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Diagnostic Accuracy of Fecal Elastase-1 Test for Pancreatic Exocrine Insufficiency: A Systematic Review and Meta-Analysis

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ABSTRACT

Introduction: Pancreatic exocrine insufficiency (PEI) results from a reduction in pancreatic secretion of enzymes, leading to malabsorption of nutrients, intestinal symptoms, nutritional deficiencies and related comorbidities. The diagnosis of pancreatic exocrine insufficiency should be based on digestive tests, mainly the coefficient of fat absorption (CFA), based on the quantification of 72 h fecal fat excretion (FFE). However, this test is rarely performed in clinical practice. Fecal elastase-1 (FE-1) is a simple and widely used alternative. This meta-analysis evaluates the diagnostic accuracy of fecal elastase-1 for the diagnosis of PEI diagnosed by CFA or 72h-FFE.

Methods: A systematic search of databases was performed to identify studies evaluating fecal elastase-1 and CFA/FFE for the diagnosis of pancreatic exocrine insufficiency. Inclusion criteria required original studies with data on sensitivity, specificity and other diagnostic metrics. Two independent reviewers performed data extraction and quality assessment using the QUADAS-2 tool. Pooled sensitivity, specificity, likelihood ratios and diagnostic odds ratio (DOR) were calculated and heterogeneity was assessed using I-squared tests.

Results: Thirteen studies with 888 patients were included. Fecal elastase-1 at a cut-off of 200 μg/g showed a pooled sensitivity and specificity of 0.94 and 0.69, respectively, with a DOR of 35.27. Lowering the cut-off to 100 μg/g improved specificity to 0.82 but decreased sensitivity to 0.88. Subgroup analyses showed different diagnostic performance in different clinical contexts, with higher sensitivity in cystic fibrosis (0.98) and higher specificity in chronic pancreatitis (0.81). The positive and negative predictive values are limited in situations with low and high probability of pancreatic exocrine insufficiency, respectively.

Conclusions: Fecal elastase-1 is a sensitive and moderately specific diagnostic tool for pancreatic exocrine insufficiency and is suitable for initial screening in high-risk populations. However, its moderate specificity requires careful interpretation in lower risk settings.

Summary

- Summarise the established knowledge on this subject
  - PEI results in malabsorption and serious nutritional consequences requiring timely diagnosis and treatment.
  - The coefficient of fat absorption (CFA) and 72-h fecal fat excretion (FFE) are considered the gold standards for diagnosing PEI, though they are cumbersome and rarely used in clinical practice.
  - The fecal elastase-1 (FE-1) test is a widely used, simple, and non-invasive method that evaluates pancreatic enzyme secretion but not digestive function directly.
  - Prior reviews of FE-1 did not adhere to current European guideline definitions of PEI, and thus its accuracy needed reassessment against CFA/FFE.
- What are the significant and/or new findings of this study?
  - FE-1 is a highly sensitive (94%) but moderately specific (69%) test for PEI using the standard 200 μg/g cut-off.
  - Due to moderate specificity, FE-1 results must be interpreted cautiously in low-risk settings; integration with clinical context and nutritional status is essential.
  - This is the first meta-analysis applying the updated definition of PEI and using CFA/FFE as the reference standard, providing more clinically relevant data for practice.

1 | Introduction

According to the recently published European guidelines, pancreatic exocrine insufficiency (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'* [1]. PEI results in malabsorption of nutrients, which can lead to intestinal symptoms and significant nutritional deficiencies [1]. Symptoms of PEI include steatorrhoea, bloating, abdominal distension and cramping, and flatulence [2]. Nutritional deficiencies include protein, fat-soluble vitamins and other micronutrients, which can be associated with weight loss, osteoporosis and sarcopenia [2–4]. In addition, PEI is associated with an increased risk of cardiovascular disease, cancer, infections and increased mortality [5, 6], and it can have a significant impact on the quality of life [7]. As a result, PEI should always be treated [1], and accurate and timely diagnosis is therefore crucial for the initiation of appropriate therapeutic interventions, such as pancreatic enzyme replacement therapy (PERT).

The direct secretin-cerulein pancreatic function test is the most accurate method of assessing pancreatic secretion and has classically been considered the gold standard for the diagnosis of PEI [8]. However, this test does not assess the ability of secreted enzymes to digest ingested food and, according to current guidelines, should not be used to diagnose PEI in clinical practice [1].

The coefficient of fat absorption (CFA) is considered the gold standard for the diagnosis of steatorrhea, which is the main clinical manifestation of PEI [1]. To calculate the CFA, patients are required to follow a standardised diet containing 100 g of fat per day for five days. The total amount of feces produced over the last 72 h of this period is then collected for fat quantification. CFA measures fat absorption efficiency as a percentage, whereas the 72-h Fecal Fat Excretion (72h-FFE) quantifies the absolute amount of fecal fat excretion in grams per day. Normal fecal fat excretion is < 7 g/day, whereas more than 7 g/day suggests steatorrhea. However, this method is cumbersome and uncomfortable for both the patient and the staff handling the samples, making the test challenging to implement in clinical practice. The ^{13}C-mixed triglyceride breath test offers an alternative, but it is not widely available [9].

The fecal elastase-1 (FE-1) test is the simplest and most widely used pancreatic function test in clinical practicebut, like the secretin-cerulein test, it evaluates pancreatic secretion but not the ability of pancreatic enzymes to digest food. Although pancreatic secretion is the main factor leading to PEI, the development and clinical manifestations of PEI are variably influenced by factors such as the intraluminal pH in the gut, gastrointestinal anatomy, and the dietary habits and nutritional needs of patients among others. The diagnosis of PEI therefore requires a combined assessment of symptoms, nutritional status and pancreatic function in an appropriate clinical context [1].

Previously published systematic reviews and meta-analyses evaluating the diagnostic accuracy of FE-1 do not meet the current definition of PEI [10]. Therefore, there is a need to know the diagnostic accuracy of FE-1 for PEI using CFA or 72h-fecal fat excretion (FFE) as the gold standard.

This meta-analysis aimed to evaluate the diagnostic accuracy of FE-1 compared to CFA or 72h-FFE, focusing on key performance metrics such as sensitivity, specificity, positive likelihood ratio (LR+), negative likelihood ratio (LR-), and diagnostic odds ratio (DOR).

2 | Methods

2.1 | Search Strategy and Selection Criteria

A comprehensive literature search was conducted in databases, including PubMed, Embase and Google Scholar, from their inception to December 2024. The search strategy was designed to identify studies evaluating the diagnostic accuracy of FE-1 compared with CFA or 72-FFE for the detection of PEI. The search strategy is described in detail in Supporting Information S1. The reference lists of identified articles were also reviewed to ensure that all relevant studies were included.

2.2 | Study Inclusion/Exclusion Criteria

Studies were considered eligible if they met all of the following inclusion criteria: (i) original research articles comparing FE-1 with 72h-FFE or CFA for the diagnosis of PEI; (ii) reported data (sensitivity, specificity, negative predictive value, positive predictive value) necessary to calculate true positive (TP), false

positive (FP), true negative (TN) and false negative (FN) rates; (iv) peer-reviewed articles published in English; (v) studies involving human participants of any age group. Studies were excluded according to the following criteria: (i) reviews, editorials and case reports and (ii) updated or duplicated studies.

2.3 | Data Extraction and Quality Assessment

Two independent reviewers (DIG and BAC) extracted data from the included studies using a standardised data extraction form. Disagreements were resolved by consensus or by consultation with a third reviewer (JEDM). Extracted data included study characteristics (author, year, country, study design), patient demographics (age, sex, underlying diseases), diagnostic test details (FE-1 cut-off values, CFA methodology) and diagnostic accuracy metrics (sensitivity, specificity, LR+, LR−, DOR).

We used the Quality Assessment of Diagnostic Accuracy Studies tool (QUADAS 2) to assess the risk of bias in four domains regarding participant selection, index test, target condition, reference standard, and flow and timing [11]. Two authors (DIG and BAC) independently assessed the risk of bias of the included studies. In case of disagreement, we resolved it by discussion with third author (JEDM).

2.4 | Statistical Analysis

Overall pooled sensitivity, specificity, positive LR, negative LR and DOR with corresponding 95% CIs were used to examine the accuracy of FE-1 for the diagnosis of PEI compared with CFA or 72h-FFE. A summary receiver operating characteristic (SROC) curve, constructed as described by Moses et al. [12], was plotted to graphically present the results. The area under the curve (AUC) was calculated, with an AUC close to 0.5 indicating a poor test and an AUC of 1.0 indicating a perfect diagnostic tool. Chi-square and I-square tests were used to assess heterogeneity. An I^2 greater than 50% or a low p value (< 0.05) of the X^2 test indicates heterogeneity between studies. The random-effects model was used for pooled analyses.

All calculations above (including TP, FP, TN, FN) were performed using RevMan5.1 (Cochrane Collaboration, Oxford, UK). All statistical analyses presented in the figures were performed using Meta-Disc version 2.0 (Unit of Clinical Biostatistics, Ramon y Cajal Hospital, Madrid, Spain). A p value < 0.05 was considered statistically significant. Deeks' funnel plot was used to assess potential publication bias using STATA 17.0 (STATA Corporation, College Station, TX), with a p-value > 0.05 indicating no potential publication bias.

3 | Result

The PRISMA flow chart is shown in Figure 1; 13 studies [13–25] were included in the meta-analysis. The study design of the included studies is shown in Table 1. The eligible articles were published between 1996 and 2018 and evaluated a total of 888 patients, with women representing 35.8% of the study population. Three studies [14, 22, 25] were conducted in the United States and 10 in Europe [13, 15–21, 23, 24]. All 13 studies were observational. The etiology of PEI was chronic pancreatitis (CP) in four studies [13, 15, 16, 21], cystic fibrosis (CF) in seven

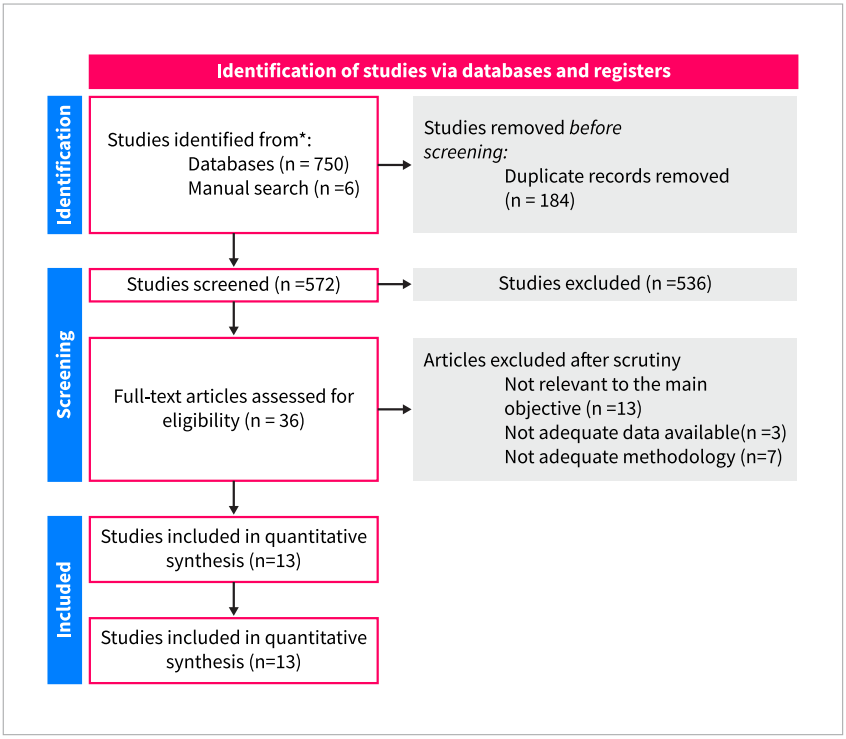

FIGURE 1 | Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram.

TABLE 1 | Design of included studies.

Study, year	Year, country	Design	Study period	Aetiology of PEI	Operated patients %	*n* (% adults)	Race/ethnicity (*n*, % white)	*n* Women, (%)
Löser, 1996 [13]	1996, Germany	Prospective	NR	Chronic pancreatitis GI disorders	NR	79 (100%)	NR	27 (34%)
Walkowiak, 1999 [18]	1999, Poland	Prospective	1993–1997	Cystic fibrosis	NR	28 (NR)	NR	11 (39%)
Lankisch, 1998 [15]	1998, Germany	Prospective, unicentre	NR	Chronic pancreatitis	NR	64 (NR)	NR	NR
Walkowiak, 2002 [17]	2002, Poland	Prospective	1997–2000	Cystic fibrosis	NR	123 (NR)	NR	60 (48,8%)
Walkowiak, 2004 [23]	2004, Poland	Prospective	NR	Cystic fibrosis	NR	90 (NR)	NR	45 (50%)
Borowitz, 2007 [22]	2007, USA	Prospective	NR	Cystic fibrosis	0%	124 (100%)	119 (95,2%)	48 (39,8%)
Hanh, 2008 [20]	2008, Germany	Prospective, unicentre	NR	Diabetes mellitus type 1	0%	33 (NR)	NR	16 (48%)
Weintraub, 2009 [14]	2009, USA	Prospective	NR	Cystic fibrosis	NR	21 (NR	NR	8 (38%)
Halloran, 2011 [19]	2011, UK	Prospective, unicentre	January 2000–December 2003	Pancreatic surgery	100%	51 (100%)	NR	18 (45%)
Benini, 2013 [21]	2013, Italy	Prospective	January 2009–May 2011	Chronic pancreatitis	48%	82 (NR)	NR	29 (35,4%)
Tardelli, 2013 [24]	2013, Italy	Prospective	December 2006–December 2008	Cystic fibrosis	NR	39 (0%)	NR	16 (41%)
Gonzalez-Sanchez, 2017 [16]	2017, Spain	Prospective, unicentre	February 2013, December 2014	Chronic pancreatitis	13 (24,1%)	54 (100)	NR	7 (13%)
Star Kent, 2018 [25]	2018, USA	Prospective, unicentre	NR	Cystic fibrosis	0%	24 (0%)	NR	10 (41,6%)

Abbreviations: NR, not reported; PEI, pancreatic exocrine insufficiency.

studies [14, 17, 18, 22–25], and pancreatic surgery [19] and diabetes mellitus [14] in one study.

3.1 | Methodological Overview of Included Studies

Diagnostic criteria and study details are shown in Table 2. A controlled dietary fat intake of 100 g per day or standardised for age, sex and weight was reported in 10 studies [14, 16–18, 21–23]. Thirteen studies [13–25] reported a 72 h fecal collection. Ten studies [13–22] set the cut-off for steathorrea as a fecal fat excretion of more than 7 g per day or a CFA of less than 93%. In all studies [13–25], the cut-off for FE-1 was set at 200 μg/g.

3.2 | Quality Assessment Using the QUADAS Questionnaire

The quality of all included studies is described in Figure S1. Most were at a high risk of bias.

3.3 | Meta-Analysis Results

A total of 13 studies [13–25] provided data on predefined outcomes of interest suitable for quantitative comparison of FE-1 with the gold standard for the diagnosis of PEI.

3.3.1 | Global Diagnostic Accuracy of FE-1

The global accuracy of FE-1 for the diagnosis of PEI based on a cut-off of 200, 100 and 15 μg/g is shown in Figures 2–4, respectively, and summarised in Table 3. The pooled sensitivity and specificity of FE-1 based on a cut-off of 200 μg/g were 0.94 (95% CI 0.82–0.98) and 0.69 (95% CI 0.52–0.82), respectively (Figure 2A). The pooled positive and negative LRs were 3.02 (95% CI 1.82–5) and 0.09 (95% CI 0.03–0.29), respectively. The pooled DOR was 35.27 (95% CI 8.19–152.01). The SROC of FE-1 for the diagnosis of PEI was 0.89 (95% CI 0.86–0.91) (Figure 2B). I-squared tests showed statistical heterogeneity in sensitivity (I-squared 84.4%) and specificity (I-squared 75.9%).

TABLE 2 | Diagnostic criteria and study details.

Study, year	FE-1 cut-off	FE-1 method	Fat in diet/ day (g)	Fecal dye	Controlled timing of fecal fat collection	Stool collection (72 h or 24 h)
Löser, 1996 [13]	< 200 μg/g < 100 μg/g	2 monoclonal antibodies	90	NR	3-day collection	FFE > 7 g/day
Walkowiak, 1999 [18]	< 200 μg/g	2 monoclonal antibodies	Standardized by age, sex, weight	NR	3-day collection	FFE > 7 g/day
Lankisch, 1998 [15]	< 200 μg/g	2 monoclonal antibodies	NR	NR	3-day collection	FFE > 7 g/day
Walkowiak, 2002 [17]	< 200 μg/g	NR	Standardized by age, sex, weight	NR	3-day collection	7 months-10 years: FFE > 5 g/day > 10 years: FFE > 7 g/day
Walkowiak, 2004 [23]	< 200 μg/g	NR	Standardized by age, sex, weight	NR	3-day collection	NR
Borowitz, 2007 [22]	< 200 μg/g < 100 μg/g	Monoclonal and polyclonal antibody	100	Yes, blue	3-day collection	CFA < 93%
Hanh, 2008 [20]	< 200 μg/g	Polyclonal	NR	NR	3-day collection	FFE > 7 g/day
Weintraub, 2009 [14]	< 200 μg/g < 100 μg/g	NR	50 g/d child 100 g/d adult	NR	3-day collection	FFE > 7 g/day CFA < 93%
Halloran, 2011 [19]	< 200 μg/g	NR	70–100	NR	3-day collection	CFA < 93%
Benini, 2013 [21]	< 200 μg/g < 100 μg/g	Monoclonal	100	NR	2-day equilibration followed by 3-day collection	FFE > 7 g/day
Tardelli, 2013 [24]	< 200 μg/g	2 monoclonal antibodies	NR	NR	3-day collection	< 6 months: FFE > 0.93 g/day. Breast fed < 6 months: FFE > 2.25 g/day. Formula fed > 6 months: FFE > 2,28 g/day
Gonzalez-Sanchez, 2017 [16]	< 15 μg/g < 100 μg/g < 200 μg/g	Monoclonal	100	72 h	2-day equilibration followed by 3-day collection	CFA < 93%
Star Kent, 2018 [25]	< 200 μg/g < 100 μg/g	Polyclonal	NR	NR	3-day collection	< 6 months: FFE > 10% > 6 months: FFE > 7%

Abbreviations: CFA, Coefficient of Fat Absorption; FE-1, Fecal Elastase −1 test; FFE, Fecal Fat Excretion; NR, Not Reported.

With a pre-test probability of PEI of 20%, a FE-1 < 200 μg/g has a 43.1% probability of diagnosing PEI, whereas a FE-1 > 200 μg/g has a 97.9% probability of excluding PEI. The positive predictive value (PPV) increases to 72.2% and 92.4% and the negative predictive value (NPV) decreases to 92.0% and 74.2% for pre-test probabilities of 50% and 80% respectively.

The efficacy of FE-1 based on a cut-off of 100 μg/g has been reported in seven studies [13, 14, 16, 18, 21, 22, 25]. The pooled sensitivity and specificity were 0.88 (95% CI 0.78–0.94) and 0.82 (95% CI 0.58–0.94), respectively (Figure 3A). The pooled positive and negative LR and summary DOR were 5.01 (95% CI 1.85–13.57), 0.14 (95% CI 0.07–0.28) and 34.88 (95% CI 8.51–142.97), respectively. The SROC of FE-1 for the diagnosis of PEI was 0.92 (95% CI 0.89–0.94) (Figure 3B). The I-squared test showed moderate heterogeneity in sensitivity (I-squared: 50%) and specificity (I-squared: 65.6%). With a pre-test probability of PEI of 20%, a FE-1 < 100 μg/g has a 55.0% probability of diagnosing PEI, whereas a FE-1 > 100 μg/g has a 96.5% probability of excluding PEI. The PPV increases to 83.0% and 95.1% and the NPV decreases to 87.2% and 63.1% for pre-test probabilities of 50% and 80% respectively.

Two studies [16, 21] reported the efficacy of FE-1 using a cut-off of 15 μg/g. The pooled sensitivity and specificity were 0.74 (95% CI 0.62–0.83) and 0.83 (95% CI 0.72–0.9), respectively (Figure 4). The pooled positive, negative LR and summary DOR were 4.33 (95% CI 2.54–7.39), 0.31 (95% CI 0.20–0.48) and 13.93 (95% CI 6.07–31.98), respectively.

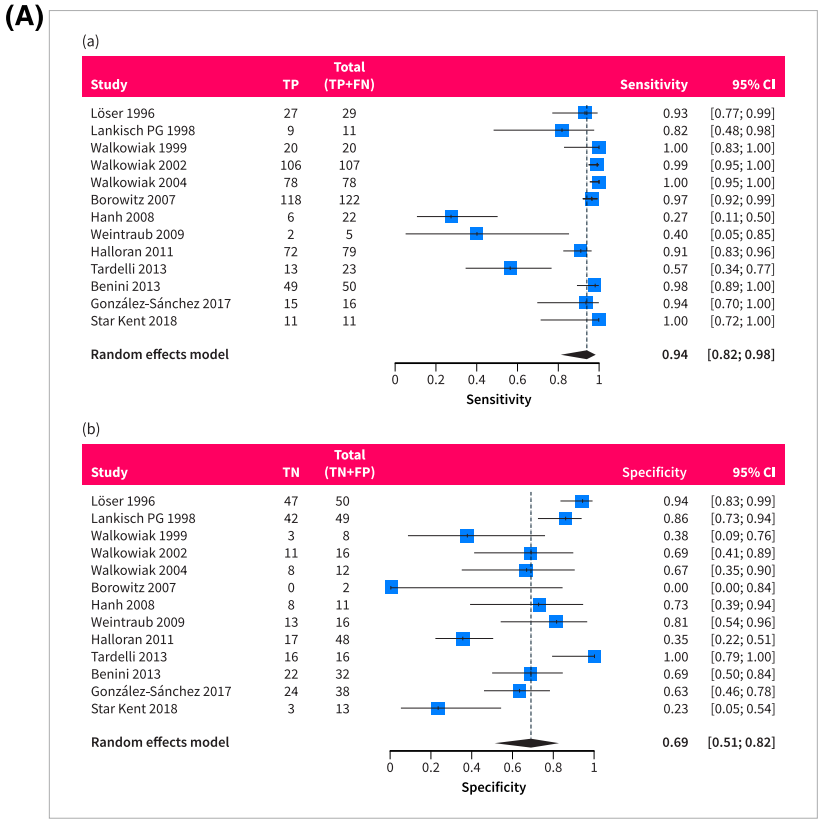

FIGURE 2 | Forest plot showing diagnostic accuracy of FE-1 compared to fecal fat excretion or CFA for pancreatic exocrine insufficiency based on a cut off of 200 μg/g (A: sensitivity and specificity; B: SROC curve).

3.3.2 | Subgroup Analysis

Subgroup analyses of the diagnostic efficacy of FE-1 for PEI were performed in different conditions causing PEI and are summarised in Table 3. In patients with CP, the global efficacy of FE-1 based on a cut-off of 200 μg/g was evaluated in four studies [13, 15, 16, 21]. The pooled sensitivity, specificity, positive and negative LR and summary DOR were 0.91 (95% CI 0.81–0.96), 0.81 (95% CI 0.65–0.91), 4.75 (95% CI 2.41–9.37), 0.11 (95% CI 0.05–0.25) and 41.65 (95% CI 12.76–136.00),

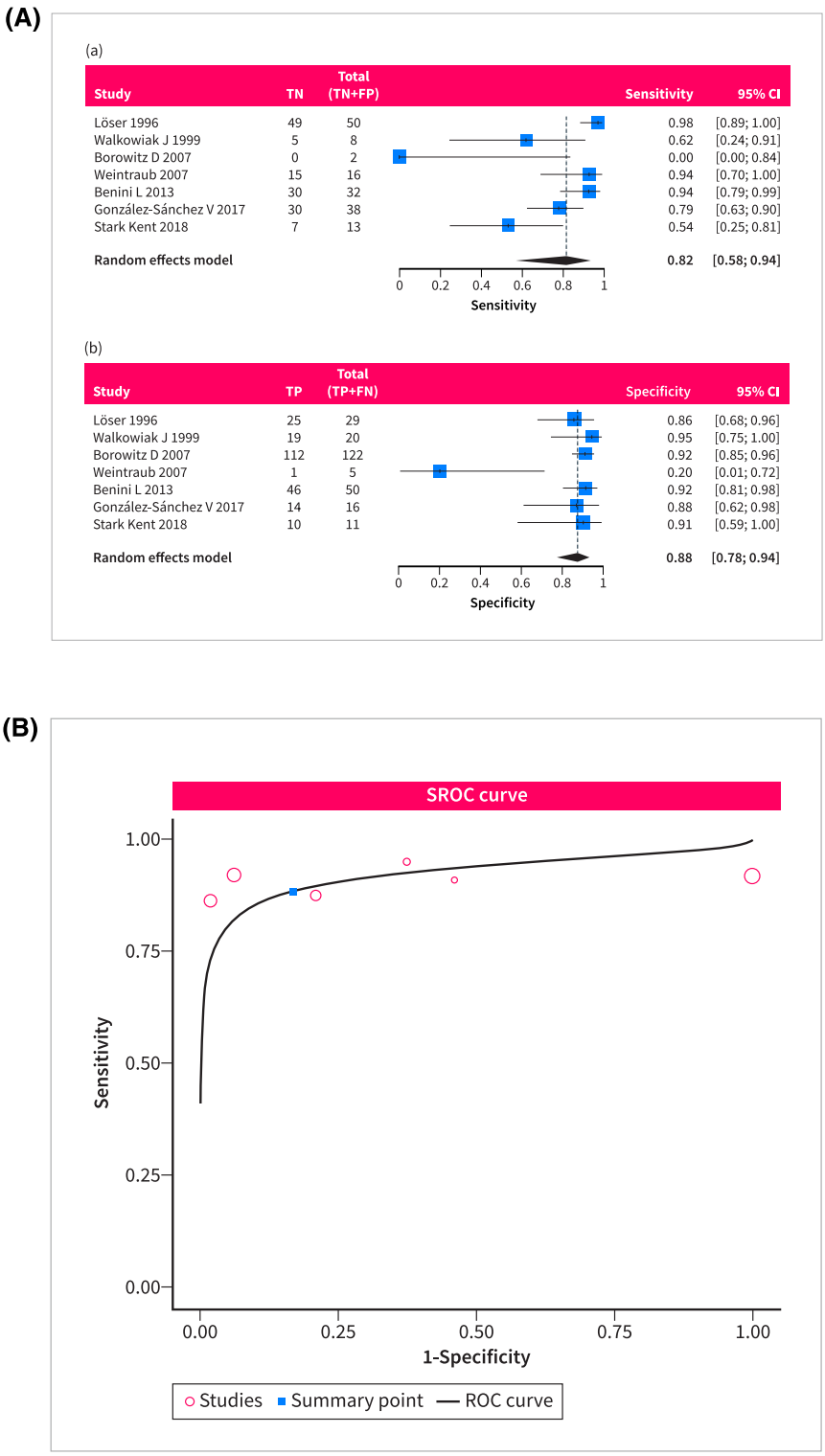

FIGURE 3 | Forest plot showing diagnostic accuracy of FE-1 compared to fecal fat excretion or CFA for pancreatic exocrine insufficiency based on a cut off at 100 μg/g (A: sensitivity and specificity; B: SROC curve).

respectively. Seven studies [14, 17, 18, 22–25] reported the efficacy of FE-1 in patients with CF using a cut-off of 200 μg/g. The pooled sensitivity, specificity, positive and negative LR and summary DOR were 0.98 (95% CI 0.77–0.99), 0.62 (95% CI 0.32–0.85), 2.60 (95% CI 1.19–5.67), 0.04 (95% CI 0.00–0.47) and 74.66 (95% CI 4.09–1363.93), respectively. Three studies [16, 19, 21] reported the efficacy of FE-1 in patients undergoing pancreatic surgery. The pooled sensitivity, specificity, positive and negative LR and summary DOR were 0.97 (95% CI 0.60–0.99), 0.45 (95% CI 0.12–0.82), 1.76 (95% CI 0.80–3.88), 0.07 (95% CI 0.00–1.52) and 26.77 (95% CI 0.77–926.09), respectively.

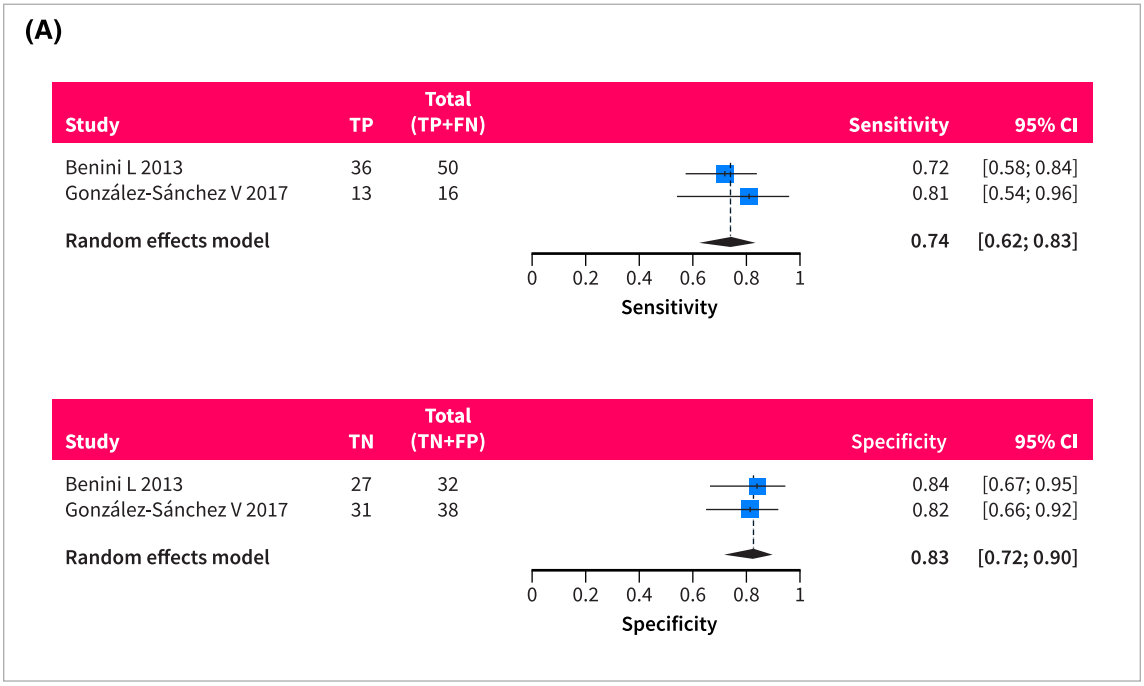

FIGURE 4 | Forest plot showing diagnostic accuracy of FE-1 compared to fecal fat excretion or CFA for pancreatic exocrine insufficiency based on a cut off of 15 μg/g (A: sensitivity and specificity).

TABLE 3 | Results of meta-analysis for outcomes of interest based on Fecal Elastase −1 test cut offs of 200 μg/g, 100 μg/g and 15 μg/g in different clinical scenarios.

Outcome of interest	Studies, *n*	Patients, *n*	Sensitivity	Specificity	Positive LR	Negative LR	DOR
[a]Global FE-1 < 200	13 [1–13]	888	0.94 (0.82–0.98)	0.69 (0.52–0.82)	3.02 (1.82–5)	0.09 (0.03–0.29)	35.27 (8.19–152.01)
[a]Global FE-1 < 100	7 [13, 14, 16, 18, 21, 22, 25]	412	0.88 (0.78–0.94)	0.82 (0.58–0.94)	5.01 (1.85–13.57)	0.14 (0.07–0.28)	34.88 (8.51–142.97)
[a]Global FE-1 < 15	2 [9, 12]	136	0.74 (0.62–0.83)	0.83 (0.72–0.9)	4.33 (2.54–7.39)	0.31 (0.20–0.48)	13.93 (6.07–31.98)
CP FE-1 < 200	4 [13, 15, 16, 21]	226	0.91 (0.81–0.96)	0.81 (0.65–0.91)	4.75 (2.41–9.37)	0.11 (0.05–0.25)	41.65 (12.76–136.00)
CP FE-1 < 100	3 [13, 16, 21]	162	0.87 (0.75–0.94)	0.90 (0.74–0.96)	8.36 (3.04–22.94)	0.15 (0.07–0.29)	57.74 (14.61–228.22)
CF FE-1 < 200	7 [14, 17, 18, 22–25]	449	0.98 (0.77–0.99)	0.62 (0.32–0.85)	2.60 (1.19–5.67)	0.04 (0.00–0.47)	74.66 (4.09–1363.93)
CF FE-1 < 100	4 [14, 18, 22, 25]	197	0.85 (0.54–0.97)	0.65 (0.31–0.88)	2.42 (0.94–6.24)	0.23 (0.05–0.98)	10.75 (1.25–92.37)
PS FE-1 < 200	3 [16, 19, 21]	180	0.97 (0.60–0.99)	0.45 (0.12–0.82)	1.76 (0.80–3.88)	0.07 (0.00–1.52)	26.77 (0.77–926.09)

Abbreviations: CF, cystic fibrosis; CP, chronic pancreatitis; DOR, diagnostic odds ratio, LR, likelihood ratio; PS, pancreatic surgery.
[a]All studies included in the meta-analysis.

3.4 | Publication Bias

Figure 5 shows the qualitative assessment of the studies using the Deeks funnel plot asymmetry test. The Deeks' funnel plots showed no significant asymmetry, suggesting no publication bias. Specifically, Deeks' test results were as follows: fecal fat test as control ($p = 0.325$), Deeks' fecal fat as control in CP ($p = 0.555$), and Deeks' fecal fat as control in CF ($p = 0.958$).

4 | Discussion

This meta-analysis provides compelling evidence that the FE-1 test is a highly sensitive diagnostic tool for PEI, with a pooled sensitivity of 0.94 (95% CI 0.82–0.98) and specificity of 0.69 (95% CI 0.52–0.82) at the 200 μg/g cut-off. These findings suggest that FE-1 is effective for diagnosing PEI in high-risk populations but has limited specificity in differentiating PEI from other

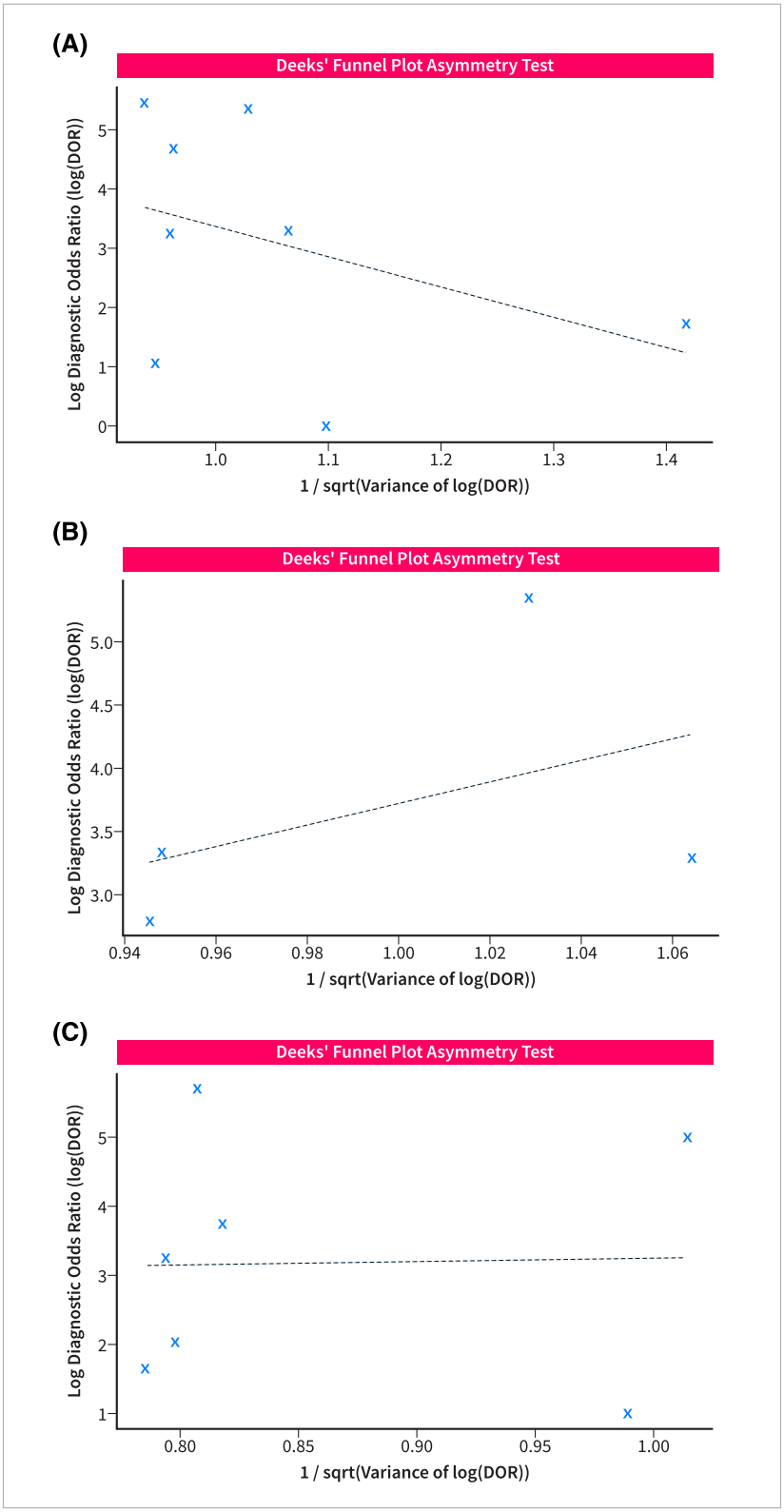

FIGURE 5 | Deeks' funnel plot asymmetry test (A: cut-off of 200 μg/g; B: chronic pancreatitis; C: cystic fibrosis).

gastrointestinal disorders. Notably, our results demonstrate that lowering the cut-off to 100 μg/g improves specificity (0.82, 95% CI 0.58–0.94) with a slight reduction in sensitivity (0.88, 95% CI 0.78–0.94), providing flexibility in test interpretation based on clinical context. Further reduction to 15 μg/g significantly increases specificity but at the expense of sensitivity, primarily identifying severe PEI while potentially missing mild to moderate cases.

Our findings emphasize the importance of interpreting FE-1 results within the appropriate clinical setting. FE-1 allows the diagnosis (high PPV) but not the exclusion (limited NPV) of PEI in cases with a high probability of this condition (e.g., patients with cystic fibrosis or advanced chronic calcifying pancreatitis). On the contrary, FE-1 allows to exclude (high NPV) but not to diagnose PEI (limited PPV) in case of low probability of this condition (e.g., patients with chronic non-calcific pancreatitis with non-dilated main pancreatic duct) [26]. Therefore, a low FE-1 result should be considered with caution in scenarios with a low probability of PEI, and a normal FE-1 result should be considered with caution in scenarios with a high probability of PEI. These findings support the current statement that FE-1 should be considered together with a global assessment of symptoms and nutritional status in an appropriate clinical scenario for PEI diagnosis [1].

Our results align with those of a previous meta-analysis by Vanga et al. [10], which reported sensitivity and specificity rates of 0.77 and 0.88, respectively, using the secretin stimulation test as a reference standard for the diagnosis of PEI, and 0.96 and 0.88, respectively, using FFE as a reference. These findings highlight the consistent diagnostic performance of FE-1 across different reference standards. Despite its accuracy in assessing pancreatic secretion, the secretin stimulation test is not currently considered the gold standard for PEI diagnosis as it does not evaluate digestive function. Furthermore, its invasiveness, complexity, and lack of standardization may contribute to variability in diagnostic accuracy across studies [27]. Notably, the meta-analysis by Vanga et al. included only six studies, three of which used 24-h fecal fat collection, limiting comparability with our findings. In contrast, our study used 72h-FFE and CFA as reference standards, which are considered more reliable for diagnosing PEI as they reflect the actual physiological impairment of fat digestion and absorption [1]. This methodological difference is likely to contribute to the differences in reported sensitivity and specificity between our study and that of Vanga et al. [10].

Although the studies included in this meta-analysis are mainly focused on CP and CF, the results obtained are likely to be applicable to other conditions associated with PEI. The pathophysiology of PEI is consistent across various etiologies that impair pancreatic enzyme secretion, including pancreatic head cancer, pancreaticoduodenectomy, and acute necrotizing pancreatitis [28, 29]. Prior studies suggest that FE-1 levels correlate with exocrine dysfunction in these conditions, supporting the applicability of our results beyond CP and CF. Future research should explore FE-1's diagnostic performance in these subgroups to validate its diagnostic accuracy across different clinical settings.

The clinical implications of our results are significant. Diagnosis of PEI using FE-1 may facilitate timely intervention with PERT, potentially preventing complications such as malnutrition, fat-soluble vitamin deficiency and related comorbidities [2, 3, 5, 6], but FE-1 results should be interpreted with caution. Despite its limitations in specificity, the high sensitivity of FE-1 makes it a valuable initial screening tool, particularly in patients with established risk factors for PEI, such as those with CP or CF. However, the moderate specificity observed suggests that FE-1 should be used in conjunction with other clinical parameters, such as symptoms and nutritional status, and the probability of PEI in different clinical scenarios should be considered to minimise the risk of false results [1]. The pre-test probability of PEI in different clinical conditions is critical. A low FE-1 result supports the diagnosis of PEI in scenarios with a high probability of PEI, and a normal FE-1 result helps to exclude the diagnosis of PEI in scenarios with a low probability of PEI. However, normal and low FE-1 results should be interpreted with caution in scenarios of high and low probability of PEI, respectively, due to low predictive values.

The subgroup analyses showed that the diagnostic performance of FE-1 varies in different clinical contexts. Sensitivity is slightly lower in the CP group (0.91) than in the CF group (0.98), whereas specificity is relatively higher in the CP group (0.81) than in the CF group (0.62). These differences may be due to the different pathophysiological mechanisms and clinical presentations of PEI in these populations. In CP, the gradual destruction of pancreatic tissue leads to a progressive decrease in enzyme production, which may result in a more gradual decrease in FE-1 levels [30]. Conversely, the more uniform and severe pancreatic damage in cystic fibrosis, often present from an early age, may result in consistently low FE-1 levels, contributing to higher sensitivity, while the involvement of other organs such as the intestine reduces specificity.

The performance of FE-1 in patients after pancreatic surgery, mainly pancreaticoduodenectomy (sensitivity 0.97, specificity 0.45), deserves special attention. The very high sensitivity suggests that FE-1 is excellent at detecting PEI in this population. However, the poor specificity indicates a high rate of false positives, possibly due to altered bowel anatomy ('post-cibal asynchrony') and function [31].

The main strength of this study is that it uses the current concept of PEI according to recently published clinical guidelines [1]. In this study, PEI was not defined as a simple impairment of pancreatic secretion but as a reduction of pancreatic secretion below the level required for normal digestion and absorption of nutrients [1]. In line with this definition, 72h-FFE and CFA are considered as the reference methods for evaluating the diagnostic accuracy of the FE-1 test for PEI. In addition, this study includes a comprehensive analysis of different clinical contexts, which increases the reliability and clinical relevance of our findings. Furthermore, the analysis of different FE-1 cut-off values provides valuable insights into optimizing test performance for different clinical scenarios. However, several limitations must be acknowledged. The moderate to high risk of bias in the included studies, coupled with substantial heterogeneity, complicates the interpretation of the overall diagnostic performance of FE-1. The retrospective nature of some studies and the lack of standardized diagnostic thresholds contribute to the observed variability in results. Furthermore, as our meta-analysis primarily included studies on high-probability PEI populations, extrapolating conclusions to low-probability cases should be approached with caution. Lastly, while most included studies focused on adults, the role of FE-1 in paediatric non-CF conditions remains unclear, necessitating further research to clarify its diagnostic utility in younger populations.

Future research should focus on prospective studies with standardized protocols to further elucidate the performance of FE-1 in different etiologies of PEI. Investigating the combination of FE-1 with other biomarkers or clinical parameters may improve overall diagnostic accuracy. In addition, studies investigating the impact of FE-1-based diagnosis on clinical outcomes and cost-effectiveness compared with traditional diagnostic approaches would provide valuable insights for clinical practice and health policy.

5 | Conclusion

In conclusion, FE-1 is a sensitive tool for the early detection of PEI. However, due to its moderate specificity, careful interpretation of results is required, especially in settings with a low risk of PEI. Clinicians should consider FE-1 results in conjunction with symptoms, nutritional assessment and risk factors; confirmatory testing may be required to optimize the diagnosis and management of PEI in clinical practice.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

References

1. J. E. Dominguez-Muñoz, M. Vujasinovic, D. de la Iglesia, 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 Gastroenterology Journal* [Internet]. (December 2024), https://pubmed.ncbi.nlm.nih.gov/39639485/.

2. B. Lindkvist, M. E. Phillips, and J. E. Domínguez-Muñoz, "Clinical, Anthropometric and Laboratory Nutritional Markers of Pancreatic Exocrine Insufficiency: Prevalence and Diagnostic Use," *Pancreatology* 15, no. 6 (2015): 589–597, https://doi.org/10.1016/j.pan.2015.07.001.

3. E. Martínez-Moneo, S. Stigliano, A. Hedström, et al., "Deficiency of Fat-Soluble Vitamins in Chronic Pancreatitis: A Systematic Review and Meta-Analysis," *Pancreatology* [Internet], 16 no. 6 (November 2016): 988–994, https://pubmed.ncbi.nlm.nih.gov/27681502/.

4. R. Shintakuya, K. Uemura, Y. Murakami, et al., "Sarcopenia Is Closely Associated With Pancreatic Exocrine Insufficiency in Patients With Pancreatic Disease," *Pancreatology* 17, no. 1 (2017): 70–75, https://doi.org/10.1016/j.pan.2016.10.005.

5. D. De La Iglesia-Garcia, N. Vallejo-Senra, J. Iglesias-Garcia, A. López-López, L. Nieto, and J. E. Domínguez-Muñoz, "Increased Risk of Mortality Associated With Pancreatic Exocrine Insufficiency in Patients With Chronic Pancreatitis," *Journal of Clinical Gastroenterology* 52, no. 8 (2018): e63–e72, https://doi.org/10.1097/mcg.0000000000000917.

6. D. de la Iglesia, N. Vallejo-Senra, A. López-López, et al., "Pancreatic Exocrine Insufficiency and Cardiovascular Risk in Patients With Chronic Pancreatitis: A Prospective, Longitudinal Cohort Study," *Journal of Gastroenterology and Hepatology* 34, no. 1 (2018): 277–283, https://doi.org/10.1111/jgh.14460.

7. C. D. Johnson, R. Arbuckle, N. Bonner, et al. "Qualitative Assessment of the Symptoms and Impact of Pancreatic Exocrine Insufficiency (PEI) to Inform the Development of a Patient-Reported Outcome (PRO) Instrument," *Patient* [Internet], 10 no.5 (October 2017): 615–628, https://pubmed.ncbi.nlm.nih.gov/28332032/.

8. J. G. Lieb, P. V. Draganov, "Pancreatic Function Testing: Here to Stay for the 21st Century," *World Journal of Gastroenterology: WJG* [Internet], 14 no. 20 (May 2008): 3149, https://pmc.ncbi.nlm.nih.gov/articles/PMC2712845/.

9. J. Keller, H. F. Hammer, P. R. Afolabi, et al., "European Guideline on Indications, Performance and Clinical Impact of 13C-Breath Tests in Adult and Pediatric Patients: An EAGEN, ESNM, and ESPGHAN Consensus, Supported by EPC," *United European Gastroenterology Journal* [Internet] 9, no. 5 (June 2021): 598–625, https://pmc.ncbi.nlm.nih.gov/articles/PMC8259225/.

10. R. R. Vanga, A. Tansel, S. Sidiq, H. B. El-Serag, and M. O. Othman, "Diagnostic Performance of Measurement of Fecal Elastase-1 in Detection of Exocrine Pancreatic Insufficiency: Systematic Review and Meta-Analysis," *Clinical Gastroenterology and Hepatology* 16, no. 8 (2018): 1220–1228.e4, https://doi.org/10.1016/j.cgh.2018.01.027.

11. P. Whiting, A. W. S. Rutjes, J. B. Reitsma, P. M. M. Bossuyt, J. Kleijnen, "The Development of QUADAS: A Tool for the Quality Assessment of Studies of Diagnostic Accuracy Included in Systematic Reviews," *BMC Medical Research Methodology* [Internet], 3 no. 1 (November 2003): 1–13, https://bmcmedresmethodol.biomedcentral.com/articles/10.1186/1471-2288-3-25.

12. L. E. Moses, D. Shapiro, and B. Littenberg, "Combining Independent Studies of a Diagnostic Test into a Summary ROC Curve: Data-Analytic Approaches and Some Additional Considerations," *Statistics in Medicine* 12, no. 14 (1993): 1293–1316: [Internet], https://pubmed.ncbi.nlm.nih.gov/8210827/.

13. C. Löser, A. Möllgaard, and U. R. Fölsch, "Faecal Elastase 1: A Novel, Highly Sensitive, and Specific Tubeless Pancreatic Function Test," *Gut* 39, no. 4 (1996): 580–586, https://doi.org/10.1136/gut.39.4.580.

14. ÃA. Weintraub, H. Blau, H. Mussaffi, et al., "Exocrine Pancreatic Function Testing in Patients With Cystic Fibrosis and Pancreatic Sufficiency: A Correlation Study," *Journal of Pediatric Gastroenterology and Nutrition* 48, no. 3 (2009): 306–310, https://doi.org/10.1097/mpg.0b013e318180af4f.

15. P. G. Lankisch, I. Schmidt, H. König, et al. "Faecal Elastase 1: Not Helpful in Diagnosing Chronic Pancreatitis Associated With Mild to Moderate Exocrine Pancreatic insuYciency" (1998).

16. V. González-Sánchez, R. Amrani, V. González, C. Trigo, A. Picó, E. de-Madaria, "Diagnosis of Exocrine Pancreatic Insufficiency in Chronic Pancreatitis: 13C-Mixed Triglyceride Breath Test Versus Fecal Elastase," *Pancreatology*, 17 no. 4 (July 2017): 580–585, https://doi.org/10.1016/j.pan.2017.03.002.

17. J. Walkowiak, K. H. Herzig, K. Strzykala, et al., "Fecal Elastase-1 Is Superior to Fecal Chymotrypsin in the Assessment of Pancreatic Involvement in Cystic Fibrosis,"[Internet], (2002), http://www.pediatrics.org/cgi/content/full/110/1/e7.

18. J. Walkowiak, W. K. Cichy, and K. H. Herzig, "Comparison of Fecal Elastase-1 Determination With the Secretin-Cholecystokinin Test in Patients With Cystic Fibrosis," *Scandinavian Journal of Gastroenterology* 34, no. 2 (1999): 202–207, https://doi.org/10.1080/00365529950173104.

19. C. M. Halloran, T. F. Cox, S. Chauhan, et al., "Partial Pancreatic Resection for Pancreatic Malignancy Is Associated With Sustained Pancreatic Exocrine Failure and Reduced Quality of Life: A Prospective Study," *Pancreatology* 11, no. 6 (2011): 535–545, https://doi.org/10.1159/000333308.

20. J. U. Hahn, W. Kerner, P. Maisonneuve, A. B. Lowenfels, and P. G. Lankisch, "Low Fecal Elastase 1 Levels Do Not Indicate Exocrine

Pancreatic Insufficiency in Type-1 Diabetes Mellitus," *Pancreas* 36, no. 3 (2008): 274–278, https://doi.org/10.1097/mpa.0b013e3181656f8.

21. L. Benini, A. Amodio, P. Campagnola, et al., "Fecal Elastase-1 Is Useful in the Detection of Steatorrhea in Patients With Pancreatic Diseases but Not After Pancreatic Resection," *Pancreatology* 13, no. 1 (2013): 38–42, https://doi.org/10.1016/j.pan.2012.11.307.

22. Ã Drucy Borowitz, R. Lin, and S. S. Baker, "Comparison of Monoclonal and Polyclonal ELISAs for Fecal Elastase in Patients With Cystic Fibrosis and Pancreatic Insufficiency,"(2006): [Internet], www.clinicaltrials.gov.

23. J. Walkowiak, A. Lisowska, J. Przyslawski, M. Grzymislawski, M. Krawczynski, K. H. Herzig, "Faecal Elastase-1 Test Is Superior to Faecal Lipase Test in the Assessment of Exocrine Pancreatic Function in Cystic Fibrosis," *Acta Paediatrica, International Journal of Paediatrics*, 93 no. 8 (August 2004): 1042–1045, https://doi.org/10.1111/j.1651-2227.2004.tb02715.x.

24. A. C. S. Tardelli, P. A. M. Camargos, F. J. Penna, P. F. B. Sarkis, E. V. Guimarães, "Comparison of Diagnostic Methods for Pancreatic Insufficiency in Infants With Cystic Fibrosis," *Journal of Pediatric Gastroenterology and Nutrition*, 56 no. 2 (February 2013): 178–181, https://doi.org/10.1097/mpg.0b013e31826f2b71.

25. D. S. Kent, T. Remer, C. Blumenthal, et al., "13 C-Mixed Triglyceride Breath Test and Fecal Elastase as an Indirect Pancreatic Function Test in Cystic Fibrosis Infants," *Journal of Pediatric Gastroenterology and Nutrition*, 66 no. 5 (May 2018): 811–815, https://doi.org/10.1097/mpg.0000000000001905.

26. J. E. D. Domínguez-Muñoz, P. Hardt, M. M. Lerch, and M. J. Löhr, "Potential for Screening for Pancreatic Exocrine Insufficiency Using the Fecal Elastase-1 Test," *Digestive Diseases and Sciences* 62, no. 5 (2017): 1119–1130, https://doi.org/10.1007/s10620-017-4524-z.

27. Conwell D. L., Lee L. S., Yadav D., et al., "American Pancreatic Association Practice Guidelines in Chronic Pancreatitis: Evidence-Based Report on Diagnostic Guidelines," *Pancreas* [Internet], 43 no. 8 (November 2014): 1143–1162, /pmc/articles/PMC5434978/, https://doi.org/10.1097/mpa.0000000000000237.

28. Iglesia D. D L., Avci B., Kiriukova M., et al., "Pancreatic Exocrine Insufficiency and Pancreatic Enzyme Replacement Therapy in Patients With Advanced Pancreatic Cancer: A Systematic Review and Meta-Analysis," *United European Gastroenterology Journal* [Internet], 8 no. 9 (November 2020): 1115–1125, https://pubmed.ncbi.nlm.nih.gov/32631175/.

29. Huang W., de la Iglesia-García D., Baston-Rey I., et al., "Exocrine Pancreatic Insufficiency Following Acute Pancreatitis: Systematic Review and Meta-Analysis," *Digestive Diseases and Sciences* [Internet], 64 no. 7 (July 2019): 1985–2005, https://pubmed.ncbi.nlm.nih.gov/31161524/.

30. Keller J., "Human Pancreatic Exocrine Response to Nutrients in Health and Disease," Supplement *Gut* [Internet], 54 no. S6 (July 2005): 1–28, www.gutjnl.com.

31. J. E. Domínguez-Muñoz, "Pancreatic exocrine insufficiency: Diagnosis and treatment,"Supplement *Journal of Gastroenterology And Hepatology* [Internet] 26, no. S2 (2011): 12–16, https://pubmed.ncbi.nlm.nih.gov/21323992/.

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