study found the majority of clinicians from both AoNZ and AUS were unaware of standard clinical guidelines (national or international) regarding PERT prescription. Standard guidelines are often disseminated through specialty societies, or relevant journals which requires clinicians to be involved in continuing education. Even when clinicians are familiar with these guidelines, barriers may exist. Adherence can be inconsistent, especially when they do not agree with the recommendations due to lack of evidence, when they receive ambiguous advice, or where there are organisational barriers [28]. However, adherence to standardised guidelines may have positive effects on health outcomes for patients and, therefore, play a role in best practice [29].

Our study found a number of AoNZ and AUS clinicians did not provide PERT education to their patients. Education is vital in improving treatment efficacy and patient compliance with treatment. A recent qualitative study exploring the experiences of AUS dietitians observed a significant gap in the education of patients on appropriate PERT use and storage, as well as appropriate PERT dosage by clinicians [30]. Dietitians are uniquely qualified to be an essential source of education of both PERT and nutritional counselling for patients. The promotion of a multi-disciplinary model of PEI management, with emphasis on ensuring that appropriate dietitians are formally trained to safely give PERT education and the ability to prescribe/change PERT dosage, is likely to produce better outcomes, significantly affecting patient quality of life and potentially even improving tolerance of cancer treatment.

4.2. Implications for future practice

Pancreatic cancer is a relatively rare malignancy with the unique feature of potentially high rates of PEI. The diagnosis of PEI in pancreatic cancer requires a clinical approach focused on the high likelihood of the ‘pancreatic failure’ and symptoms as the deciding factor for PERT administration. Faecal elastase testing may complete the picture but should not be utilised in isolation. The management of PEI can be complex and requires continuing education in best practice. As guidelines state, PERT should be recommended routinely to all patients with PC. We recommend clinicians prescribe PERT to patients with pancreatic malignancy to initiate between 50,000 and 75,000IU/meal at mealtimes, and 25,000 and 50,000IU/meal for snack, and further that they monitor and titrate doses to effect. It is important for clinicians to educate patients correctly regarding dose titration and how to monitor their own symptoms. This will empower the patient in the decision-making process of titrating their dose with the clinician to achieve the best outcome. Dietitians are also strongly positioned to monitor and titrate dosing as dosing is dependent on meal composition.

The development of a short online module in the management of PEI in pancreatic malignancy may be a way of addressing some of the knowledge gaps for clinicians in all settings. This module could be administered through specialty societies, Royal Colleges and other forums. Knowledge of international or local guidelines recommending routine PERT administration would also help clinicians to feel confident in prescribing PERT consistently to PC patients. Guidelines may empower clinicians to provide high-quality education to their patients with pancreatic cancer about PERT.

4.3. Strengths and weaknesses of the study

Limitations of the study include the potentially restricted reach of the mixed media advertisements, which only reached clinicians who accessed the relevant social media platforms, and therefore may favour certain groups. However, this was partly circumvented by disseminating the survey through professional and health groups. The study did not measure the response rate of the overall survey, thus is susceptible to non-response bias. The proportion of the overall target population included in our study is unknown, thus undermining external validity of our findings. Responder bias may have underestimated the scale of the problem. The main strength of the study was the strong connections with health groups and their networks, which allowed for targeted promotion of the study throughout multiple regions in AoNZ and AUS.

5. Conclusions

Pancreatic exocrine insufficiency is a prevalent complication secondary to unresectable pancreatic cancer. This ‘pancreatic failure’ may significantly affect patient quality of life and has implications for survival. The diagnosis of PEI hinges mainly on clinical signs and symptoms, with objective tests only adding to the overall picture. PEI can be effectively treated with PERT, a well-tolerated medication with few side effects. Supportive care services may need to ensure clinicians are educated and aware of recent international guidelines regarding PERT administration so patients with pancreatic cancer have consistent and high-quality care.

Authors’ contributions

AL, HB, CM, KR, VY and MA designed the study concept and the design. AL, HB and KR assisted with the data acquisition. Data interpretation was AL and FF. AL, HB, KR, CM, KC, JW helped with the consumer and professional group relationships. AL and FF wrote the first draft of the manuscript. All authors contributed to the drafting and editing of the manuscript.

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Declaration of competing interest

None.

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